CONFIDENTIAL

Clinical Study Protocol

RBM-007-001
Phase 1/2
Amendment 1

Phase 1/2 Open label, Dose-escalation Study of the Safety and OcUlar Tolerability of a Single Intravitreal Injection of RBM-007 in Subjects witH ExudatIve Age-related Macular Degeneration (SUSHI)

RIBOMIC USA Inc.
2120 University Ave.
Berkeley, CA 94704

Version:	**25 September 2018**
Original:	**2 June 2018**
Amendments included:	**One**

Investigator Agreement

I have read the Protocol and agree to conduct the study as outlined and in accordance with 21CFR Parts 11,50,54,56, and 312,42 USC282 (j), the Declaration of Helsinki, ICH GCPs, and applicable local regulations. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and RIBOMIC USA Inc. as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study specific procedures.

I understand that my electronic signature on an electronic case report form indicates that the data therein has been reviewed and accepted by me as the Investigator. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

INVESTIGATOR:

Signature/Date: _____

Name: _____

Address: _____

_____

Phone: _____

Contact Information and Protocol Authorization

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Abbreviations and Terms

Abbreviation	Expression (Name) in full
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine transaminase
AMD	age-related macular degeneration
AST	aspartate aminotransferase
BCVA	best corrected visual acuity
BUN	blood urea nitrogen
CNV	choroidal neo-vascularization
CRF	Case report form
CST	central subfield thickness
dL	deciliter
eCRF(s)	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EC	Ethics Committee
EKG	electrocardiogram (= ECG)
ESI(s)	event(s) of special interest
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
FGF	fibroblast growth factor
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
HCT	hematocrit
HDL	high density lipoprotein
HGB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	intraocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat
IVT, i.vt.	intravitreal
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LOCF	Last Observation Carried Forward
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NOAEL	no observed adverse effect level
µL	microliter
mL	milliliter
mmHg	millimeter of mercury
PLT	platelet
RBC	red blood cell

Abbreviation	Expression (Name) in full
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD-OCT	spectral domain optical coherence tomography
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRT	Safety Review Team
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WBC	white blood cell

1 SYNOPSIS

Study Number:	RBM-007-001
Name of Sponsor/Company:	RIBOMIC USA Inc.
Name of Investigational Product:	RBM-007 injectable solution
Name of Active Ingredient:	RBM-007
Title of Study	Phase 1/2 Open label, Dose-escalation Study of the Safety and OcUlar Tolerability of a Single Intravitreal Injection of RBM-007 in Subjects witH ExudatIve Age-related Macular Degeneration (SUSHI)
Study Period:	Approximately 1 year Estimated date first subject enrolled: August 2018 Estimated date last subject completed: August 2019
Phase of Development:	Phase ½
Primary Objective:	To assess the safety and tolerability of a single intravitreal injection of three dose levels of RBM-007 (0.2 mg/eye, 1.0 mg/eye and 2.0 mg/eye) in subjects with exudative age-related macular degeneration.
Secondary Objective:	To evaluate the bioactivity of three dose levels of RBM-007 in subjects with exudative age-related macular degeneration.
Methodology:	This is an open label, non-controlled, dose-escalating study assessing the safety, tolerability, and bioactivity of a single intravitreal (i.vt.) injection of RBM-007 in approximately nine subjects with exudative age-related macular degeneration (AMD). Following a screening evaluation, subjects will receive a single intravitreal injection of RBM-007 in the study eye. The primary endpoint of the study is at 28 days post-injection of RBM-007, with safety evaluation through 56 days. The study will initiate with the lowest dose of 0.2 mg in the first cohort of three subjects, proceeding to a second cohort of three subjects at a dose of 1.0 mg, then a third cohort of three subjects at a dose of 2.0 mg. Decisions regarding proceeding to each sequential cohort will be based on the recommendations of the Safety Review Team (SRT), consisting of external Retina Specialists and the Medical Monitor. The first subject of each dose cohort will be assessed by the SRT at 7 days after injection of RBM-007 to determine if safety is acceptable. If so, RBM-007 treatment will be given to the remaining 2 subjects in that dose cohort. Upon completion of the primary endpoint at 28 days post-RBM-007 injection by all 3 subjects in the cohort, the SRT will review. If acceptable safety is seen, then the next dose cohort will be initiated, and the same schedule of interval SRT evaluations repeated for that cohort. Toxicity events observed in any subject will curtail treatment of other subjects in that cohort, as well as curtail progression to the next dose cohort. For eligibility, subjects age 55 years or older must be diagnosed with exudative AMD in the study eye, for which

	previous standard treatment with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents has recently demonstrated incomplete resolution of exudation, as assessed by spectral domain optical coherence tomography (SD-OCT). Other inclusion criteria are: ETDRS best-corrected visual acuity (BCVA) of 65 to 10 letters (≤20/50 and ≥20/640 Snellen vision equivalent); presence of macular edema or subretinal fluid on SD-OCT; choroidal neovascular lesions ≤9 disc areas (DA); lesion composed of ≤50% subretinal hemorrhage
Number of Subjects (planned):	Approximately nine subjects (3 subjects per cohort) with exudative age-related macular degeneration will be enrolled at 4-5 clinical trial sites. The final number of subjects enrolled may be adjusted based on the presence of dose limiting toxicities.
Duration of the Study:	Following a Screening Visit, at Baseline Visit (Day 0) the study eye will receive injection of RBM-007. The primary study endpoint will be at 28 days after RBM-007 injection, at which time anti-VEGF treatment can be resumed according to the investigating physician. Follow up will continue to the exit visit at 56 days.
Diagnosis and Main Criteria for Inclusion:	• Provide signed written informed consent on the IRB / EC approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations. • Male or female 55 years of age or older on the date of signing the ICF and able and willing to comply with all treatment and follow-up study procedures. At Screening Visit, subjects must meet all the following inclusion criteria: • Must have had prior treatment in the study eye with any intravitreal anti-VEGF medication (at least 3 anti-VEGF treatments within the prior 2-6 months), throughout which clinical examination and SD-OCT imaging has shown recurrent or persistent exudative activity, as shown by the presence of intraretinal or subretinal fluid, and/or subretinal exudation or hemorrhage. • BCVA of 65 to 10 ETDRS letters (20/50 to ≥20/640) in the study eye. • Presence of significant subretinal fluid and/or cystoid macular edema secondary to exudative age-related macular degeneration as assessed by SD-OCT in the study eye, with a minimum of 300 μm within the central subfield. • Total lesion size of ≤9 disc areas, lesion containing ≤50% hemorrhage in the study eye. • Reasonably clear media and reasonable fixation ability in the study eye to allow for good quality SD-OCT and fundus photography.

	At Baseline Visit (Day 0), subjects must meet all the following inclusion criteria: • BCVA of 65 to 10 ETDRS letters (20/50 to ≥20/640) in the study eye. • Presence of significant subretinal and/or intraretinal fluid secondary to exudative age-related macular degeneration as assessed by SD-OCT in the study eye, with a minimum of 300 µm within the central subfield. • Total lesion size of ≤9 disc areas, lesion containing ≤50% hemorrhage in the study eye.
Study Eye	If both eyes of a subject meet the eligibility criteria, then study eye will be determined as the eye with the worse vision. If both eyes have the same vision, the right eye (OD) should be determined as the study eye.
Investigational product, dosage and mode of administration:	Subjects will receive one of the following three dose levels of the investigational product, RBM-007 injectable solution by intravitreal injection: 0.2 mg (100 µL of 2 mg/mL) RBM-007 injectable solution 1.0 mg (50 µL of 20 mg/mL) RBM-007 injectable solution 2.0 mg (100 µL of 20 mg/mL) RBM-007 injectable solution
Route of Administration of Investigational product:	Single intravitreal injection in the study eye
Criteria for Evaluation:	Safety: The safety assessments will include adverse events (AEs), slit-lamp exam and biomicroscopy, indirect ophthalmoscopy, BCVA, IOP, fundus photography, fluorescein angiography, serum chemistry, hematology, vital signs, physical exam, EKG and pregnancy. Biological activity: The bioactivity of RBM-007 will be assessed using the change in retinal fluid measured by CST based on SD-OCT at each visit post RBM-007 treatment as compared to the Baseline Visit.
Statistical Methods:	Descriptive statistics will be provided for safety and bioactivity parameters by dose level.

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2 INTRODUCTION

RBM-007 injectable solution is a novel oligonucleotide-based aptamer having potent anti-FGF2 activity (Jin et al, 2016) and anti-VEGF-expression activity (Belgore et al, 2003). In the rat and mouse models of laser-induced choroidal neovascularization, it showed activity after intravitreal injection at doses as low as 5 µg/eye. In the laser-induced choroidal neovascularization (CNV) fibrosis model in rats, it showed activity after intravitreal injection at doses as low as 15 µg/eye. It is hypothesized to have potential effects in the treatment of wet age-related macular degeneration (AMD) because of these activities. Thus, the Sponsor plans to evaluate the safety and bioactivity of RBM-007 Injectable Solution as an intravitreal treatment for exudative AMD.

In this submission, the Sponsor provides nonclinical pharmacology, pharmacokinetic and toxicology information and chemistry, manufacturing and control (CMC) to support the intended clinical evaluation of RBM-007 Injectable Solution in patients with wet AMD.

Approximately 1.2 million persons in the United States are estimated to have neovascular AMD and 970 000 to have geographic atrophy; >8 million have at least large drusen in 1 eye and 3.6 million of these have bilateral large drusen.

Without methods to slow AMD progression over the next 20 years, these prevalence figures are expected to increase by approximately 50% (Chew et al, 2012; Friedman et al, 2004). From the initial stage of dry AMD, characterized by lipofuscin deposits under the retina known as drusen, 10% are at risk for severe, acute loss of central vision due to the onset of wet AMD, characterized by the growth of abnormal CNV in the macula, which leads to subretinal bleeding, fluid exudation, and fibrotic scar formation. Over 200,000 new patients each year in the U.S. develop wet AMD (Ferris, et al, 1984).

Current FDA-approved therapies for AMD are pegaptanib (Macugen®), ranibizumab (Lucentis®) and aflibercept (Eylea®). Also used off-label is aliquoted bevacizumab (Avastin®). All of these molecules act against the same target: vascular endothelial growth factor (VEGF). VEGF, a potent endothelial cell mitogen and vascular permeability factor, is a major contributor to the pathogenesis of neovascular AMD. Treatments with anti-VEGF drugs, which are delivered by frequent intravitreal injections, have shown dramatic visual benefits for AMD patients (Brown et al, 2006; Heier et al, 2012; Martin et al, 2012). However, there are some critical limitations; in formal clinical trials, despite consistent monthly treatment, 23% of eyes treated monthly with ranibizumab proceeded to vision worse than 20/200, and 20% to 40% fail to resolve macular fluid even after 2 years of therapy (Brown et al, 2006; Heier et al, 2012). Furthermore, in the “real-world” setting, patients receive intravitreal injections at much lower frequency than the established protocols, so that on average, long-term visual outcomes in AMD treatment are poor (Rofagha et al, 2013; Maguire et al, 2016). Factors associated with poor vision outcomes, in addition to persistent exudation, include macular atrophy and submacular fibrotic scar formation. Thus, there is a need for additive or alternative therapy to anti-VEGF treatments for wet AMD.

Fibroblast growth factor (FGF) has been implicated in the pathophysiology of both angiogenesis and fibrosis in retinal diseases (Schultz and Grant, 1991; Vinding, 1990). FGF comprises a family of 22 members, including FGF2, having many biological activities (Bikfalvi et al., 1997). FGF2 promotes growth of vascular endothelial cells and tubular structure formation (Strutz et al, 2002), and stimulates both VEGF production and scar formation in retina.

3 OBJECTIVES

Primary Objective:

To assess the safety and tolerability of a single intravitreal injection of three dose levels of RBM-007 (0.2 mg/eye, 1.0 mg/eye and 2.0 mg/eye) in subjects with exudative age-related macular degeneration.

Secondary Objective:

To evaluate the bioactivity of three dose levels of RBM-007 in subjects with exudative age-related macular degeneration.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open label, dose-escalating, sequential cohort study assessing the safety, tolerability, and biological activity of a single i.vt. injection of 0.2 mg, 1.0 mg and 2.0 mg RBM-007 administered in a total of approximately nine subjects with exudative AMD.

Nine subjects in three dose cohorts (3 subjects each cohort) will receive a single i.vt. injection of RBM-007 in the study eye. Decisions regarding dose escalation will be based on the recommendations of the Safety Review Team consisting of external Retina Specialists and the Medical Monitor. Dose-Limiting Toxicity response observed in any cohort will result in termination of the dose escalation.

The study is designed to include a primary endpoint at Day 28 following RBM-007 injection, and Day 56 follow-up for each subject.

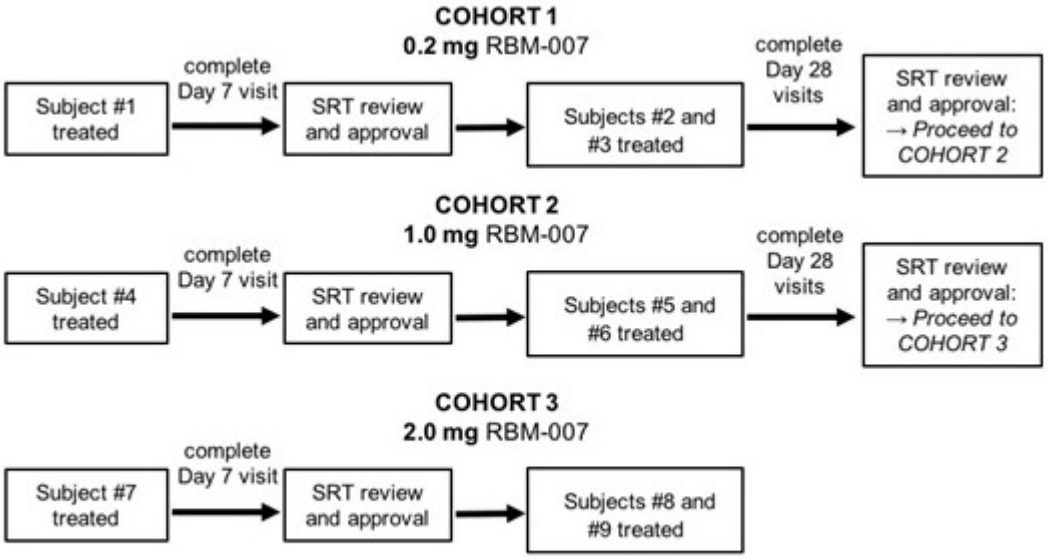
Subjects eligible for the study are 55 years or older with exudative AMD. The study eye must have a history of having received at least 3 intravitreal anti-VEGF treatments (ranibizumab, aflibercept, and/or bevacizumab) without resolution of exudation (persistent or recurrent subretinal and/or intraretinal fluid on SD-OCT), with such fluid present at the Screening Visit and at the Baseline Visit (Day 0). Leading up to the Baseline Visit, there is a minimum 4-week washout period in which the study eye has received no anti-VEGF injections or other treatments for exudative AMD.

The first eligible subject in Cohort 1 will receive a single i.vt. injection of 0.2 mg RBM-007 in the study eye at Baseline Visit (Day 0) and will be evaluated through Visit Day 7 ($\pm$1). The Safety Review Team will assess the safety and tolerability of the RBM-007 in the first subject of the cohort. If satisfactory, RBM-007 will be given to the remaining 2 subjects in that dose cohort. After all 3 subjects in the Cohort 1 have completed Visit Day 28 ($\pm$2), the Safety Review Team will again assess safety and tolerability. When the safety and tolerability of the lower dose have been deemed acceptable, dosing of the first subject in the next cohort will begin. The same treatment sequence and interval SRT evaluations will be followed for Cohort 2 (1.0 mg of RBM-007), and Cohort 3 (2.0 mg of RBM-007).

At Visit Day 7 ($\pm$1), study eyes may receive rescue treatment with i.vt. anti-VEGF, based on worsening from baseline according to criteria or investigator discretion (See Section 4.6.3). All subjects may resume i.vt. anti-VEGF treatment 28 days after RBM-007 i.vt. injection, at or after Visit Day 28 ($\pm$2).

Randomization is not employed in this study due to the small sample size and the dose-escalating design. Refer to Figure 1 for a pictorial representation of the study design.

Figure 1: Dose Escalation Sequence Schema



4.1.1 Selection of Concentrations in the Study

A wide range of animal toxicology studies were conducted with RBM-007 Injectable Solution by both systemic and ocular routes. Systemic toxicity was seen only with high doses far above those doses contemplated for ocular administration. The NOAEL in GLP intravitreal monkey studies is 1 mg/eye. Using a volume of vitreous of 2.2 mL for monkey, this is a concentration of 0.45 mg/mL (Atsumi et al, 2013). The intended human doses for the first in human study (RBM-007-001) are 0.2 mg, 1.0 mg and 2.0 mg per eye administered once. Considering a value of human vitreous to be 5.2 mL (Panda-Jonas, 1994), these concentrations are 0.038, 0.19 and 0.38 mg/mL for these clinical doses. Therefore, the NOAEL in monkey is 11-fold higher than the intended starting clinical dose and 1.1-fold higher than intended maximum human dose. The safety factor would have been even higher if the viscosity and injectable volume for RBM-007 Injectable Solution in animals (monkey and rabbit) were not limiting parameters. It should also be noted that the clinical protocol requires the review of safety data for each cohort (and also first patient in each cohort) by a Safety Review Team independent of Principal Investigators before escalating the clinical dose.

With regard to systemic exposure, the highest concentration of RBM-007 seen in plasma after single intravitreal dosing was 1,560 ng/mL at a dose of 1 mg/eye in monkey and 65.1 ng/mL at a dose of 0.5 mg/eye (injection to both eyes at a dose of 0.5 mg/eye, total 1 mg/body) in rabbit. Toxicokinetic evaluation in GLP systemic studies in monkey suggests that blood level at which toxicity might occur is 691,000 ng/mL. Thus, even without correcting for the body weight differences between animals and humans, the safety margin is 221–5,307 at the maximum dose of 2.0 mg/eye for human. If the body weight for animals

is taken into account (rabbit and monkey at 3 Kg and human at 70 Kg.), the safety margin is 5,156–123,830. Thus, the Sponsor contends that the preclinical toxicology studies support the planned clinical studies.

4.2 Number of Subjects

Approximately nine subjects (3 subjects per cohort) with exudative age-related macular degeneration will be enrolled at 4-5 clinical sites. The final number of subjects enrolled may be adjusted based on the presence of dose limiting toxicities.

4.3 Treatment Assignment

Three dose levels will be administered by a single i.vt. injection in the study eye as noted in Table 1.

Table 1: Dose Groups and Associated RBM-007 Concentration

Dose Group	RBM-007 Concentration
Cohort 1: 0.2 mg	100 microliters of 2 mg/mL RBM-007
Cohort 2: 1.0 mg	50 microliters of 20 mg/mL RBM-007
Cohort 3: 2.0 mg	100 microliters of 20 mg/mL RBM-007

4.4 Dose Adjustment Criteria

The Safety Review Team will review safety parameters after the first subject in each cohort has completed Visit Day 7. The remaining 2 subjects in the cohort will receive the same dose if neither the safety criteria for adjusting or stopping doses (Section 4.4.1) nor the criteria for study termination (Section 4.5) preclude their treatment.

When all subjects in the cohort have completed Visit Day 28, the Safety Review Team will again evaluate the safety parameters. If the safety criteria for adjusting or stopping doses and the criteria for study termination are not met, the first subject in the next cohort will receive the next higher RBM-007 dose level.

The same treatment sequence and interval safety evaluations will be performed for each cohort.

4.4.1 Safety Criteria for Adjusting or Stopping Doses

If more than one of the following dose limiting toxicities is observed in any one cohort, planned doses may be adjusted or stopped by the Safety Review Team.

- Visual acuity loss from Baseline Visit defined as:
  - Loss of best corrected visual activity (BCVA) of 15 or more letters **OR**
  - Progression to no light perception vision (NLP) not due to injection procedure
- Clinically significant inflammation defined as:
  - Anterior chamber cell and/or flare of grade 2+ or more **OR**
  - >3+ vitreous haze as measured by the National Eye Institute Grading Scheme (Nussenblatt et al., 1985) **OR**

  - Sterile endophthalmitis (including the presence of hypopyon)
- Severe Intraocular Pressure (IOP) elevation as measured by tonometry, on two separate exams, at least one day apart, excluding day of injection (despite pharmaceutical intervention):
  - >30 mmHg **OR**
  - Increase of > 15 mmHg from baseline

If any of the following adverse events (AEs) occur in any one subject in any cohort, planned doses will be adjusted by treating additional subjects at the same or lower dose level (the occurrence of a second adverse event in either the same or different subjects in one cohort will qualify for study termination, Section 4.5):

- Retinal non-perfusion/vascular occlusion of the study eye
- Retinal vasculitis
- Retinitis
- 2+ disc edema
- > 2 quadrants of retinal hemorrhage

If there is insufficient safety information in a given cohort at any time, the Safety Review Team may determine to treat additional subjects within that cohort before moving to the next cohort.

4.5 Criteria for Study Termination

Unacceptable safety signals will prevent moving to the next higher dose cohort or result in stopping the study, including any of the following, if deemed to be related to study drug RBM-007 (distinct from complications related to the i.vt. injection procedures):

- A pattern of systemic AEs
- Any of the following AEs in any 2 subjects in any cohort:
  - Retinal non-perfusion/vascular occlusion of the study eye
  - Retinal vasculitis
  - Retinitis
    - > 2+ disc edema
    - > 2 quadrants of retinal hemorrhage

4.6 Study Procedures

All subjects must sign a written informed consent before participating in any study-related activity. Enrollment will occur at Baseline Visit (Day 0) after a subject meets all eligibility requirements at Screening Visit and Baseline Visit (Day 0). Each enrolled subject will be assigned a unique subject number. If a subject is discontinued from the study for any reason, the subject number will remain in effect and will not be reused.

A Schedule of Events can be found below and detailed procedures for examinations can be found in Appendix 4.

Table 2: Schedule of Events

Visit Number	Screening Visit	Baseline Visit		Visit Day 1	Visit Day 7	Visit Day 28	Visit Day 56
Visit Schedule (Time window; days)		Day 0 RBM-007 injection		Day 1	Day 7 (±1)	Day 28 (±2)	Day 56 (±3)
		Pre	Post				
Informed consent[a]	X						
Demographics/Eligibility	X						
AMD Treatment history review	X	X					
Medical/surgical history, Concomitant medication	X						
Physical exam	X						X
Vital signs	X	X		X	X	X	X
EKG	X						
BCVA (ETDRS)	X	X		X	X	X	X
Slit-lamp exam and biomicroscopy[b]	X	X	X	X	X	X	X
Intraocular pressure[c]	X	X	X	X	X	X	X
Indirect ophthalmoscopy[b]	X	X	X	X	X	X	X
SD-OCT	X	X		X	X	X	X
Fundus photography		X				X	X
Fluorescein angiography		X				X	X
OCT-angiography		X				X	X
Serum pregnancy test[d]	X						
Hematology, serum chemistry[e]	X					X	
Plasma RBM-007 level[f]			X	X	X	X	
RBM-007 i.vt. Injection		X					
Anti-VEGF rescue treatment[g]					X		
Option Anti-VEGF Injection[h]						X	X
Adverse events			X	X	X	X	X

[a] Informed Consent Form - obtain prior to conducting any study-related activities.

[b] Slit-lamp exam and biomicroscopy and indirect ophthalmoscopy at Baseline Visit (Day 0) will be performed prior to RBM-007 injection and within 30 minutes after injection.

[c] IOP measurement will be performed before RBM-007 Intravitreal injection and 30±10 minutes after injection. If IOP is increased ≥10 mmHg above pre-injection baseline, repeat IOP measurement is to be done 60±10 minutes after the injection.

[d] Serum pregnancy tests are to be performed on all women of child-bearing potential.

[e] Order blood tests at local laboratory; review results.

[f] Collect blood specimen for RBM-007 plasma drug level 1 hour after RBM-007 injection; document time of both RBM-007 injection and post-injection blood draw.

[g] Visit Day 7 anti-VEGF rescue based on rescue criteria: compared to Baseline Visit (Day 0) there is: 1) worsening of BCVA from Baseline Visit (Day 0) of more than 10 ETDRS letters, or 2) increased thickness in the central subfield of more than 100 μm. Clinical Investigator may also rescue if it is required by their clinical assessment. For rescue, the investigator may use ranibizumab, aflibercept or bevacizumab at their choice.

[h] Clinical Investigator may resume intravitreal anti-VEGF injection at their clinical discretion, using ranibizumab, aflibercept or bevacizumab at their choice.

4.6.1 Screening Phase

4.6.1.1 Screening Visit

- Treatment History Review:
  - Ascertain the patient has exudative AMD that has not resolved with anti-VEGF therapy:
  - Minimum of 3 prior anti-VEGF injections within the past 2-6 months, DURING WHICH
  - SD-OCT has shown recurrent or persistent macular fluid despite this anti-VEGF treatment, defined as the presence of significant subretinal fluid or cystoid macular edema, with macular thickness a minimum of 300 μm within the central macular subfield
- Discuss the purpose and details of the study to the subject and obtain written informed consent prior to the subject's participation in any study related activity.
- Review subject's demographic information, medical, surgical and medication history.
- Perform the following: (all ophthalmic procedures to be performed OU)
  - Physical examination
  - Blood Pressure, Pulse Rate
  - EKG
  - BCVA (ETDRS)
  - Slit-lamp exam and biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
- Review the inclusion and exclusion criteria. Do not continue screening any subject who does not meet the screening eligibility requirements.
- If the subject continues to be eligible for the study, order and review the following tests to be performed at a local laboratory:
  - Serum pregnancy test (for females of child-bearing potential)
  - Hematology, serum chemistry
- Upload all collected images to Sponsor or representative.
- Schedule the subject to return for Baseline Visit (Day 0).

4.6.2 Treatment/follow-up phase

4.6.2.1 Baseline Visit (Day 0)

- Review results of the evaluations and tests performed at Screening Visit to determine continuation in the study

- Treatment History Review:
  - Confirm that the study eye has not received any anti-VEGF injection or other AMD therapy for at least 4 weeks prior to Baseline Visit/RBM-007 injection
- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Vital signs: Blood Pressure, Pulse Rate
  - BCVA (ETDRS)
  - Slit-lamp exam and biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - Fundus photography
  - Fluorescein angiography
  - OCT-angiography
- Perform final review of inclusion/exclusion criteria. If the subject meets all eligibility criteria, determine the study eye (Section 11.1.5).
- Perform intravitreal injection of RBM-007 to the study eye (according to steps described in Section 7):
  - Prepare the RBM-007 (Section 7.4)
  - Load the syringe (Section 7.5)
  - Prepare the eye including ocular antisepsis of study eye (Section 7.6)
  - Administer RBM-007 (Section 7.7)
- Document time of RBM-007 injection
- Assess for Count Fingers vision 1 to 5 minutes post-injection
- The following assessments must be performed after the administration of RBM-007:
  - WITHIN 30 MINUTES following RBM-007 injection
    - Slit-lamp exam and biomicroscopy
    - Indirect ophthalmoscopy
- AT 30 (±10) MINUTES FOLLOWING RBM-007 injection, measure IOP in study eye
  - If post-injection IOP is increased ≥10 mmHg from pre-injection IOP, the IOP will be measured gain 60 (±10) minutes following injection. If there is an increase of ≥10 mmHg at 60 (±10) minutes post-injection compared to pre-injection IOP, the subject should be prescribed a topical IOP-lowering medication and monitored for resolution of the event by the Clinical Investigator. An IOP increase of ≥10 mmHg shall be reported as an AE.
- AT 60 (±10) MINUTES FOLLOWING RBM-007 injection, collect blood specimen for RBM-007 plasma level
  - Document time of blood specimen collection
- AE assessments must be performed after the RBM-007 administration

- Upload all collected images to Sponsor or representative
- Schedule the subject to return for Visit Day 1 (following day).

4.6.2.2 Visit Day 1

Perform the following assessments:

- Query for AEs
- Vital signs (Blood Pressure, Pulse Rate)
- BCVA (ETDRS)
- Slit-lamp exam and biomicroscopy
- IOP
- Indirect ophthalmoscopy
- SD-OCT
- Collect Blood Specimen for RBM-007 plasma level
- Upload all collected images to Sponsor or representative.
- Schedule the subject to return for the Visit Day 7 (±1).

4.6.2.3 Visit Day 7 (Day 7±1)

Perform the following assessments:

- Query for AEs
- Vital signs (Blood Pressure, Pulse Rate)
- BCVA (ETDRS)
- Slit-lamp exam and biomicroscopy
- IOP
- Indirect ophthalmoscopy
- SD-OCT
- Collect blood specimen for RBM-007 plasma levels
- Review Rescue Criteria for anti-VEGF intravitreal injection in study eye
  - Rescue Criteria:
    - Vision loss in study eye from Baseline Visit of more than 10 ETDRS letters
    - Increase from Baseline Visit of more than 100 μm in the central subfield on SD-OCT
  - Clinical investigator assessment that rescue with standard therapy is indicated

IF RESCUE CRITERIA ARE MET, proceed with intravitreal injection of anti-VEGF in study eye. Clinical Investigator may select which intravitreal anti-VEGF injection to use at their clinical discretion, using ranibizumab, aflibercept or bevacizumab at their choice.

- Any anti-VEGF injection should be performed only after all evaluations and procedures for the study visit are completed.

- Upload all collected images to Sponsor or representative.
- Schedule the subject to return for Visit 28 (Day 28±2).

4.6.2.4 Visit Day 28 (Day 28±2)

The following assessments must be performed, prior to optional administration of anti-VEGF medication at investigator discretion:

- Query for AEs
- Vital signs (Blood Pressure, Pulse Rate)
- BCVA (ETDRS)
- Slit-lamp exam and biomicroscopy
- IOP
- Indirect ophthalmoscopy
- SD-OCT
- Fundus photography
- Fluorescein angiography
- OCT-angiography
- Collect blood specimen for RBM-007 plasma level
- Order and review the following tests to be performed at local laboratory:
- hematology and serum chemistry.
- At completion of the study visit, the clinical Investigator may resume intravitreal anti-VEGF injection at their clinical discretion, using ranibizumab, aflibercept or bevacizumab at their choice.
    - Any anti-VEGF treatment should be performed only after completing all evaluations and procedures for the study visit
- Upload all collected images to Sponsor or representative.
- Schedule the subject to return for Visit Day 56 (±3).

4.6.3 Study Exit

4.6.3.1 Visit Day 56 (±3)

Perform the following assessments:

- Query for AEs
- Physical exam
- Vital signs (Blood Pressure, Pulse Rate)
- BCVA (ETDRS)
- Slit-lamp exam and biomicroscopy
- IOP
- Indirect ophthalmoscopy

- SD-OCT
- Fundus photography
- Fluorescein angiography
- OCT angiography
- At completion of the study visit, the clinical Investigator may administer intravitreal anti-VEGF injection at their clinical discretion, using ranibizumab, aflibercept or bevacizumab at their choice.
    - Any anti-VEGF treatment is performed only after completing all other evaluations and procedures for the study visit
- Upload all collected images to Sponsor or representative.
- Exit subject from study.

4.6.4 Unscheduled Visits

If a subject requires evaluation between scheduled visits, complete all applicable study specified procedures as necessary and record the information on the Unscheduled Visit form.

5 SELECTION AND WITHDRAWAL OF SUBJECTS

Eligible subjects must meet all eligibility criteria described in this section.

5.1 Subject Inclusion Criteria

Provide signed written informed consent on the IRB / EC approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.

1. Male or female 55 years of age or older on the date of signing the ICF and able and willing to comply with all treatment and follow-up study procedures.

At Screening Visit, subjects must meet all the following inclusion criteria:

2. Must have had prior treatment in the study eye with any intravitreal anti-VEGF medication (at least 3 anti-VEGF treatments within the prior 2-6 months), throughout which clinical examination and SD-OCT imaging has shown recurrent or persistent exudative activity, as shown by the presence of intraretinal or subretinal fluid, and/or subretinal exudation or hemorrhage.
3. BCVA of 65 to 10 ETDRS letters (20/50 to $\geq$20/640) in the study eye.
4. Presence of significant subretinal fluid and/or cystoid macular edema secondary to exudative age-related macular degeneration as assessed by SD-OCT in the study eye, with a minimum of 300 μm within the central subfield.
5. Total lesion size of $\leq$9 disc areas, lesion containing $\leq$50% hemorrhage in the study eye.
6. Reasonably clear media and reasonable fixation ability in the study eye to allow for good quality SD-OCT and fundus photography.

At Baseline Visit (Day 0), subjects must meet all the following inclusion criteria:

7. BCVA of 65 to 10 ETDRS letters (20/50 to$\geq$ 20/640) in the study eye.
8. Presence of significant subretinal and/or intraretinal fluid secondary to exudative age-related macular degeneration as assessed by SD-OCT in the study eye, with a minimum of 300 μm within the central subfield.

9. Total lesion size of ≤ 9 disc areas, lesion containing ≤ 50% hemorrhage in the study eye.

5.2 Subject Exclusion Criteria

A subject with any of the following conditions is not eligible to participate in the study:

Ocular exclusion criteria:

1. BCVA better than 65 ETDRS letters (20/50) in the study eye.
2. BCVA worse than 10 ETDRS letters (20/640) in the study eye.
3. Fellow eye BCVA worse than 35 ETDRS letters (20/200).

Use of any of the following treatments to the study eye:

4. Intravitreal anti-VEGF injection (ranibizumab, aflibercept or bevacizumab) in the study eye within the past 4 weeks or less prior to Baseline Visit and RBM-007 injection.
5. Intravitreal or periocular corticosteroid, within 3 months prior to Baseline Visit (Day 0) and throughout the study;
6. Fluocinolone acetonide intravitreal implant, within 12 months prior to Baseline Visit (Day 0) and throughout the study;
7. Visudyne® (verteprofin) photodynamic therapy, within 3 months prior to Baseline Visit (Day 0) and throughout the study.
8. Uncontrolled or advanced glaucoma, defined by an intraocular pressure (IOP) of >21 mmHg or cup/disc ratio > 0.8 while on medical therapy, or chronic ocular hypotony (<6 mmHg) in the study eye.
9. Evidence of ocular disease other than exudative AMD in the study eye that may confound the outcome of the study (e.g., active diabetic retinopathy, posterior uveitis, adult vitelliform dystrophy, moderate/severe myopic degeneration).
10. History of vitrectomy surgery in the study eye.
11. Anticipated need for any ocular surgery involving the study eye during the course of the study.
12. Nd:YAG laser capsulotomy within 28 days prior to Baseline Visit (Day 0) in the study eye.
13. Intraocular surgery, including lens removal or ophthalmologic laser procedure, within 90 days prior to Baseline Visit (Day 0) in the study eye.
14. Ocular or periocular infection in either eye.
15. Pupillary dilation inadequate for good quality fundus photography in the study eye.
16. Media opacity that would limit clinical visualization, fundus photography, fluorescein angiography, or SD-OCT evaluation in the study eye.
17. History of herpetic ophthalmic infection in the study eye or adnexa.
18. Presence of known toxoplasmosis or toxoplasmosis scar in either eye.
19. Presence or history of any form of ocular malignancy including choroidal melanoma in the study eye.

Non-Ocular exclusion criteria:

20. Systemic treatment with anti-VEGF agents (e.g., intravenous bevacizumab).
21. Allergy or hypersensitivity to study drug product, fluorescein dye, or other study related procedures/medications.
22. Inadequate renal function: serum creatinine > 1.3 mg/dL and BUN > 2 x the the upper limit of normal (ULN).
23. Inadequate hematologic function: hemoglobin < 12 g/dL; platelet count < 130 x 109 /L; WBC < 3.5 x 109 /L or> 10.5 x 109 /L.

24. Inadequate liver function: serum bilirubin > 1.5 mg/dL, GGT, SGOT/ALT, SGPT/AST, and alkaline phosphatase outside 2 x ULN.
25. Myocardial infarction, stroke or history of transient ischemic attacks within 180 days prior to Baseline Visit (Day 0).
26. Major surgery within 90 days prior to Baseline Visit (Day 0). Major surgery is defined as any surgery involving a risk to the life of the subject, including any operation upon an organ within the cranium, chest, abdomen, or pelvic cavity.
27. Therapeutic radiation to the head or neck within 90 days prior to Baseline Visit (Day 0).
28. Participation in other investigational drug or device clinical trials within 30 days prior to Baseline Visit (Day 0) or planning to participate in other investigational drug or device clinical trials for the duration of the study. This includes both ocular and non-ocular clinical trials.
29. Uncontrolled blood pressure (defined as systolic >180 mmHg and/or diastolic >110 mmHg while subject is sitting). If a subject's initial reading exceeds these values, a second reading may be taken 30 or more minutes later. If a subject's blood pressure needs to be controlled by antihypertensive medication, the subject can be eligible if medication is taken continuously for at least 30 days prior to Baseline Visit (Day 0).
30. Atrial fibrillation not controlled by treatment under the care of the subject's primary care physician or cardiologist within 30 days prior to Baseline Visit (Day 0).
31. Clinically significant concurrent illness, laboratory or EKG abnormality.
32. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.
33. Any systemic infection within 30 days prior to Baseline Visit (Day 0).
34. Unable to comply with study procedures or follow-up visits.
35. In addition, the Clinical Investigator or Medical Monitor may declare a subject ineligible for any sound reason.

5.3 Subject Withdrawal Criteria

An early termination occurs when a subject who provides written informed consent ceases participation in the study, regardless of circumstances, before the completion of the study. Subjects may voluntarily withdraw from the study at any time for any reason. In addition, the Clinical Investigator or the Medical Monitor may terminate a subject's study participation for reasons related to the best interest of the subject. Subjects who terminate from the study may be replaced. Subjects may be terminated from the study due to any of the following reasons:

1. Non-compliance
2. Lost to follow-up
3. Protocol violation
4. Withdrawal by subject
5. AEs
6. Death
7. Other

If a subject is discontinued from the study before completing Visit Day 56 (±3), then to the extent possible, all assessments, including safety, that are scheduled to be performed at Visit Day 56 exit should be performed on the day of discontinuation.

Subjects who discontinue prematurely may be replaced *with prior approval from Sponsor.*

6 TREATMENT OF SUBJECTS

6.1 Description of Study Drug

RBM-007 is a pegylated oligonucleotide-based aptamer. RBM-007 injectable solution is a formulation designed for intravitreal injection.

6.2 Concomitant Medications

The use of any concomitant prescription or over-the-counter medication will be recorded during the study. Therapy considered necessary for the subject's welfare may be given at the discretion of the Clinical Investigator during the study. Whenever possible, concomitant medications should be administered in dosages that remain constant throughout the study. The generic name, indication, route of administration, frequency, dose, start date and stop date (if applicable) will be recorded for each medication.

6.2.1 Prohibited Medications or Treatments

Any treatments for exudative AMD in the study eye other than RBM-007 are prohibited during the study, except anti-VEGF treatment as a rescue therapy at Visit Day 7 (Day 7±1) and/or resumption of anti-VEGF treatment at Visit Day 28 (Day 28±2) and/or Visit Day 56 (Day 56±3), as described in Section 6.2.2.

Any systemic treatments with anti-VEGF agents (e.g., intravenous bevacizumab) are prohibited during the study.

The decision to administer a prohibited concomitant medication or treatment during the study should be made with the safety of the subject as the primary consideration. Whenever possible, RIBOMIC should be notified before any prohibited medication or treatment is administered or if the permissibility of a specific medication or treatment is in question.

6.2.2 Anti-VEGF treatment at Visit Day 28 (Day 28±2) and Visit Day 56 (Day 56±3)

For subjects who did not receive rescue therapy with anti-VEGF medication at Visit Day 7 (Day 7±1), on Visit Day 28 (28±2) the study eye may be considered at investigator discretion to receive i.vt. anti-VEGF treatment after completion of evaluations and procedures for Visit Day 28 (28±2). Selection of which anti-VEGF agent to administer is at the clinical investigator’s decision. Similarly, at Exit Visit (Day 56±3), the study eye may receive i.vt. anti-VEGF at investigator discretion after completion of evaluations and procedures for Exit Visit (Day 56±3).

6.3 Treatment Compliance

To obtain reliable safety and bioactivity data, it is critical that the treatment regimen and visit schedule specified in this protocol are followed. The Clinical Investigator is required to administer the RBM-007 injection and is responsible for scheduling the subject for follow-up visits as specified in the protocol. Study monitors will verify pertinent data to confirm the study is conducted according to the protocol.

6.4 Randomization and Masking

Randomization is not employed in this study due to the small sample size and the open-label, dose-escalating design.

7 STUDY DRUG MATERIALS AND MANAGEMENT

7.1 Study Drug

7.1.1 Investigational Drug

RBM-007 for i.vt. injection is formulated in a proprietary, clear, aqueous solution at two concentrations. The three dose levels of RBM-007 to be administered in the study eye are shown in Table 3.

Table 3: RBM-007 Dosing

Injection Volume of:	Will deliver approximately:
100 microliters of 2 mg/mL RBM-007	0.2 mg RBM-007
50 microliters of 20 mg/mL RBM-007	1.0 mg RBM-007
100 microliters of 20 mg/mL RBM-007	2.0 mg RBM-007

[i] The Clinical Investigator will use syringes and needles supplied by RIBOMIC /Representative.

7.1.2 Study Drug Complaint Reporting

Complaints regarding the RBM-007 for i.vt. injection should be reported to RIBOMIC Product Complaint at (707) 287 4313.

7.2 Study Drug Packaging and Labeling

RBM-007 injectable solutions are filled (0.5 mL fill) in 2-mL Type 1 Glass (borosilicate) clear vials, capped with 13 mm Gray Butyl stoppers with B2-40 coating (on top) and FluroTec coating (on bottom), and sealed. Each single use vial will be placed in a unit carton, and the labeling will include protocol number, kit number, and storage conditions.

7.3 Study Drug Storage

RBM-007 injectable solutions will be provided by RIBOMIC/Representative and will be stored in an appropriate secure area at the investigational site. RBM-007 vials should be protected from light, stored upright, and kept at -20°C.

7.4 Study Drug Preparation

Once an investigational drug vial number has been assigned to the subject, the vial of investigational drug with the assigned vial number will be removed from the freezer. The contents should be thawed by rotating the vials between the palms of the hands, or by setting the vial at room temperature. Care should be taken to protect the product from light.

Investigational drug should be used for intravitreal injection in the study subject **within 1 hour** after removing the vial from the freezer.

Each vial contains enough RBM-007 to inject one subject. Each vial will be used one time only.

7.5 Loading the Syringe

A sterile, single-use syringe will be provided separately for i.vt. injection of RBM-007. Instructions for filling the syringe are as follows:

- Remove the sterile, single-use 250 µL custom marked syringe from the packaging.
- Attach a 19-gauge x 1½-inch filter needle to the syringe. RBM-007 is dispensed in a 0.5 mL fill in a 2 mL vial.
- Using sterile technique, carefully draw up approximately 200 µL of RBM-007 into the syringe. (Sufficiently larger volume than 50 or 100 µL is needed to allow for dead space in syringe and needles prior to i.vt. injection).
- Remove the 19-gauge x 1½-inch filter needle from the syringe and replace with a 30-gauge x 0.5-inch needle for the i.vt. injection.
- Ensure that the 30-gauge x 0.5-inch needle is affixed tightly to the syringe.
- Align the top edge of the red O-ring of the plunger with appropriate mark on the syringe, expelling the excess fluid drawn up.
- Ensure there are no air bubbles within the syringe or the needle hub prior to injection, and prior to expelling the excess fluid drawn up

7.6 Eye Preparation

Prior to RBM-007 administration, the study eye should be prepared as follows:

- Dilate pupil (1% tropicamide and 2.5% phenylephrine or equivalent applied topically) approximately 10 minutes prior to injection.
- Administer 1 drop of topical anesthetic (0.5% proparacaine hydrochloride ophthalmic solution or an equivalent topical ophthalmic anesthetic).
- Take 2 sterile cotton tipped applicators and thoroughly soak with 0.5% proparacaine topical anesthetic eye drops or an equivalent topical ophthalmic anesthetic. Place the soaked applicators, side by side, gently but firmly on the conjunctival surface at the area of the entry site described below in Step 2 (Section 7.7) and hold in place for approximately 1 minute.
- Insert sterile eyelid speculum.
- Administer 5% povidone iodine flush over the ocular surface and lids.

7.7 Study Drug Administration

- Prior to starting the injection procedure, RBM-007 should have been prepared as described in Section 7.4 and Section 7.5, and the study eye should have been prepared as described in Section 7.6.
- The entry site for injection is 4.0 mm posterior to the corneal limbus. A caliper may be used to identify the needle entry site.
- Insert the needle perpendicular to the eye wall at the location specified in Step 2 (Section 7.7) to inject the study solution into the vitreous cavity. Note: If paracentesis is considered necessary, it should be performed prior to injection of the RBM-007 and noted in the source documents.

- Very slowly, inject the entire RBM-007 dose volume (50 µL or 100 µL) and slowly withdraw the needle. Do not pull back on the plunger at any time prior to withdrawing the needle.
- Briefly apply pressure for approximately 30 seconds to the needle entry site with sterile cotton tipped applicator (may be skipped per Clinical Investigator's discretion).
- Remove the eyelid speculum and rinse the eye with sterile eye wash solution.
- Patch the study eye at the Clinical Investigator's discretion.
- Prescribe fluoroquinolone equivalent antibiotic eye drops three times/day for two days following injection, to be initiated as soon as possible.

7.8 Study Drug Accountability

The Principal Investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. The temperature recorder from the shipment will be deactivated and authorized study staff will verify that the temperature was maintained at -20°C during transit. The clinical supplies shipment form should be completed, signed, and returned as directed. A copy must be maintained at the site for the Principal Investigator's records.

The Principal Investigator will keep a current record of the inventory, storage conditions and dispensing of all study drugs. This record will be made available to RIBOMIC (or designee) for accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the Principal Investigator must be accounted for and in no case will study drugs be used in any unauthorized situation. It is the responsibility of the Principal Investigator to ensure that any used and unused supplies are available to RIBOMIC (or designee) throughout the study.

7.9 Study Drug Handling and Disposal

All investigational products including unused vials of RBM-007 supplied by RIBOMIC/Representative will be fully accounted for by the monitor with the help of the person responsible for dispensing the RBM-007 and will be returned to RIBOMIC/Representative or designee. Accountability will be documented by use of drug accountability forms.

The used vials of RBM-007 will be stored at the investigational site upon completion of accountability procedures and returned to RIBOMIC or designee after the trial is completed.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

8.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and does not necessarily have a causal relationship with RBM-007. An AE, therefore, can be an unintended sign (including an abnormal laboratory finding), symptom, or disease that has clinical significance and is temporally associated with the use of a

medicinal (investigational) product, whether related or not related to the medicinal (investigational) product.

In clinical studies, an undesirable medical condition occurring at any time, including-baseline or pre-treatment period, may be recorded as an AE even if no RBM-007 has been administered.

Any significant adverse change in a subject's condition from baseline, regardless of causality, is to be considered an AE, unless the change is determined to be a continuation of a pre-existing condition that is documented in the subject's medical history. However, a clinically significant worsening in severity, intensity, or frequency of a pre-existing condition may indicate an AE. In addition, all conditions that lead to hospitalizations, defined as an overnight hospital stay, are considered as AEs. This includes planned elective surgeries.

Lack of efficacy of the i.vt. RBM-007 for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the Clinical Investigator. An elective surgical procedure scheduled or planned prior to study entry is not considered an AE if an overnight hospital stay is not required, and the underlying diagnosis for which surgery is to be performed should be captured in the medical history as a pre-existing condition. The surgical procedure should also include the term "elective" in all reports.

8.1.1.1 Assessment of Adverse Events

Clinical Investigators will seek information on AEs at each subject contact. Subjects should be asked, using a general, non-direct question, if there has been any change in their general health. Direct questioning and examination should then be performed as appropriate.

Severity of the AE should be assessed according to the following criteria:

Mild: No interference with the subject's daily activities; no medical intervention/therapy required

Moderate: Possible interference with the subject's daily activities; no or minimal medical intervention/therapy required

Severe: Considerable interference with the subject's daily activities; medical intervention/therapy required

Regardless of severity, some AEs may also meet regulatory serious criteria refer to definitions and reporting of serious adverse events (SAEs) in Section 8.1.2.

A Clinical Investigator who is qualified in medicine must make the determination of the relationship of the investigational drug, RBM-007 to each AE (related or not related). The Clinical Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the RBM-007 caused the AE/SAE based on facts, evidence, scientific rationales, and clinical judgment. When assessing causality, the Clinical Investigator may consider the following information when determining the relationship to the RBM-007 for each AE: mechanism of action, biologic plausibility, confounding risk factors (i.e., medical history, concomitant medications), temporal relationship, dechallenge/rechallenge, and lack of alternative explanation. It should be specified if the AE is related to the injection procedure and not the study drug.

- **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.

- **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.

8.1.1.2 Reporting Adverse Events

AEs, whether spontaneously reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the appropriate AE CRF. Each recorded AE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria if applicable, suspected relationship to the RBM-007, actions taken and outcome.

AEs that occur after any subject has provided written informed consent, before treatment, during treatment, or within 30 days following the cessation of treatment, whether they are related to the study, must be recorded. To improve the quality and precision of acquired AE data, Clinical Investigators should observe the following guidelines:

1. Whenever possible, use recognized medical terms when recording. Do not use colloquialisms and/or abbreviations.
2. If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms and /or laboratory or test findings (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis, and enlarged heart on chest x-ray). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).
3. If the diagnosis is not known, then record the leading component sign, symptom or test finding and describe the other clinically related findings in the narrative description of the case. A suspected diagnosis can be used and described as such (e.g., record suspected or probable myocardial infarction); this has to be updated in the clinical database once the diagnosis is confirmed. AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term. If a primary AE is recorded, events occurring secondary to the primary event should be described in the narrative description of the case. For example:
    a. The subject developed orthostatic hypotension and subsequently fainted and fell to the floor wherein she experienced a head trauma and neck pain.
    b. The primary AE in this example is orthostatic hypotension. The fall, head trauma and neck pain should be described in the narrative description of the case.
4. For intermittent events (e.g., intermittent headache), the event onset date should be recorded as the date the subject first started to experience the event and resolution date should reflect when the last occurrence resolved or stopped. Separate AEs for each event should not be recorded. For example, if a subject experienced headache on

14SEP2017 lasting for three hours, then subsequently experienced intermittent episodes of headache every day for approximately 3 hours until 21SEP2017, then the AE date of onset is 14SEP2017 and the resolution date is 21SEP2017.

5. For intermittent events, record the maximum severity of the individual events. For example, if a subject complains of intermittent headaches for one week and the severity of each headache ranges from mild to moderate, then the severity would be moderate.
6. For intermittent hospitalizations occurring for a primary AE (e.g., in a subject with multiple sclerosis, commonly known for its relapsing and remitting course, in some cases leading to multiple hospital confinements), the subsequent hospitalizations should be described in the narrative description of the case.
7. If treatment was initiated, include the treatment and duration of the medication(s) in the CRF.

8.1.2 Serious Adverse Events

SAEs are defined as any findings that suggest a significant hazard, contraindication, side effect, or precaution. Any adverse event is considered a serious adverse event if it results in any of the following outcomes:

1. Death
2. Life threatening event:
   A life-threatening event is any event that places the subject at immediate risk of death from the event as it occurred; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Hospitalization, at the minimum an overnight stay
4. A persistent or significant disability/incapacity
5. A congenital anomaly/birth defect
6. Other medically significant events:
   Other medically significant events are events that may not result in death, be life-threatening, or require hospitalization but may be considered a serious adverse drug experience 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 above.
7. Sight threatening event:
   A sight-threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event.

8.1.2.1 Reporting Serious Adverse Events

A SAE CRFmust be completed with as much information available within 24 hours of knowledge of the event.

To improve the quality and precision of acquired SAE data, Clinical Investigators should observe the following guidelines:

- **Death** - Death is an outcome of an event. The event that resulted in the death should be recorded and reported as a SAE.
- **Hospitalizations for Surgical or Diagnostic Procedures** - The illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

When new significant information (including the outcome of the event) is obtained, the Clinical Investigator should enter the information directly into the CRF within 24 hours or as soon as possible after knowledge of the information.

Depending on the nature and seriousness of the AE, RIBOMIC may request additional documentation, for example, copies of the ophthalmic and medical record of the subject as well as results of laboratory tests. If the subject was hospitalized, the site should summarize the hospital discharge summary and provide to RIBOMIC upon request.

8.1.2.2 Expedited Reporting of Serious Adverse Events

RIBOMIC (or designee) will provide the Principal Investigator with a reporting cover letter and an anonymized MedWatch 3500A for expedited reporting of SAEs to the IRB or Independent Ethics Committee (IEC). The Principal Investigator is responsible for receiving and reviewing expedited safety reports, submitting expedited safety reports to the IRB or IEC, and maintaining copies of expedited safety reports in the study records.

8.1.3 Events of Special Interest

Events of Special Interest (ESIs) are events that may require special attention for the purposes of on-going patient safety review during this study. The following are considered ESIs and should be reported on the appropriate CRF with as much information as available within 24 hours of knowledge of the event:

- **Study medication administration error** - Study medication administration errors determined to be significant by the Clinical Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include but are not limited to: overdose of study medication and administration of study medication from an incorrect kit.
- **Pregnancy** - There are no controlled data with the investigational product in human pregnancy. It is required that women of childbearing potential use effective contraception during the study and recommended for 12 weeks after the completion of the study. Any pregnancy occurring during study treatment should be reported and the subject removed from the study. The subject should be followed until the end of pregnancy or until the end of the study, whichever is longer.

8.1.4 Follow-up of Adverse Events

All reported AEs at study exit will be followed by the Clinical Investigator (or his/her designee) until the event is resolved or determined to be irreversible, chronic, or stable.

In addition, on a case-by-case basis, RIBOMIC (or designee) may request follow up beyond the end of the study.

If RIBOMIC requests follow-up on an individual SAE or designated SAE, site response to follow-up requests should be e-mailed to yusuf.ali@ribomic.com.

8.1.5 Manual Back-Up Reporting Procedures

This study may utilize an electronic data capture (EDC) system for data collection. In the event that an EDC system is utilized, but unavailable for electronic reporting, the manual back-up reporting procedures below should be followed.

- Complete an AE and SAE form.
- Email the AE and SAE form to RIBOMIC at yusuf.ali@ribomic.com.

When the EDC system becomes available, update the EDC system with all previously reported information.

8.2 Safety Parameters

The safety assessments will include adverse events (AEs), BCVA, slit-lamp exam and biomicroscopy, indirect ophthalmoscopy, intraocular pressure (TOP), serum chemistry, hematology, vital signs, physical exam, fundus photography, fluorescein angiography, EKG, pregnancy.

8.2.1 Physical Examination

A full body systematic physical exam will be conducted by the Clinical Investigator or an external internist during Screening Visit and Visit Day 56 (±3).

8.2.2 Electrocardiogram (EKG)

EKG will be performed at Screening Visit. The Clinical Investigator will review the EKG report for abnormalities.

8.2.3 Vital Signs

Blood pressure and heart rate will be measured at each visit using an automated or manual blood pressure monitor. Systolic and diastolic blood pressures will be recorded in millimeters of mercury (mmHg), and heart rate will be recorded in beats per minute (bpm).

8.2.4 Best Corrected Visual Acuity

The BCVA will be recorded using the ETDRS chart and total number of letters at 4 meters and 1 meter will be recorded at each visit. If a subject could not read ETDRS chart, Finger Counts, Hand Motion, Light Perception, or No Light Perception will be recorded.

8.2.5 Slit-lamp exam and Biomicroscopy

Slit-lamp exam and biomicroscopy will be performed at each visit. At the Baseline Visit (Day 0), a biomicroscopy examination will be performed prior to RBM-007, and a second biomicroscopy exam will be performed within 30 minutes after injection.

8.2.6 Intraocular Pressure

IOP will be measured by applanation tonometry and reported in millimeters of mercury (mmHg) at each study visit. On the visit for RBM-007 injection or any anti-VEGF injections, IOP will be measured before RBM-007 or anti-VEGF injection and 30 (±10) minutes after injection. If post-injection IOP is increased ≥ 10 mmHg from pre-injection IOP, the IOP will be measured again 60 (±10) minutes following injection. If there is an increase of ≥ 10 mmHg at 60 (±10) minutes post-injection compared to pre-injection IOP, the subject will be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion (an unscheduled visit may apply), and the IOP increase of ≥ 10 mmHg shall be reported as an AE.

8.2.7 Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed at each visit. On the visit of RBM-007 or anti-VEGF injection, an ophthalmoscopy examination will be performed prior to RBM-007 or anti-VEGF injection and a second one within 30 minutes after injection.

8.2.8 Serum Pregnancy Test

A serum pregnancy test will be conducted at Screening Visit for all women of childbearing potential.

8.2.9 Serum Chemistry, Hematology

Patients will be sent for laboratory tests at Screening Visit and Visit Day 28 (±2).

8.2.10 Fundus Photography

Digital color fundus photography will be taken at Baseline Visit (Day 0), Visit Day 28 (±2), and Visit Day 56 (±3) in both eyes. It will be performed prior to any intravitreal injections. Required fields to be captured are: 1) Nasal to macula (the image is centered on the optic nerve), 2) Posterior pole (the image is centered on the macula).

8.2.11 Fluorescein Angiography

Fundus fluorescein angiography will be taken at Baseline Visit (Day 0), Visit Day 28 (±2), and Visit Day 56 (±3) in both eyes, with early studies in the study eye. It will be performed prior to any intravitreal injections. Required fields to be captured are: Nasal to macula (the image is centered on the optic nerve), Posterior pole (the image is centered on the macula).

8.2.12 OCT-Angiography

OCT-angiography will be taken at Baseline Visit (Day 0), Visit Day 28, and Visit Day 56 in both eyes. It will be performed prior to any intravitreal injections.

8.2.13 Adverse Events

AEs will be elicited from the subjects starting at every visit from Baseline Visit (Day 0) through Visit Day 56. The information will include at least a description of the event, whether it is serious, onset and duration, frequency, severity, relation to RBM-007, relation to injection procedure, location (OD, OS, OU or NA), action taken and outcome. Prior to evaluating the incidences, all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, 2013). Ocular and non-ocular AEs will be summarized separately. See Section 8.1 for complete information regarding AE reporting.

9 ASSESSMENT OF BIOACTIVITY

Bioactivity will be assess by both structural and functional measures.

Resolution of subretinal fluid will be assessed using the change in CST and the macular volume based on SD-OCT. SD-OCT will be performed for both eyes at each visit. CST, an average of central subfield thickness, will be recorded. In addition, macular volume will be determined. Assessment of CNV size and activity will be measured with fundus photography, fluorescein angiography, and OCT-angiography at Baseline Visit (Day 0), Visit Day 28 endpoint, and Visit Day 56 exit.

Functional changes in vision will be assessed by best corrected visual acuity, measured using ETDRS eye charts.

10 OTHER ASSESSMENTS

10.1 Demographics and Baseline Characteristics

Subject demographics include age, race, sex, and ethnicity. Baseline characteristics include medical history, prior medications, and baseline results of physical exam, EKG, heart rate and blood pressure, BCVA, slit-lamp exam and biomicroscopy, IOP, indirect ophthalmoscopy, SD-OCT, pregnancy test, laboratory tests (hematology, serum chemistry), fundus photography, fluorescein angiography, and OCT-angiography. For assessments performed multiple times before the injection of i.vt. RBM-007, the last pre-injection value will be used as the baseline value.

10.2 Other Assessments

Other assessments include concomitant medications and exposure to study drug.

11 STATISTICAL METHODS

11.1 General Considerations

All study parameters will be listed, and a selected list of parameters will be summarized descriptively by dose level and overall. The descriptive statistics will include number of observations (n), mean, standard deviation, minimum, and maximum for continuous parameter and frequency (n) and percent (%) for categorical parameters.

Details about the statistical analyses for this study will be provided in the statistical analysis plan (SAP).

11.1.1 Study Endpoints

Safety:

- Incidence and severity of adverse events (AEs), slit-lamp exam and biomicroscopy, indirect ophthalmoscopy, BCVA, IOP, SD-OCT, fundus photography, fluorescein angiography, serum chemistry, hematology, heart rate and blood pressure, physical exam, EKG and pregnancy

Bioactivity:

- Change in CST and macular volume based on SD-OCT at each visit post RBM-007 treatment.
- Change in CNV lesion size and activity based on fundus photography, fluorescein angiography, and OCT-angiography.
- Change from baseline in BCVA

11.1.2 Sample Size

Approximately nine subjects (3 subjects per cohort) with exudative age-related macular degeneration will be enrolled at 4-5 sites. The final number of subjects enrolled may be

adjusted based on the presence of dose limiting toxicities. This sample size is not planned based on statistical considerations.

11.1.3 Statistical Hypotheses and Level of Significance

No statistical hypothesis is defined for this study.

11.1.4 Randomization

This is an open-label, non-randomized study.

11.1.5 Study Eye

The study eye is defined as the eye with worse vision. If both eyes have the same vision, the right eye (OD) should be determined as the study eye.

11.2 Study Populations

The following study populations are defined for analysis: Intention-to-treat (ITT) and Safety.

ITT Population: The ITT population will include all subjects in the study. It will be the primary study population for bioactivity analyses, where subjects are grouped by planned dose level unless specified otherwise.

Safety Population: The Safety population will include all subjects who receive the injection of i.vt. RBM-007. It will be the study population for safety analyses performed with subjects as treated.

11.3 Handling of Missing Values

For safety measures, missing scores will not be imputed for data summaries.

Completely or partially missing onset and resolution dates for AEs and completely or partially missing start and end dates of concomitant medications will be imputed in a conservative fashion that will be detailed in the SAP.

For Bioactivity endpoints, missing post-injection values will be imputed using the last-observation-carried-forward (LOCF) approach.

11.4 Demographics and Baseline Characteristics

Age, sex, race, ethnicity, and baseline assessments will be summarized descriptively by dose level.

Subjects with abnormal medical history will be tabulated by treatment arm and body system.

Subjects using any prior medications will be tabulated by dose level, Anatomical Therapeutic Chemical levels, and preferred term specified in the World Health Organization Drug Dictionary Enhanced (World Health Organization Drug Dictionary Enhanced, 2011)

11.5 Bioactivity Analyses

Changes from baseline in BCVA, retinal thickness (CST), and macular volume will be summarized descriptively by dose level of RBM-007. CNV size and activity will be summarized from fundus photography, fluorescein angiography, and OCT-angiography.

11.6 Safety Analysis

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include adverse events (AEs), BCVA, slit-lamp exam and biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP), serum chemistry, hematology, heart rate and blood pressure, physical exam, fundus photography, fluorescein angiography, EKG and pregnancy test.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Subjects with any AEs will be tabulated by system organ classification and preferred term specified in the MedDRA. Similarly, subjects with any ocular and non-ocular AEs and ESIs will be tabulated separately. AEs, ocular and non-ocular, as well as SAE will also be summarized by relationship to treatment and maximum severity. In addition, SAEs and discontinuations due to AEs will be summarized.

Ocular safety outcome measures will be summarized using descriptive statistics.

12 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Principal Investigator will allow representatives of RIBOMIC's monitoring team (or designee), the governing institutional review board (IRB), the FDA, and other applicable regulatory agencies to inspect all study records, CRF, recruitment materials and corresponding portions of the subject's medical records at regular intervals throughout the study. These inspections are for verifying adherence to the protocol, completeness, and exactness of the data being entered onto the CRF, and compliance with the FDA or other regulatory agency regulations.

12.1 Study Monitoring

Before an investigational site can enter a subject into the study, a representative of RIBOMIC (or designee) will evaluate the investigational study site to:

- Determine the adequacy of the study facilities.
- Review with the Principal Investigator(s) and authorized study staff their responsibilities regarding protocol procedures adherence, and the responsibilities of RIBOMIC (or designee).
- During the study, RIBOMIC (or designee) will have regular contact with the investigational site, for the following:
  - Provide information and support to the Principal Investigator(s).
  - Confirm that facilities remain acceptable.
  - Assess adherence to the protocol and GCP.
  - Perform investigational product accountability checks and quality control procedures.
  - Ensure the on-going implementation of accurate data entry in the CRF.
  - Perform source data verification, including a comparison of the data in the CRFs with the subject's medical records and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
  - Record and report any protocol deviations not previously sent to RIBOMIC (or designee).

- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to RIBOMIC and those SAEs that met criteria for reporting have been forwarded to the IRB or Independent Ethics Committee (IEC).

RIBOMIC (or designee) may remotely access the CRFs, as applicable, at any time during the study for centralized monitoring. RIBOMIC (or designee) will be available between visits if authorized study staff needs study related information or support.

12.2 Audits and Inspections

The Principal Investigator will allow RIBOMIC (or designee), the governing IRB or IEC, and applicable regulatory agencies to audit and inspect any aspect of the study, including all study records, CRFs, recruitment materials, and corresponding portions of the subject's charts and medical records at any time during the study. These study records must be retained at the study site and made available for audits and inspections. The purpose of these audits and inspections is to verify adherence to the protocol, completeness and accuracy of the CRF data, and compliance with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

The Principal Investigator or authorized study staff will notify RIBOMIC (or designee) should the site be audited or inspected by the governing IRB or IEC, and applicable regulatory agencies. RIBOMIC (or designee) will also notify the investigational site of any known pending site audits or inspections planned by RIBOMIC (or designee), governing IRB or IEC and regulatory agencies.

12.3 Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Principal Investigator and made available for inspection.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Quality Control

RIBOMIC (or designee) will provide instructional material to the study sites, as appropriate; including but not limited to instruction on the protocol, the completion of CRFs, and study procedures. RIBOMIC (or designee) will communicate regularly with site personnel via mail, email, telephone, and/or fax; and make periodic visits to the study site. During those visits, RIBOMIC (or designee) will perform source data verification with the subject's medical records and other records relevant to the study. Upon receiving the CRFs, as applicable, RIBOMIC (or designee) will review and evaluate CRF data and use standard system edits and may use centralized monitoring to detect errors in data collection.

13.2 Quality Assurance

RIBOMIC (or designee) may conduct a quality assurance audit at any time.

14 ETHICS

14.1 Ethics Review

The final study protocol and the final version of the ICF, and other study related material, as appropriate, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Principal Investigator must submit written approval to RIBOMIC (or designee) before study initiation. See Appendix 1 for a list of obligations of Investigators.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local regulations and guidelines. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and at least annually.

The Principal Investigator is also responsible for providing the IRB or IEC with progress reports and notifications of any reportable SAEs attributable to the investigational product.

14.2 Ethical Conduct of the Study

This study will be conducted in compliance with IRB or IEC, and regulatory requirements. This study will also be conducted in compliance with the protocol, GCP guidelines, International Conference on Harmonization (ICH) guidelines, the Declaration of Helsinki, and Health Insurance Portability and Accountability Act of 1996 (HIPAA).

14.3 Written Informed Consent

The Principal Investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and possible benefit of the study. Subjects must also be notified that they are free to withdraw from the study at any time. Subjects should be given the opportunity to ask questions and allowed time to consider the information provided. Before participating in any study-related activity, voluntary informed consent must be documented by the use of a written ICF approved by the IRE or IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The original signed and dated ICF will be retained with the study records, and a copy of the signed ICF will be given to the subject or the subject's legally authorized representative.

15 DATA HANDLING AND RECORDKEEPING

15.1 Inspection of Records

The Principal Investigator will allow RIBOMIC (or designee), the governing IRB or IEC and applicable regulatory agencies to inspect any aspect of the study, including all study records, CRFs, recruitment materials and corresponding portions of the subject's charts and medical records at any time during the study. The purpose of these inspections is to verify adherence to the protocol, completeness and accuracy of the CRF data, and compliance with GCP guidelines and applicable regulatory requirements.

15.2 Retention of Records

All records relating to the conduct of this study are to be retained by the Principal Investigator until notified by RIBOMIC (or designee) that the records may be destroyed.

15.2.1 Source Documents

The Principal Investigator must maintain detailed source documents on all study subjects who provide informed consent. Source documents include subject medical records, hospital charts, study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be entered into the subject's medical record:

- The date the subject was enrolled and the subject number
- The study protocol number and the name of RIBOMIC.
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study-related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concomitant medications
- Documentation of study drug accountability
- Occurrence and status of any AEs
- The date the subject exited the study and a notation as to whether the subject completed or terminated early from the study, including the reason for early termination.

15.2.2 Data Collection

The Principal Investigator must maintain detailed records on all subjects who provide informed consent. Data for screened and enrolled subjects will be entered in CRFs. Review of the CRFs will be completed remotely by RIBOMIC (or designee). At designated intervals, a study monitor will perform source data verification on site. During those visits, RIBOMIC (or designee) will monitor the subject data recorded in the CRF against source documents at the study site.

RIBOMIC (or designee) will review and evaluate CRF data and use standard system edits, and may use centralized monitoring evaluations, to detect errors in data collection. At the end of the study, a copy of the completed CRFs will be sent to the site to be maintained as study records.

16 PUBLICATION POLICY

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied that is indicated as confidential Information pertaining to this study will be published on www.clinicaltrials.gov as required by the Food and Drug Administration (FDA).

The data generated by this clinical study are the property of RIBOMIC and should not be disclosed without the prior written permission of RIBOMIC. These data may be used by

RIBOMIC now and in the future for presentation or publication at RIBOMIC's discretion or for submission to governmental regulatory agencies. RIBOMIC reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the Principal Investigator agrees to the release of the data from this study and acknowledges the above publication policy.

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Appendix 1: Obligations of Investigators

In summary, the Clinical Investigator has agreed to the following obligations:

- Obtaining informed consent from every subject prior to the subject's participation in any study related activity and maintaining records of consent as part of the study records.
- Obtaining approval from the IRB before involving any subject in any study related activity; submitting verification of the approval to the Sponsor; submitting periodic progress reports (at least annually) and final report to IRB and to the Sponsor.
- Approving the protocol and conducting the study according to the protocol and applicable regulations; informing the Sponsor of all deviations from the protocol.
- Informing the IRB of all protocol amendments/modifications; sending the Sponsor a copy of the letter from the IRB approving the amendment/modification.
- Reporting to the Sponsor and the IRB any adverse experiences that occur in the course of the investigation, this includes Serious Adverse Events within 24 hours.
- Keeping careful and accurate records of all clinical study data (study records must be considerably more exact and complete than those kept in ordinary medical practice); maintaining records of all materials submitted to the IRB and of all action by the IRB regarding the study.
- Making study records available for inspection by the Sponsor and representatives of the Food and Drug Administration and other regulatory agencies; keeping records until notified by the Sponsor that they may be destroyed.
- Maintaining proper control and documentation of all test and control articles, where applicable.
- Submitting the following records and reporting to the Sponsor.

I. Prior to the Beginning of the Study

- A signed Form FDA-1572, Statement of Investigator.
- A current curriculum vitae (CV) if not submitted to RIBOMIC previously or if updated.
- CVs for all sub-Investigators listed on the 1572.
- A letter from the IRB indicating that the protocol was approved, including the name and address of the IRB.
- A copy of the consent form approved by IRB.
- A list of current members of the IRB.

II. While the Study Is in Progress

- Acknowledgment of receipt of the test and control articles; documentation of disposition of all test and control articles.
- Original Case Report Forms for each subject enrolled in the study.
- Information regarding all deviations from the protocol.
- Information regarding all adverse events occurring to a subject while enrolled in the study.

- Annual progress report (if study is ongoing for more than one year). Letter from the IRB indicating approval of the annual progress report.

III. Once the Study Is Completed

- Disposition of all used and/or unused test and control articles (where applicable), as well as documentation of all drug accountability.
- A final study reports.

Appendix 2: Elements of Informed Consent

I. Elements of Informed Consent

The following information must be provided to each subject in obtaining informed consent. If written consent is being obtained, the subject (or subject's legal representative) should be provided with a copy of the signed written ICF.

- State that the study involves RESEARCH.
- Explain the PURPOSE of the research.
- Trial treatments and the probability for random assignment to each treatment.
- State the expected DURATION of the subject's participation.
- Describe the PROCEDURES to be followed.
- Identify any EXPERIMENTAL procedures.
- Describe any reasonably foreseeable RISKS OR DISCOMFORTS to the subject.
- Describe any BENEFITS to the subject and responsibility for the subject or to others that may reasonably be expected from the research.
- Note appropriate ALTERNATIVE procedures or courses of treatment, if any, that might be advantageous to the subject.
- A. Describe the extent, if any, to which CONFIDENTIALITY of records identifying the subject will be maintained.
- B. Note that the FDA MAY INSPECT the records.
- For research involving more than minimal risk, explain if any COMPENSATION or medical treatments are available should injury occur. If so, explain (a) what they consist of, OR (b) where further information may be obtained.
- A. Tell whom to contact for ANSWERS to pertinent questions about (a) the research, and (b) research subjects' rights.
- B. Tell whom to contact in the event of a research-related INJURY to the subject.
- State that:
- Participation is VOLUNTARY,
- Refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled
- The subject MAY DISCONTINUE participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

II. Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

- A statement that particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.
- Any additional costs to the subject that may result from participation in the research.
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
- A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
- The approximate number of subjects involved in the study.

The informed consent requirements in this protocol are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in this protocol is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

REFERENCE: 21 CFR Part 50.25 - PROTECTION OF HUMAN SUBJECTS, Elements of Informed Consent.

Appendix 3: Declaration of Helsinki

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individual or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non- vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial

provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations, the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of

providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable;
    or
    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th'Wl'v.IA General Assembly; Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added) 55th

WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Appendix 4: Procedures for Examinations

1. Demographics/Eligibility, Medical/Surgical History and Concomitant Medication

Demographics/Eligibility, medical/surgical history and concomitant medication will be obtained through subject interviews at Screening Visit. Changes in concomitant medications will also be obtained through subject interviews at each visit.

2. Physical Examination

A full body systematic physical exam will be conducted during Screening Visit and Visit Day 56. Clinical investigator or an external internist will confirm subject's overall condition noting any abnormalities by a review of the following systems: e.g., head, eyes, ears, nose and throat (HEENT), cardiopulmonary, endocrine, gastrointestinal, musculoskeletal/rheumatic, neurologic/psychiatric, dermatologic, hepatic/renal systems, and other.

The Clinical Investigator will assess subject's overall condition to determine qualification for study entry. Newly noted abnormalities or worsening of previously noted abnormalities found at Study Exit, or at any safety assessment visit, will be assessed as an AE. The Clinical Investigator should use his or her clinical judgment for appropriate treatment and/or medical referral.

3. Vital Signs

Blood pressure and heart rate will be measured at each visit using an automated or manual blood pressure monitor. Systolic and diastolic blood pressures will be recorded in millimeters of mercury (mmHg) and heart rate will be recorded in beats per minute (bpm).

- Subject should be seated quietly in a chair with the back supported, feet on the floor, arm bared, and arm supported at heart level.
- Begin the measurement after at least 5 minutes of rest
- To ensure an accurate measurement, use an appropriately sized cuff. The cuff bladder should encircle at least 80% of the arm. Many adults need a large cuff
- Take two (2) systolic/diastolic pressure and heart rate measurements separated by at least 30 seconds. Record each measurement in the subject's source document.
- If the two pressure measurements differ by 5 mmHg or less, then the average of the two becomes the recorded pressure. For example, if the two measurements are 120/90 and 125/95, then 122.5/92.5 is the recorded systolic/diastolic pressure.
- If the two pressure measurements differ by more than 5 mmHg, then a third reading measurement is made, and the average of the three becomes the recorded pressure. For example, if the three measurements are 115/90, 124/96, and 120/92, then 119.7/92.7 is the recorded systolic/diastolic pressure. The recorded blood pressure will be the average of the measurements.
- Record the heart rate. For heart rate, the average of the two (or three, if performed) measurements obtained becomes the recorded heart rate.

4. EKG

EKGs will be ordered at Screening Visit and reviewed for abnormalities by the Clinical Investigator prior to enrollment.

5. Best Corrected Visual Acuity

ETDRS chart will be used to examine BCVA at each study visit. See Appendix 4 for additional information.

6. Slit-Lamp exam and Biomicroscopy

Slit-lamp biomicroscopy will be used to examine eye structures at each study visit. A 90-diopter lens (or equivalent) will be used to examine the retina (vitreous, optic disc, macula and posterior pole). Biomicroscopy will be performed prior to injection and then again within 30 minutes after injection on the visit of RBM-007 or anti-VEGF injection.

The lid, conjunctiva, cornea, anterior chamber, iris and lens will be observed with the slit-lamp beam approximately 0.3 mm in width and 1.0 mm in length and graded on a 4-point scale (0-3 scale) as described below:

Lid Redness

None	(0) = Normal
Mild	(1) = Redness of most or all the lid(s) margin OR skin
Moderate	(2) = Redness of most or all the lid(s) margin AND skin
Severe	(3) = Marked diffuse redness of both lid(s) margin AND skin

Lid Edema

None	(0) = Normal
Mild	(1) = Localized to a small region of the lid(s)
Moderate	(2) = Diffuse, most or all the lid(s) but not prominent/protruding
Severe	(3) = Diffuse, most or all the lid(s) AND prominent/protruding

Conjunctival (Palpebral and Bulbar) Hyperemia

None	(0) = Normal
Mild	(1) = Slight localized injection
Moderate	(2) = Pink color, confined to palpebral OR bulbar conjunctiva
Severe	(3) = Red color of the palpebral AND/OR bulbar conjunctiva

Conjunctival Edema

None	(0) = Normal
Mild	(1) = Slight localized swelling
Moderate	(2) = Mild/medium localized swelling or mild diffuse swelling
Severe	(3) = Moderate diffuse swelling

Corneal Edema

None	(0) = Normal
Mild	(1) = Mild, diffuse stromal haze
Moderate	(2) = Dense, diffuse stromal haze or bullae
Severe	(3) = Dense, diffuse bullae or stromal haze AND stromal edema

Lens

The lens will be noted as phakic, aphakic, or pseudophakic. Phakic lens will be graded as described below:

None	(0) = No lens discoloration nor opacification
Mild	(1) = Yellow lens discoloration or small lens opacity (axial or peripheral)
Moderate peripheral)	(2) = Amber lens discoloration or medium lens opacity (axial or
Severe reflex.)	(3) = Brunescent lens discoloration or complete lens opacification (no red

Anterior chamber cells and flare will be observed with a 1.0 mm in width and 1.0 mm in length slit beam and graded using the Standardization of Uveitis Nomenclature (SUN) scale (Jabs et al, 2005).

Anterior Chamber Cells

(0) = No cells

(0.5) = 1-5 cells

(1) = 6-15 cells

(2) = 16-25 cells

(3) = 26-50 cells

(4) = >50 cells

Anterior Chamber Flare

(0) =None

(1) = Faint

(2) = Moderate (iris/lens details clear)

(3) = Marked (iris/lens details hazy)

(4) = Intense (fibrin/plastic aqueous)

Iris

The iris will be evaluated for the presence of any clinically significant abnormalities, and graded as either normal (within normal limits) or abnormal (clinically significant abnormality present). A description of any clinically significant abnormalities will be noted.

Pupil

The pupil will be evaluated for the presence of any clinically significant abnormalities, and graded as either normal (within normal limits) or abnormal (clinically significant abnormality present). A description of any clinically significant abnormalities will be noted.

7. Intraocular Pressure

IOP will be measured by applanation tonometry at each study visit. At the visit of RBM-007 or anti-VEGF medication injection, IOP will be measured before RBM-007 or anti-VEGF medication injection and 30 (±10) minutes after injection. If post-injection IOP is

increased ≥10 mmHg from pre-injection IOP, the IOP will be measured again 60(±10) minutes following injection. If there is an increase of ≥10mmHg at 60(±10) minutes post-injection compared to pre-injection IOP, the subject will be prescribed a topical IOP lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion (an unscheduled visit may apply), and the IOP increase of≥10 mmHg shall be reported as an AE.

IOP should be measured only after the biomicroscopy examination has been completed.

The applanation tonometer must be calibrated for accuracy before the first subject undergoes screening, and periodically until the last subject has exited the study. For checking calibration, follow the manufacturer's instructions.

The right eye is always tested first. At least two, and sometimes three, consecutive measurements are made to obtain a determination of intraocular pressure. Each IOP measurement should be recorded in the subject's source document and in the CRFs.

If the two measurements differ by 2 mmHg or less, then the average of the two measurements becomes the recorded IOP. For example, if the two measurements are 22 and 23, then 22.5 is the final recorded IOP.

However, if the two measurements differ by 3 mmHg or more, then a third measurement is made, and the median of the three measurements becomes the recorded IOP (the median is the middle measurement after arraying the measurements from low to high). For example, if the three measurements are 15, 19, and 16, then 16 is the final recorded IOP (Sherwood et al 2001).

The IOP in the left eye is then measured using the same technique.

8. Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed for each eye at each visit with pupil dilation.

Indirect ophthalmoscopy will be used to examine the retina at each study visit. Indirect ophthalmoscopy will be performed prior to and within 30 minutes after each RBM-007 or anti-VEGF medication injection. Areas to be assessed include cup to disc ratio, retina, macula and choroid, and vitreous.

9. Cup/Disc Ratio

The cup/disc ratio will be determined by the examiner and recorded using two decimal places (e.g., 0.8).

10. Retina, Macula and Choroid

The retina, macula and choroid will be evaluated for the presence of any clinically significant abnormalities, and graded as either normal (within normal limits) or abnormal (clinically significant abnormality present). A description of any abnormalities will be noted.

11. Vitreous

The following National Eye Institute Grading Scheme will be used to measure vitreous haze and opacification (Nussenblatt et al., 1985).

Vitreous Haze Scale

Step	Description
(0)	Clear
(Trace or 0.5+)	Trace
(1+)	Few opacities, mild blurring
(2+)	Significant blurring but still visible
(3+)	Optic nerve visible, no vessels seen
(4+)	Dense opacity obscures the optic nerve head

12. Spectral Domain Optical Coherence Tomography
Spectralis, Cirrus or 3D OCT will be utilized to take optical images of both eyes at each study visit. The same machine must be used consistently throughout the study for any given subject. SD-OCT will be performed at every study visit.

13. Fundus Photography
Digital color fundus photography will be taken at Baseline Visit (Day), Visit Day 28 and Visit Day 56. Required fields to be captured are:

- The optic disc, Field 1
- The macula, Field 2

14. Fluorescein Angiography
Fundus fluorescein angiography will be taken at Baseline Visit, Visit Day 28, and Visit Day 56 in both eyes. Required fields to be captured are:

- The optic disc, Field 1
- The macula, Field 2

15. OCT-angiography
OCT-angiography will be taken at Baseline Visit, Visit Day 28, and Visit Day 56 in both eyes.

16. Serum Pregnancy Test
A serum pregnancy test will be conducted at Screening Visit and Visit Day 56 for all women of childbearing potential. A female is considered of childbearing potential unless she is post-menopausal (at least 24 months since last menses occurred), has had her uterus and/or both ovaries removed, or has had a bilateral tubal ligation. To perform the pregnancy test, Human chorionic gonadotropin (hCG) will be contained into serum parameters that will be measured.

17. Hematology, Serum Chemistry
Hematology and serum chemistry will be ordered to be performed at a local laboratory at Screening Visit and Visit Day 28.

Serum Chemistry, Hematology

The following is a list of the minimum parameters that will be measured. Other additional parameters may also be reported.

Serum Chemistry	**Hematology**
Albumin	red blood cells (RBC)
Creatinine	white blood cells (WBC)
lactate dehydrogenase (LDH)	differential WBC
glucose	platelets (PLT)
calcium	hemoglobin (HGB)
potassium	hematocrit (HCT)
sodium	mean corpuscular volume (MCV)
cholesterol (total, HDL and LDL)	mean corpuscular hemoglobin (MCH)
triglycerides	mean corpuscular hemoglobin concentration (MCHC)
urea nitrogen	
bilirubin (total, direct, indirect)	
alkaline phosphatase (ALP)	
alanine aminotransferase (ALT)	
aspartate aminotransferase(AST)	
gamma glutamyl transferase (GGT)	
Human chorionic gonadotropin(hCG)*	

Prior to enrolling a subject, the Clinical Investigator will indicate on the source document if any screening laboratory values exclude the subject from participating in the study (e.g., serum creatinine > 1.3 mg/dL).

*conduct only at Screening Visit.

Prior to emailing a subject, the Clinical Investigator will indicate on the source document if any screening laboratory values exclude the subject from participating in the study.

18. Procedure for Plasma levels of RBM-007

Approximately 5 mL of blood will be collected from the subject for RBM-007 analysis at Baseline Visit (Day 0); Visit Day 1, a Visit Day 7 (**±1**) and Visit Day 28 (**±1**)

Table 4: Protocol Amendment 01 Summary of Changes

Page	Section Number and Title	Description of Change
7-8	1.SYNOPSIS	Modifications were made to reflect the study design changes made throughout the protocol
23	5.1 Subject Inclusion Criteria 3 and 7	Rationale: To avoid narrowing the opportunities for the subjects to participate in the study. Original Text: BCVA of 65 to 20 ETDRS letters (20/50 to 20/400) in the study eye. Amendment 01 Text: BCVA of 65 to 10 ETDRS letters (20/50 to ≥20/640) in the study eye.
23	5.1 Subject Inclusion Criteria 5 and 9	Rationale: To avoid narrowing the opportunities for the subjects to participate in the study. Original Text: Total lesion size of ≤9 disc areas, lesion containing ≤50% hemorrhage and ≤50% subretinal fibrosis and ≤50% retinal pigment atrophy in the study eye Amendment 01 Text: Total lesion size of ≤9 disc areas, lesion containing ≤50% hemorrhage in the study eye
23-24	5.2 Subject Exclusion Criteria 2	Rationale: To avoid narrowing the opportunities for the subjects to participate in the study. Original Text: BCVA worse than 20 ETDRS letters (20/400) in the study eye. Amendment 01 Text: BCVA worse than 10 ETDRS letters (20/640) in the study eye.

No subjects have been enrolled as of September 25, 2018. This change does not affect subject safety.