Clinical protocol:

Title: A Multi-Center, Open Label, TOFU Extension Study Assessing the Efficacy and Safety of Additional Intravitreal Injections of RBM-007 in Subjects with Wet Age-related Macular Degeneration – RAMEN Study

NCT04640272

Date: 01 October 2021

RBM-007
Protocol RBM 007-003

TITLE: A Multi-Center, Open Label, TOFU Extension Study Assessing the Efficacy and Safety of Additional Intravitreal Injections of **RBM-007** in Subjects with Wet Age-related **Macular Degeneration** – RAMEN Study

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

STUDY DRUG:
2.0 mg (100µL of 20 mg/mL) RBM-007 injectable solution

I have read the protocol and agree to conduct the study as outlined and in accordance with the ethical principles in 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 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: _____
(Typed or Printed)

Address: _____

_____

Phone: _____

APPROVERS

Company/Sponsor signatory [redacted].	[redacted]

1 PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Physician/Medical Monitor	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

2 SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company:
RIBOMIC USA Inc.
2120 University Ave.
Berkeley, CA 94704</td></tr>
<tr><td colspan="2">Name of Investigational Product: RBM-007 injectable solution</td></tr>
<tr><td colspan="2">Name of Active Ingredient: RBM-007</td></tr>
<tr><td colspan="2">Title of Study: A Multi-Center, Open Label, TOFU Extension Study Assessing the Efficacy and Safety of Additional Intravitreal Injections of RBM-007 in Subjects with Wet Age-related Macular Degeneration – RAMEN Study</td></tr>
<tr><td>Study Period: Approximately 12 months
Estimated date first subject enrolled: October 2020
Estimated date last subject completed: November 2021</td><td>Phase of Development:
Phase II</td></tr>
<tr><td colspan="2">Primary Objective:
To assess the safety and efficacy of additional intravitreal injections of RBM-007 (2.0 mg/eye) in subjects with wet age-related macular degeneration (AMD) rolled over from TOFU Study (Protocol RBM-007-002).
Secondary Objective:
To evaluate anti-fibrotic effect for RBM-007 in subjects with exudative age-related macular degeneration.</td></tr>
</table>

Methodology:

This is a multi-center, open label, extension study assessing the efficacy and safety of additional intravitreal injections of RBM-007 in subjects with wet age-related macular degeneration.

Subjects who meet all eligibility criteria at the time of exit visit of TOFU study will receive treatment for up to three months in the study eye. Subjects that successfully exited TOFU study on or before approximately September 1, 2021 will be considered for RAMEN Study.

Approximately forty subjects with exudative age-related macular degeneration (AMD) will receive RBM-007 injectable solution (2.0 mg/eye)

The primary endpoint of the study is at one month post the last injection with safety evaluation through two months post the last injection.

For eligibility, subjects must be diagnosed with exudative AMD in the study eye, for which previous TOFU masked treatment arms with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agent Eylea® and/or RBM-007 has not demonstrated improvement in vision, with less than 15 letter BCVA improvement in TOFU study at the exit visit of TOFU over its baseline. Subjects must have completed all visits in the TOFU study.

Subject must demonstrate absence of central atrophy or retinal epithelial tear in the fovea or any condition preventing VA improvement in the study eye.

Eligible subjects who are enrolled in the study will be seen for at least 6 visits that include a Baseline/Day 1 (Visit 1), and months 1-5 (Visit 2-6)

Subjects are eligible for rescue with Eylea® or other treatment at the discretion of investigator anytime during the study if one of the following rescue criteria is met.

Rescue Criteria:

- BCVA decrease of > 10 letters AND central subfield thickness (CST) increase of > 50 µm from baseline (visit 1 RAMEN).
- The discretion of investigator

Number of Subjects (planned):

Approximately 40 subjects with wet AMD will be enrolled at approximately 10 sites. Subjects that successfully exited TOFU study on or before approximately September 1, 2021 will be considered for RAMEN Study

Duration of the Study:

The total study period for each subject will include a treatment period and follow up period (total up to five months).

Masking:

This is an open label study.

The designated Safety Review Team (SRT) will review the safety data periodically to determine if the safety and tolerability of the doses are acceptable.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

At *Visit 1 (Baseline (Day 1))*, subjects must meet all of the following inclusion criteria:

1. Provide signed written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.
2. 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 study procedures.
3. Subjects must have completed all scheduled visits of TOFU study. Subjects can only enter this study after exiting TOFU study
4. Subjects for which previous TOFU masked treatment arms with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents Eylea® and/or RBM-007 has not demonstrated improvement in vision; subjects with less than 15 letter BCVA improvement in TOFU study at exit visit over its baseline.
5. Diagnosis of exudative AMD in the study eye, as assessed by spectral domain optical coherence tomography (SD-OCT).
6. Absence of central atrophy or retinal epithelial tear in the fovea or any condition preventing VA improvement in the study eye.
7. BCVA of 24 ETDRS letters (20/320) or better in the fellow eye.
8. Reasonably clear media and some fixation in the study eye to allow for good quality SD-OCT and fundus photography.

Exclusion Criteria:

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

Ocular:

1. Subjects whose vision have improved >15 BCVA letters at exit visit of TOFU study over its baseline
2. Subjects who experienced any drug related serious adverse event during TOFU study
3. Use of any of the following treatments or anticipated use of any of the following treatments to the study eye:
    a. Intravitreal or periocular corticosteroid, within 90 days prior to Visit 1 (Day 1) and throughout the study.
    b. Fluocinolone acetonide intravitreal implant, within 12 months prior to Visit 1 (Day 1) and throughout the study.
    c. Visudyne® photodynamic therapy, within 90 days prior to Visit 1 (Day 1) and throughout the study.
4. Uncontrolled or advanced glaucoma, evidenced by an intraocular pressure (IOP) of > 21 mmHg or cup/disc ratio > 0.8 while on medical therapy, or chronic hypotony (< 6 mmHg) in the study eye.
5. Evidence of any other ocular disease other than wet AMD in the study eye that may confound the outcome of the study (e.g., active diabetic retinopathy, posterior uveitis, pseudo vitelliform macular degeneration, moderate/severe myopia).
6. History of vitrectomy in the study eye.
7. Need for ocular surgery in the study eye during the course of the study.
8. YAG laser capsulotomy within 30 days prior to Visit 1 (Day 1) in the study eye.
9. Intraocular surgery, including lens removal or laser, within 90 days prior to Visit 1 (Baseline (Day 1)) in the study eye.
10. Ocular or periocular infection in either eye.
11. Pupillary dilation inadequate for quality fundus photography in the study eye.
12. Media opacity that would limit clinical visualization, fundus photography, fundus autofluorescence, or spectral domain optical coherence tomography (SD-OCT) evaluation in the study eye.
13. History of herpetic infection in the study eye or adnexa.
14. Presence of known active toxoplasmosis, inactive toxoplasmosis or toxoplasmosis scar in either eye.
15. Presence of any form of ocular malignancy including choroidal melanoma in either eye.

Non-Ocular:

16. Prior systemic treatment with RBM-007 injectable solution.
17. Use of any of the following treatments or anticipated use of any of the following treatments during the study:
    a. Systemic treatment with anti-VEGF agents (e.g., bevacizumab)
    b. Agents targeting the FGF-2 pathway
18. Allergy or hypersensitivity to study drug product, fluorescein dye, or other study related procedures/medications.
19. Major surgery within 90 days prior to Visit 1 (Baseline (Day 1)). 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.
20. Therapeutic radiation to the head or neck within 90 days prior to Visit 1 (Day 1).
21. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1 (Baseline (Day 1)) 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.
22. 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.
23. Females who are pregnant or lactating and females of child-bearing potential who are not using adequate contraceptive precautions (i.e., IUD, oral contraceptives, barrier method, or other contraception deemed adequate by the Clinical Investigator).
24. Unable to comply with study procedures or follow-up visits.

In addition, the Clinical Investigator or RIBOMIC Medical Monitor may declare a subject ineligible for any sound reason.

Study Eye

The study eye must meet all inclusion and exclusion criteria. The study eye must be the same as the eye in TOFU study.

Route of Administration of Investigational product:

Intravitreal injection in the study eye.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable assessed at Month 4:

- Mean change in BCVA from Baseline

The secondary efficacy variables assessed at Month 4:

- Proportion of subjects gaining more than 15 letters as measured by BCVA from Baseline (3-line gainers)
- Proportion of subjects with BCVA: 1) gain of ≥10 ETDRS letters; 2) gain of ≥5 ETDRS letters; and 3) loss of ≥ 15 letters from Baseline
- Change from Baseline in CST and macular volume by SD-OCT
- Change from Baseline in characteristics of subretinal hyper reflective material (SHRM)
- Change from Baseline in characteristics of fibrosis
- Proportion of subjects that do not require anti-VEGF rescue treatment during follow-up period
- Mean number of rescue injections
- Proportion of subjects requiring rescue

Safety:

The safety assessments will include adverse events (AEs), pregnancy test, external ocular exam, BCVA, IOP, slit lamp biomicroscopy, indirect ophthalmoscopy, SD-OCT, fundus photography, fundus autofluorescence, vital signs and physical examination.

Statistical Methods:

The primary analysis will be after the study is completed. All safety and efficacy data will be summarized with descriptive statistics. BCVA and CST data will also be presented graphically.

Due to the exploratory nature of this study, the sample size was not based on a statistical power.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviations and Terms

Abbreviation	Expression (Name) in full
AE(s)	adverse event(s)
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
CNV	choroidal neo-vascularization
CRF	Case report form
CST	central subfield thickness
eCRF(s)	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EC	Ethics Committee
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
GLP	Good Laboratory Practice
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	intravitreal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
NOAEL	no observed adverse effect level
µL	microliter
mL	milliliter
mmHg	millimeter of mercury
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD-OCT	spectral domain optical coherence tomography
SHRM	subretinal hyper reflective material
SRT	Safety Review Team
VEGF	vascular endothelial growth factor

5 INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in developed countries. AMD is characterized by extracellular matrix deposits, known as drusen, accumulating between the retinal pigment epithelium and Bruch's membrane. In exudative or wet AMD, unwanted blood vessels grow into the macula which leads to hemorrhage and subretinal fluid. In addition, retinal pigment epithelial detachment, retinal tears, fibrovascular scarring and vitreous hemorrhage may occur. The aberrant growth of leaky vessels is the result of local inflammatory responses leading to disruption of the balance of cytokines that control angiogenesis (Lim et al., 2007).

Angiogenesis is a complex and coordinated process of the growth and sprouting of new blood vessels from pre-existing vasculature. Although several angiogenic factors have been identified, VEGF family proteins, their receptors and intracellular signaling molecules appear to be the key mediators of angiogenesis (Kane et al., 2007).

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. 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 choroidal neovascularization (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®), aflibercept (Eylea®) and brolucizumab (Beovu®). Also, off-label use of aliquoted bevacizumab (Avastin®) is used to treat AMD. 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.

RBM-007 Injectable Solution is a novel oligonucleotide-based aptamer having potent anti-Fibroblast Growth Factor (FGF2) activity (Jin et al, 2016), which holds anti-angiogenic and anti-scarring dual action (Matsuda et al., 2019) as well as a negative action for VEGF expression (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 (Matsuda et al., 2019). 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 (Matsuda et al., 2019). It is hypothesized to have potential effects in the treatment of wet 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.

RIBOMIC has conducted a Phase I/II, open-label, dose-escalating, sequential cohort study assessing the safety, tolerability and bioactivity of a single IVT injection of RBM-007 injectable solution in the study eye of nine subjects with refractory wet AMD (Protocol RBM-007-001). Three dose levels of RBM-007 have been assessed in this Phase I/II study, 0.2 mg/eye, 1.0 mg/eye and 2.0 mg/eye. In this study (SUSHI), there were no reported SAEs. No dose-dependent events were reported and no safety concerns were identified at all investigated doses. Ocular AEs were reported in 3 subjects (33.3%). Most common AE was subconjunctival hemorrhage (2 subjects) and this was considered to be due to the injection procedure. The only drug related AE was mild iritis that was resolved after one day of topical steroid eye drops.

The Phase II TOFU study (RBM-007-002) is currently ongoing, with the first patient randomized on 17 February 2020 and an expected last patient visit (at week 24) in July 2021. As of the data cut-off date of Development Safety Update Report (DSUR) - RBM-007 (19 July 2020), a total of 23 subjects have been randomized in the Phase II TOFU study, and the treatment assignments have not been unmasked. A total of one SAE has been reported in TOFU, but was considered unrelated to the study medication. A total of 24 AEs have been reported. Conjunctival hemorrhage was most common AE and it was related to injection procedure. Only one possibly drug related AE was noted which was Injection site inflammation that resolved after administration of topical steroid drops. Two patients withdrew from the study due to COVID-19 schedule issues and one subject was found to be ineligible after randomization.

Study results mentioned above, in addition to the results of the non-clinical studies, support the use of repeated IVT injections of 2.0 mg/eye of RBM-007 in humans in the Phase II TOFU extension clinical trial, namely RAMEN (Protocol RBM-007-003).

6 OBJECTIVES

Primary Objective:

To assess the safety and efficacy of additional intravitreal injections of RBM-007 (2.0 mg/eye) in subjects with wet age-related macular degeneration (AMD) rolled over from TOFU Study.

Secondary Objective:

To evaluate anti-fibrotic effect for RBM-007 in subjects with exudative age-related macular degeneration.

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This is a multi-center, open label, extension study assessing the efficacy and safety of additional intravitreal injections of RBM-007 in subjects with wet age-related macular degeneration rolled over from TOFU Study.

Subjects who meet all eligibility criteria at the time of exit visit of TOFU study will receive treatment for up to three months in the study eye. Subjects that successfully exited TOFU study on or before approximately September 1, 2021 will be considered for RAMEN Study.

Approximately forty subjects with exudative age-related macular degeneration (AMD) will receive RBM-007 Injectable Solution (2.0 mg/eye).

The primary endpoint of the study is at one month post the last injection with safety evaluation through additional two months post the last injection.

For eligibility, subjects must be diagnosed with exudative AMD in the study eye, for which previous TOFU masked treatment arms with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agent Eylea® and/or RBM-007 has not demonstrated improvement in vision, with less than 15 letter BCVA improvement in TOFU study at the exit visit of TOFU over its baseline. Subjects must have completed all visits in the TOFU study.

Subject must demonstrate absence of central atrophy or retinal epithelial tear in the fovea or any condition preventing VA improvement in the study eye.

Eligible subjects who are enrolled in the study are expected to be seen for at least 6 visits that include a Baseline/Day 1 (Visit 1), and months 1-5 (Visit 2-6).

Subjects are eligible for rescue with Eylea® or other treatment at the discretion of investigator anytime during the study if one of the following rescue criteria is met.

Rescue Criteria:

Eligibility criteria for Rescue are as follow:

- BCVA decrease of > 10 letters AND central subfield thickness (CST) increase of > 50 µm from RAMEN baseline visit.
- The discretion of investigator.

Rescue therapy is defined as IVT injection of Eylea® or other treatment at the discretion of investigator in the study eye.

Whenever possible, RIBOMIC should be notified before any rescue procedure.

If rescue with anti-VEGF agent is considered, the subject must receive the injection of RBM-007 scheduled for the specific visit prior to the injection of anti-VEGF agent for rescue.

If rescue is performed, the following assessments must be performed after the administration of each one of the injections (RBM-007 and Rescue treatment):

(all ophthalmic procedures to be performed in the treated eye)

- Within 30 minutes following each one of the injections:
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy

- IOP will be measured at 30 (±10) minutes following the intravitreal injection.
- If post-injection IOP is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 60 (±10) minutes post-injection.
- If post-injection IOP at 60 (±10) minutes is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 90 (±10) minutes post-injection.
- If there is an increase of ≥ 10 mmHg at 90 (±10) minutes post-injection compared to pre-injection IOP, the subject should 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).
- On the other hand, a subject with IOP measurement of > 21 mmHg will be managed according to the discretion of the Clinical Investigator.
- The IOP increase of ≥ 10 mmHg from pre-injection AND IOP measurement of > 21 mmHg will be reported as an AE.

• Aqueous tap can be performed at any time per the Clinical Investigator`s discretion for treatment or prevention of increasing in the IOP.

7.1.1 Selection of Concentrations in the Study

In this clinical study (Protocol No. RBM-007-003), RBM-007 (2.0 mg/eye) is being tested in subjects with wet AMD. The maximum amount of RBM-007 that a subject can possibly receive is 8 mg over a 5-month period. Systemic exposure of RBM-007 in this study given 4 times by IVT injection is anticipated to be significantly lower. In the SUSHI study, the systemic human exposure was measured and shown to be very small. Therefore, no concerns regarding systemic toxicity are anticipated in this study.

Furthermore, in the SUSHI study (Protocol No. RBM-007-001), three dose levels of RBM-007 (0.2 mg, 1.0 mg and 2.0 mg) were tested in nine subjects with refractory wet AMD. No dose-dependent events were reported and no safety concerns were identified at all investigated doses. Most common AE was subconjunctival hemorrhage (2 subjects, 22%). One case of mild irritation was reported. All ocular AEs, except one, were considered to be due to the injection procedure. Only one drug related AE was noted, which was mild iritis that resolved after one day administration of topical steroid drops.

Additionally, Phase II TOFU study (Protocol No. RBM-007-002) in the United States is a randomized, double masked, active controlled study assessing the safety and efficacy of repeated intravitreal injections of RBM-007 (2.0 mg/eye) monotherapy and in combination with Eylea® compared to Eylea® monotherapy in subjects with exudative age-related macular degeneration

(wAMD). Eighty-one (81) subjects with wAMD will be randomly assigned to one of three treatment arms:

Arm 1: Sham + RBM-007 2.0 mg/eye

Arm 2: RBM-007 2.0 mg/eye + Eylea® 2.0 mg/eye

Arm 3: Sham + Eylea® 2.0 mg /eye

Subjects receive 4 monthly intravitreal injections of RBM-007 (2.0 mg) or RBM0-007 (2.0 mg) + sham in the first treatment arm, 4 monthly intravitreal injections of RBM-007 (2.0 mg) or RBM-007 (2.0 mg) in combination with two Eylea® injections at every other month for the second arm, and 4 monthly intravitreal injections of sham or sham + Eylea® every other month in the third treatment arm.

The Phase II TOFU study (RBM-007-002) is currently ongoing, with the first patient randomized on 17 February 2020 and an expected last patient visit (at week 24) in July 2021. As of the data cut-off date of Development Safety Update Report (DSUR) - RBM-007 (19 July 2020), a total of 23 subjects have been randomized in the Phase II TOFU study, and the treatment assignments have not been unmasked. A total of one SAE has been reported in TOFU, but was considered unrelated to the study medication. A total of 24 AEs have been reported. Conjunctival hemorrhage was the most common AE and it was related to injection procedure. Only one possibly drug related AE was noted which was Injection site inflammation that resolved after administration of topical steroid drops. Two patients withdrew from the study due to COVID-19 schedule issues and one subject was found to be ineligible after randomization.

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 Good Laboratory Practice (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 human doses for the first in human study (RBM-007-001) were 0.2 mg, 1.0 mg and 2.0 mg per eye administered once. Considering the 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. Additionally, the long-term ocular monkey study with monthly injection of RBM-007 at 1 mg/eye monotherapy and RBM-007 at 0.5 or 1 mg/eye in addition to Eylea® at 2 mg/eye for up to seven injections did not show any treatment-related adverse effect.

With regard to systemic exposure, the highest concentration of RBM-007 seen in plasma after single intravitreal dosing was 2,100 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 165–5,207 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 3,850–123,830.

Thus, the Sponsor contends that the preclinical toxicology as well as clinical trials with RBM-007 support the planned clinical studies.

7.2 Number of Subjects

Approximately 40 subjects with wet AMD will be enrolled at approximately 10 sites. The final number of subjects enrolled may be adjusted based on drop-out rate. Subjects that successfully exited TOFU study on or before approximately September 1, 2021 will be considered for RAMEN Study

7.3 Treatment Assignment

RBM-007 injectable solution 2.0 mg (100 µL of 20 mg/mL) will be administered by IVT injection in the study eye.

7.4 Dose Adjustment Criteria

The Safety Review Team will review safety parameters periodically and in the event of any SAE for adjusting or stopping doses.

7.5 Study Procedures

All subjects must sign a written ICF before participating in any study-related activity. Once the subject meets all eligibility requirements at Screening Procedure - Visit 1 (Baseline (Day1)), each subject will continue to be assigned with the unique subject number provided in TOFU study. 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 Section 21.4, Appendix D – Procedures for Examinations.

Table 2: Schedule of Events

Visit Number	Visit 1 (SCRN/Injection)		Visit 2 (Injection)		Visit 3 (Injection)		Visit 4 (Injection)		Visit 5	Visit 6 (Exit)
Visit Schedule (Time window; days)	D1		M1 D29 (±4)		M2 D57 (±4)		M3 D85 (±4)		M4 D113 (±7)	M5 D141 (±7)
	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
Informed consent [a]	X									
Demographics/Eligibility	X									
Medical/surgical history, Concomitant medication	X		X		X		X		X	X
Physical examination	X									X
Vital signs	X									X
BCVA (ETDRS)	X		X		X		X		X	X
External ocular exam	X		X		X		X		X	X
Intraocular pressure (IOP) [b]	X	X	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy [c]	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy [c]	X	X	X	X	X	X	X	X	X	X
SD-OCT	X		X		X		X		X	X
OCT Angiography [d]	X								X	
Fundus photography	X		X		X		X		X	X
Fundus autofluorescence	X								X	
Urine pregnancy test [e]	X									X
IVT injection	X		X		X		X			
Adverse event	X		X		X		X		X	X

SCRN = Screening; D = Day; M = Month;

[a] Informed Consent to be obtained prior to conducting any study-related activities.

[b] IOP will be performed before the IVT injection and 30 (±10) minutes after the IVT injection. If IOP is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, perform IOP again at 60 (±10) minutes after the injection. If IOP is still > 21 mmHg after eye massage and/or aqueous tap performed per PI discretion, perform IOP again at 90 (±10) minutes after the injection. This will be also applied for the post IVT injection of Rescue treatment.

[c] On days when any IVT injections are administered, slit lamp biomicroscopy and indirect ophthalmoscopy will be performed prior to the injection and within 30 minutes after the injections. This will be also applied for the post IVT injection of Rescue treatment.

[d] Selected sites will conduct OCT angiography in all subjects.

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

7.5.1 Study Visits

7.5.1.1 Visit 1 (Baseline (Day 1))

Screening Procedure:

- Ascertain the patient has successfully exited TOFU study.
- Visit 1 should happen during 0 to 60 days after the exit Visit in TOFU Study.
- Ascertain the patient has exudative AMD.
- Ascertain the patient did not have improvement of vision more than 15 letters of BCVA at the exit visit of TOFU study over its baseline.

- Explain 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.
- If the subject continues to be eligible for the study, ask female subject whether she is postmenopausal (Section 21.4.4). Perform urine pregnancy test to the subject who answered "No" to the question.
- Perform the following assessments (all ophthalmic procedures to be performed on both eyes):
  - Physical examination
  - Vital signs
  - BCVA (ETDRS)
  - External ocular exam
  - IOP
  - Slit-lamp biomicroscopy
  - Indirect ophthalmoscopy
  - SD-OCT
  - OCT Angiography
  - Fundus photography
  - Fundus Autofluorescence
- Review the inclusion and exclusion criteria. Do not continue screening any subject who does not meet the screening eligibility requirements.

Treatment Procedure

- After review, if the subject continues meeting all eligibility criteria, confirm the study eye is same as in TOFU study, and proceed for the injection that will be administered as per drug labeling.
- Administer IVT RBM-007 as per drug labeling.
- The following assessments must be performed after the injection (only on the treated Study Eye):

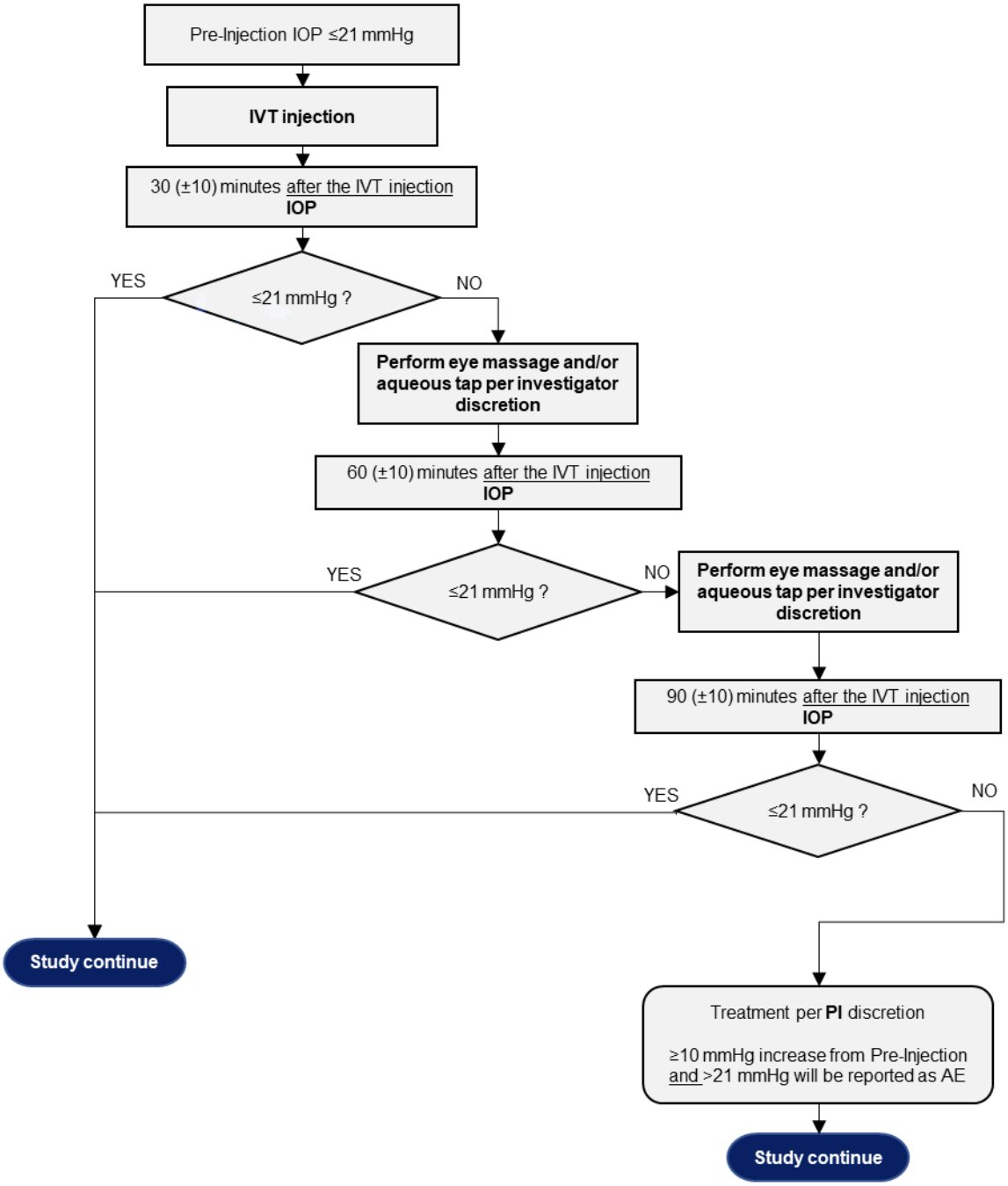
  - Within 30 minutes post-injection:
    - ✓ Slit-lamp biomicroscopy
    - ✓ Indirect ophthalmoscopy
  - IOP will be measured at 30 (±10) minutes post-injection.
  - If post-injection IOP is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - If post-injection IOP at 60 (±10) minutes is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 90 (±10) minutes post-injection.
  - If there is an increase of ≥ 10 mmHg at 90 (±10) minutes post-injection compared to pre-injection IOP, the subject should 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).
  - On the other hand, a subject with IOP measurement of > 21 mmHg will be managed according to the discretion of the Clinical Investigator.
  - The IOP increase of ≥ 10 mmHg from pre-injection AND IOP measurement of > 21 mmHg will be reported as an AE.

- Aqueous tap can be performed at any time per the Clinical Investigator`s discretion for treatment or prevention of an increase in the IOP **(see** Figure 1**).**

- AE assessments must be performed after IVT injection.

- Upload collected images (SD-OCT and Fundus photography) of the study eye to the Egnyte server.
- Schedule the subject to return for Visit 2 (Month 1 (D29±4)).

Figure 1: Decision IOP Process for IVT Injection



7.5.1.2 Visit 2 (Month 1 (D29±4))

- Perform the following assessments (all ophthalmic procedures to be performed on both eyes):
  - Query for AEs

- Update medical history and medications
- BCVA (ETDRS)
- External ocular exam
- IOP
- Slit-lamp biomicroscopy
- Indirect ophthalmoscopy
- SD-OCT
- Fundus photography

- **Injection/ IOP control procedures are same as Visit 1 (Baseline (Day1)), described in Section 7.5.1.1**

- Upload collected images (SD-OCT and Fundus photography) of the study eye to the Egnyte server.
- Schedule the subject to return for Visit 3 (Month 2(D57±4)).

7.5.1.3 Visit 3 (Month 2 (D57±4))

- Perform the following assessments (all ophthalmic procedures to be performed on both eyes):
  - Query for AEs
  - Update medical history and medications
  - BCVA (ETDRS)
  - External ocular exam
  - IOP
  - Slit-lamp biomicroscopy
  - Indirect ophthalmoscopy
  - SD-OCT
  - Fundus photography

- **Injection/ IOP control procedures are same as Visit 1 (Baseline (Day1)), described in Section 7.5.1.1**

- Upload collected images (SD-OCT and Fundus photography) of the study eye to the Egnyte server.
- Schedule the subject to return for Visit 4 (Month 3 (D85±4)).

7.5.1.4 Visit 4 (Month 3(D85±4))

- Perform the following assessments (all ophthalmic procedures to be performed on both eyes):
  - Query for AEs
  - Update medical history and medications
  - BCVA (ETDRS)
  - External ocular exam
  - IOP
  - Slit-lamp biomicroscopy
  - Indirect ophthalmoscopy
  - SD-OCT
  - Fundus photography

- **Injection/ IOP control procedures are same as Visit 1 (Baseline (Day1)), described in Section 7.5.1.1**

- Upload collected images (SD-OCT and Fundus photography) of the study eye to the Egnyte server.
- Schedule the subject to return for Visit 5 (Month 4 (D113±7)).

7.5.1.5 Visit 5 (Month 4 (D113±7)): Primary Endpoint

- Perform the following assessments (all ophthalmic procedures to be performed on both eyes):
  - Query for AEs
  - Update medical history and medications
  - BCVA (ETDRS)
  - External ocular exam
  - IOP
  - Slit-lamp biomicroscopy
  - Indirect ophthalmoscopy
  - SD-OCT
  - OCT Angiography
  - Fundus photography
  - Fundus autofluorescence
- Upload collected images (SD- OCT, Fundus photography and Fundus autofluorescence) of the study eye to the Egnyte server.
- Schedule the subject to return for Visit 6 (Month 5 (D141±7)).

7.5.1.6 Visit 6/Exit (Month 5 (D141±7))

- Perform the following assessments:
  - Query for AEs
  - Physical Exam
  - Vital Signs
  - Update medical history and medications
  - Perform urine pregnancy test to the subject who answered "No" to the question on postmenopausal at *Visit 1 (Baseline (Day 1))*.
  - BCVA (ETDRS)
  - External ocular exam
  - IOP
  - Slit-lamp biomicroscopy
  - Indirect ophthalmoscopy
  - SD-OCT
  - Fundus photography
- Upload collected images (SD-OCT and Fundus photography) of the study eye to the Egnyte server.

7.5.2 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(s).

8 SELECTION AND WITHDRAWAL OF SUBJECTS

Eligible subjects must meet all eligibility criteria described in Section 8.1 and Section 8.2.

8.1 Subject Inclusion Criteria

At *Visit 1 (Baseline (Day 1))*, subjects must meet all of the following inclusion criteria:

1. Provide signed written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.
2. 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 study procedures.
3. Subjects must have completed all scheduled visits of TOFU study. Subjects can only enter this study after exiting TOFU study
4. Subjects for which previous TOFU masked treatment arms with intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents Eylea® and/or RBM-007 has not demonstrated improvement in vision; subjects with less than 15 letter BCVA improvement in TOFU study at exit visit over its baseline.
5. Diagnosis of exudative AMD in the study eye, as assessed by spectral domain optical coherence tomography (SD-OCT).
6. Absence of central atrophy or retinal epithelial tear in the fovea or any condition preventing VA improvement in the study eye.
7. BCVA of 24 ETDRS letters (20/320) or better in the fellow eye
8. Reasonably clear media and some fixation in the study eye to allow for good quality SD-OCT and fundus photography.

8.2 Subject Exclusion Criteria

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

Ocular:

1. Subjects whose vision have improved >15 BCVA letters at exit visit of TOFU study over its baseline
2. Subjects who experienced any drug related serious adverse event during TOFU study
3. Use of any of the following treatments or anticipated use of any of the following treatments to the study eye:

a. Intravitreal or periocular corticosteroid, within 90 days prior to Visit 1 (Day 1) and throughout the study.

b. Fluocinolone acetonide intravitreal implant, within 12 months prior to Visit 1 (Day 1) and throughout the study.

c. Visudyne® photodynamic therapy, within 90 days prior to Visit 1 (Day 1) and throughout the study.

4. Uncontrolled or advanced glaucoma, evidenced by an IOP of > 21 mmHg or cup/disc ratio > 0.8 while on medical therapy, or chronic hypotony (< 6 mmHg) in the study eye.
5. Evidence of any other ocular disease other than wet AMD in the study eye that may confound the outcome of the study (e.g., active diabetic retinopathy, posterior uveitis, pseudo vitelliform macular degeneration, moderate/severe myopia).
6. History of vitrectomy in the study eye.
7. Need for ocular surgery in the study eye during the course of the study.
8. YAG laser capsulotomy within 30 days prior to Visit 1 (Day 1) in the study eye.
9. Intraocular surgery, including lens removal or laser, within 90 days prior to Visit 1 (Baseline (Day 1)) in the study eye.
10. Ocular or periocular infection in either eye.
11. Pupillary dilation inadequate for quality fundus photography in the study eye.
12. Media opacity that would limit clinical visualization, fundus photography, fundus autofluorescence, or SD-OCT evaluation in the study eye.
13. History of herpetic infection in the study eye or adnexa.
14. Presence of known active toxoplasmosis, inactive toxoplasmosis or toxoplasmosis scar in either eye.
15. Presence of any form of ocular malignancy including choroidal melanoma in either eye.

Non-Ocular:

16. Prior systemic treatment with RBM-007 injectable solution.
17. Use of any of the following treatments or anticipated use of any of the following treatments during the study:

    a. Systemic treatment with anti-VEGF agents (e.g., bevacizumab)

    b. Agents targeting the FGF-2 pathway

18. Allergy or hypersensitivity to study drug product, fluorescein dye, or other study related procedures/medications.
19. Major surgery within 90 days prior to Visit 1 (Baseline (Day 1)). 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.

20. Therapeutic radiation to the head or neck within 90 days prior to Visit 1 (Day 1).
21. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1 (Baseline (Day 1)) 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.
22. 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.
23. Females who are pregnant or lactating and females of child-bearing potential who are not using adequate contraceptive precautions (i.e., IUD, oral contraceptives, barrier method, or other contraception deemed adequate by the Clinical Investigator).
24. Unable to comply with study procedures or follow-up visits.

In addition, the Clinical Investigator or RIBOMIC Medical Monitor may declare a subject ineligible for any sound reason.

8.3 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:

- Non-compliance
- Lost to follow-up
- Protocol violation
- Withdrawal by subject
- AEs
- Death
- Other

If a subject is discontinued from the study before completing Visit 6/Exit (Month 5) (D141±7)), then to the extent possible, all assessments, including safety, that are scheduled to be performed at Visit 6/Exit should be performed on the day of discontinuation.

9 TREATMENT OF SUBJECTS

9.1 Description of Study Drug

RBM-007 is a pegylated oligonucleotide-based aptamer. RBM-007 injectable solution is a formulation designed for intravitreal injection. RBM-007 has an approximate molecular weight of 54kDa.

9.2 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.

9.2.1 Prohibited Medications or Treatments

Any systemic treatments with anti-VEGF agents (e.g., 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.

9.2.2 Rescue Therapy

Rescue therapy is defined as IVT injection of Eylea® or any other treatment at the discretion of investigator in the study eye.

Whenever possible, RIBOMIC should be notified before any rescue procedure.

If rescue with anti-VEGF agent is considered, the subject must receive the injection of RBM-007 prior to the injection of anti-VEGF agent for rescue.

Eligibility criteria for Rescue are as follow:

- BCVA decrease of > 10 letters AND central subfield thickness (CST) increase of > 50 µm from the RAMEN baseline visit.
- The discretion of investigator.

If rescue is performed, the following assessments must be performed after the administration of each one of the injections (RBM-007 and Rescue treatment) (all ophthalmic procedures to be performed in the treated eye):

- Within 30 minutes following each one of the injections:
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy

- IOP will be measured at 30 (±10) minutes following the intravitreal injection.
- If post-injection IOP is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 60 (±10) minutes post-injection.
- If post-injection IOP at 60 (±10) minutes is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 90 (±10) minutes post-injection.
- If there is an increase of ≥ 10 mmHg at 90 (±10) minutes post-injection compared to pre-injection IOP, the subject should 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).
- On the other hand, a subject with IOP measurement of > 21 mmHg will be managed according to the discretion of the Clinical Investigator.
- The IOP increase of ≥ 10 mmHg from pre-injection AND IOP measurement of > 21 mmHg will be reported as an AE.

• Aqueous tap can be performed at any time per the Clinical Investigator`s discretion for treatment or prevention of increasing in the IOP.

9.3 Treatment Compliance

In order to obtain efficacy and safety 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.

9.4 Randomization and Masking

Randomization is not employed in this study due to the open-label design.

10 STUDY DRUG MATERIALS AND MANAGEMENT

10.1 Study Drug

10.1.1 Investigational Drug

RBM-007 for IVT injection is formulated in a proprietary, clear, aqueous solution. RBM-007 to be administered in the study eye is shown in Table 3.

Table 3: RBM-007 Dosing

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

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

10.1.2 Concomitant drug

No concomitant drug is administered in the study.

10.1.3 Study Drug Complaint Reporting

Complaints regarding the RBM-007 for IVT injection should be reported to RIBOMIC/Representative Product Complaint at [redacted]

10.1.4 Other Study Supplies

RIBOMIC or its Representative will supply needles and syringes.

10.2 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. Four single use vials will be placed in a carton, and the labeling will include protocol number, kit number, drug concentration, and storage conditions.

10.3 Study Drug Storage

RBM-007 injectable solutions will be provided by RIBOMIC or its 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.

10.4 Study Drug Preparation

<Investigational drug: RBM-007>

Once an investigational drug kit has been assigned to a subject, the vial of investigational drug for the visit will be removed from the kit in the freezer. The content should be thawed by rotating the vial 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.

Study drug preparation should be performed by the designated injecting physician.

Each vial contains enough RBM-007 to inject one subject. Each vial will be used one time only. Write the subject number on the carton label. After use, return the vial in the carton, seal and initial the carton.

10.5 Loading the Syringe

<Investigational drug: RBM-007>

1. A sterile, single-use 250 µL syringe with several custom markings, including 0.1 mL (100 µL), will be provided separately for IVT injection of RBM-007. Instructions for filling the syringe are as follows:
2. Remove the sterile, single-use 250 µL syringe from the packaging.
3. Attach a 19-gauge x 1 ½ inch filter needle to the syringe. RBM-007 is dispensed in a 0.5 ml fill in a 2 mL vial. See Figure 2.
4. Using sterile technique, carefully draw up approximately 200 µL of RBM-007 into the syringe (sufficiently larger volume than 100 µL is needed to allow for dead space in syringe and needles prior to IVT injection).
5. 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 IVT injection.
   A. Ensure that the 30-gauge x 0.5 inch needle is affixed tightly to the syringe.
   B. Align the top edge of the red O-ring of the plunger with the 100 µL black mark on the syringe, expelling the excess fluid drawn up.
   C. 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.

Figure 2: 0.5 mL fill in a 2 mL vial

<Investigational drug>

10.6 Eye Preparation

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

1. Dilate pupil (1 % mydriacyl and 2.5 % phenylephrine or equivalent applied topically) approximately 10 minutes prior to injection.
2. Administer 1 eye drop of topical anesthetic (0.5 % proparacaine hydrochloride ophthalmic solution or an equivalent topical ophthalmic anesthetic).
3. Administer 5 % povidone iodine.
4. Use a sterile cotton-tipped applicator to remove excess fluid from the lower conjunctival sac.
5. 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 10.7) and hold in place for approximately 1 minute.
6. Insert sterile eyelid speculum.

10.7 Study Drug Administration

<Investigational drug: RBM-007>

1. Prior to starting the injection procedure, RBM-007 should have been prepared as described in Section 10.4 and Section 10.5, and the study eye should have been prepared as described in Section 10.6.
2. 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.
3. Insert the needle perpendicular to the eye wall at the location specified in Step 2 (Section 10.7) to inject the study solution into the vitreous cavity. Note: If aqueous tap is considered necessary, it should be performed preferably prior to injection of the RBM-007 and noted in the source documents.
4. Very slowly, inject the entire RBM-007 dose volume (100 µL) and slowly withdraw the needle. Do not pull back on the plunger at any time prior to withdrawing the needle.
5. 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).
6. Remove the eyelid speculum and rinse the eye with sterile eye wash solution.
7. Patch the study eye at the Clinical Investigator's discretion.
8. Prescribe topical antibiotic per PI discretion.

10.8 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.

10.9 Study Drug Handling and Return

All investigational products including unused vials of RBM-007 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 or its Representative. 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.

Refer to Study Drug Manual for study drug handling.

11 ASSESSMENT OF EFFICACY

11.1 Best Corrected Visual Acuity (BCVA)

Mean change in BCVA from Baseline at Month 4 is the primary efficacy variable for this study. Proportion of subjects with BCVA: 1) gain of ≥15 ETDRS letters (3-line gainers); 2) gain of ≥10 ETDRS letters; 3) gain of ≥5 ETDRS letters and 4) ≥ 15 letter loss from Baseline at Month 4 are other secondary endpoints.

The visual acuity will be recorded using the ETDRS chart and total number of letters at 4 meter and 1 meter will be recorded. The "non stopping" rule must be applied during the ETDRS BCVA evaluation, considering every letter the subject can read. If a subject could not read ETDRS chart, Finger Counts, Hand Motion, Light Perception, or No Light Perception will be recorded.

11.2 Central Subfield Thickness (CST), Macular Volume (MV), Fibrosis and SHRM

CST, MV, fibrosis and SHRM are secondary efficacy variables, and change in CST, MV, fibrosis and SHRM from Baseline at Month 4 are secondary endpoints.

12 ASSESSMENT OF SAFETY

12.1 Adverse Events

12.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the study drug(s). 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 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 study drug 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 study drug(s) 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.

Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be monitored following the injection.

12.1.1.1 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 12.1.2.

A Clinical Investigator who is qualified in medicine must make the determination of the relationship of the study drug(s) 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 injection could have 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 study drug(s) 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.

- The AE may be recorded as **Related** to the study drug(s) if there is a plausible temporal relationship between the onset of the AE and administration of the study drug(s); and the AE cannot be readily explained by the subject's clinical state, concurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug(s); and/or the AE abates or resolves upon discontinuation of the study drug(s).
- Reporting the AE as **Not Related** to study drug(s), may be considered if, for example, there is good evidence that the AE has an etiology other than the study drug(s) (e.g., pre-existing medical condition, underlying disease, concurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug(s) (e.g., cancer diagnosed 2 days after dose of study drug(s)).

12.1.1.2 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 eCRF. Each recorded AE will be described by its duration (i.e., start and end dates), frequency, severity, regulatory seriousness criteria if applicable, suspected relationship to the study drug(s), relation to injection procedure, location, 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 or not 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:

- Whenever possible, use recognized medical terms when recording. Do not use colloquialisms and/or abbreviations.
- 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).
- 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:the subject developed orthostatic hypotension and subsequently fainted and fell to the floor wherein she experienced a head trauma and neck pain.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.
- 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 14SEP2015 lasting for three hours, then subsequently experienced intermittent episodes of headache every day for approximately 3 hours until 21SEP2015, then the AE date of onset is 14SEP2015 and the resolution date is 21SEP2015.
- 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.
- 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.
- If treatment was initiated, include the treatment and duration of the medication(s) in the eCRF.

12.1.2 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:

- Death
- Life threatening:

  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.
- Hospitalization, at the minimum an overnight stay
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

- 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.

- 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. It is defined as a loss of ≥ 30 letters or 6 lines of vision from Baseline.

12.1.2.1 Reporting Serious Adverse Events

An AE CRF must be completed in EDC 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 eCRF 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.

12.1.2.2 Expedited Reporting of Serious Adverse Events

RIBOMIC (or designee) will provide the Principal Investigator with a reporting cover letter and an anonymized MedWatch 3500A or CIOMs form as appropriate for expedited reporting of SAEs to the IRB or 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.

12.1.3 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 eCRF 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 recommend 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.

12.1.4 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. If the subject is being followed for a SAE beyond the last protocol scheduled visit (Month 5), the visit should be completed when scheduled according to the protocol and the AE Date of Resolution and the End of Study Date of Completion should be the date when following the SAE ended.

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

If the RIBOMIC Pharmacovigilance Department requests follow-up on an individual SAE or designated ESI, the site's response to follow-up requests should be emailed to RIBOMIC Pharmacovigilance: tofu.safety@ribomic.com.

12.1.5 Manual Back-Up Reporting Procedures

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

- Complete an AE form manually.
- Attach a cover sheet with your contact information, including site number.
- Email the AE form to RIBOMIC Pharmacovigilance at tofu.safety@ribomic.com

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

12.2 Safety Parameters

The safety assessments will include AEs, slit lamp biomicroscopy, indirect ophthalmoscopy, BCVA, IOP, fundus photography, fundus autofluorescence, vital signs, pregnancy test and physical examination.

12.2.1 Physical Examination

A full body systematic physical examination will be conducted by the Clinical Investigator or an external internist.

12.2.2 Vital Signs

Blood pressure and heart rate will be measured 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).

12.2.3 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. The "non stopping" rule must be applied during the ETDRS BCVA evaluation, considering every letter the subject can read. If a subject could not read ETDRS chart, Finger Counts, Hand Motion, Light Perception, or No Light Perception will be recorded.

12.2.4 External ocular exam

The Clinical Investigator will assess external ocular examination evaluating lid and lashes.

12.2.5 Slit-lamp Biomicroscopy

The Clinical Investigator will assess Slit-lamp biomicroscopy examination using Slit-lamp microscope. On the visit of any IVT treatment, a biomicroscopy examination will be performed prior to the first injection and a second one within 30 minutes after the second injection. This will be also applied for the post IVT injection of Rescue treatment.

12.2.6 Intraocular Pressure

IOP will be measured in each visit as described in Section 7.5.1

The IOP for the post IVT injection of Rescue treatment will be measured as described in Section 21.4.8.

12.2.7 Indirect Ophthalmoscopy

The Clinical Investigator will assess indirect ophthalmoscopy using indirect ophthalmoscope. On the visit of any IVT treatment, an ophthalmoscopy examination will be performed prior to the injection and a second one within 30 minutes after the injection. This will be also applied for the post IVT injection of Rescue treatment.

12.2.8 Urine Pregnancy Test

A urine pregnancy test will be conducted for all females of childbearing potential.

12.2.9 Fundus Photography

Digital color fundus photography will be taken following the procedure provided by the sponsor. It will be performed prior to any intravitreal injections.

12.2.10Fundus Autofluorescence

Fundus autofluorescence will be taken on Visit 1 (Baseline (Day 1)) and Visit 5 (Month 4), following the procedure provided by the sponsor. It will be performed prior to any intravitreal injections.

12.2.11Spectral Domain Optical Coherence Tomography (SD-OCT)

SD-OCT images will be taken following the procedure provided by the sponsor. It will be performed prior to any intravitreal injections.

12.2.12 Adverse Events

AEs will be elicited from the subjects starting at the Screening through study exit. The information will include at least a description of the event, whether or not it is serious, onset and duration, , severity, relation to masked study therapy, relation to injection procedure, location (OD, OS, OU or non-ocular), action taken and outcome. Prior to evaluating the incidences, all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Ocular and non-ocular AEs will be summarized separately. See Section 12.1 for complete information regarding AEs reporting.

13 OTHER ASSESSMENTS

13.1 Demographics and Baseline Characteristics

Subject demographics include age, race, sex, and ethnicity. Baseline characteristics include medical history, prior or concomitant medications, and Baseline results of physical examination, vital signs, urine pregnancy test, BCVA, slit-lamp biomicroscopy, IOP, indirect ophthalmoscopy, SD-OCT, fundus photography, and fundus autofluorescence. For assessments performed multiple times before the IVT injection of RBM-007, the last pre-injection value will be used as the Baseline value.

13.2 OCT Angiography

For future exploratory research, OCT Angiography will be taken at selected sites on Visit 1 (Baseline (Day1)) and Visit5 (Month 4) in all subjects.

14 STATISTICAL METHODS

14.1 Analysis Time Points

The primary analysis will be performed after the study is completed.

14.1.1 Primary Analysis

Descriptive summaries of the following efficacy and safety measures will be provided at the Month 4 visit:

- Mean change in BCVA from Baseline
- Proportion of subjects with BCVA: 1) gain of ≥15 ETDRS letters (3-line gainers); 2) gain of ≥10 ETDRS letters; 3) gain of ≥5 ETDRS letters and 4) ≥ 15 letter loss from Baseline at Month 4 are other secondary endpoints
- Change from Baseline in CST, and macular volume by SD-OCT
- Change from Baseline in characteristics of SHRM
- Change from Baseline in characteristics of fibrosis
- Proportion of subjects that do not require anti-VEGF treatment during follow-up period (including Month 5)
- Mean numbers of rescue injections in the monotherapy arm
- Proportion of subjects requiring rescue (including Month 5)

- Safety assessment include AEs, physical examination, vital signs, external ocular exam, BCVA, IOP, slit lamp biomicroscopy, indirect ophthalmoscopy, SD-OCT, fundus photography, fundus autofluorescence and pregnancy test
- Additional variables of interest will also be provided

14.2 General Considerations

All study parameters will be listed and a selected list of parameters will be summarized descriptively. 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).

All data manipulations and descriptive summaries will be implemented using SAS®, Version 9.1.3 or later.

14.2.1 Sample Size

Approximately 40 subjects with wet AMD will be enrolled at approximately 10 sites. Subjects that successfully exited TOFU study on or before approximately September 1, 2021 will be considered for RAMEN Study. The final number of subjects enrolled may be adjusted based on the judgments from Safety Review Team.

14.2.2 Statistical Hypotheses and Level of Significance

No statistical hypothesis is defined for this study.

14.2.3 Randomization

Randomization is not employed in this study due to the open-label design.

14.2.4 Study Eye

The study eye must meet all inclusion and exclusion criteria and must be the same as in TOFU study.

14.3 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.
- **Safety Population:** The Safety population will include all subjects who received at least one study medication. It will be the study population for safety analysis.
- **Full Analysis Set:** The Full Analysis Set (FAS) will include all subjects who received at least one study medication and provided at least one post-Baseline BCVA measurement. The efficacy analysis will be performed on the FAS or a subset of the FAS.

- **Per-Protocol Population:** The Per-Protocol (PP) Population is a subset of the FAS. It includes all FAS subjects without major protocol violations that could affect the primary efficacy endpoint.

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

14.5 Demographics and Baseline Characteristics

Age, sex, race, ethnicity, and Baseline assessments will be summarized descriptively.

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

Subjects using any prior medications will be tabulated, Anatomical Therapeutic Chemical levels, and preferred term specified in the World Health Organization WHODrug Global.

14.6 Efficacy Analyses

14.6.1 Analysis of Primary Efficacy Endpoints

- Mean change in BCVA from Baseline at Month 4 will be analyzed using descriptive statistics. Observed BCVA in the study eye will be presented descriptively and graphically by study visit.

The primary analysis will be based on the FAS and repeat analysis will be performed on the PP Population.

14.6.2 Analysis of Secondary Efficacy Endpoints

The following will be analyzed at Month 4:

- Proportion of subjects with BCVA: 1) gain of ≥15 ETDRS letters (3-line gainers); 2) gain of ≥10 ETDRS letters; 3) gain of ≥5 ETDRS letters and 4) ≥ 15 letter loss from Baseline
- Change from Baseline in CST, and macular volume by SD-OCT
- Change from Baseline in characteristics of SHRM
- Change from Baseline in characteristics of fibrosis
- Proportion of subjects that do not require anti-VEGF treatment during follow-up period (including Month 5)
- Mean numbers of rescue injections

- Proportion of subjects requiring rescue (including Month 5)

14.7 Safety Analysis

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include adverse events (AEs), external ocular exam, BCVA, slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP), vital signs, pregnancy test, physical examination, fundus photography, fundus autofluorescence, and SD-OCT.

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 ESIs 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.

15 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, eCRFs, recruitment materials and corresponding portions of the subject's medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness, and exactness of the data being entered onto the eCRF, and compliance with the FDA or other regulatory agency regulations.

15.1 Study Monitoring

Before an investigational site can enter a subject into the study, RIBOMIC or 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 with regard to 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 Good Clinical Practice (GCP).
- Perform investigational product accountability checks and quality control procedures.

- Ensure the on-going implementation of accurate data entry in the eCRF.
- Perform source data verification, including a comparison of the data in the eCRFs 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.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to RIBOMIC and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

RIBOMIC (or designee) may remotely access the eCRFs 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.

15.2 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, eCRFs, 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 eCRF 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.

15.3 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.

16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 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 eCRFs, 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 eCRFs, RIBOMIC (or designee) will

review and evaluate eCRF data and use standard system edits and may use centralized monitoring to detect errors in data collection.

16.2 Quality Assurance

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

17 ETHICS

17.1 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 Section 21.1 Appendix A 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 serious adverse drug reactions from the investigational product.

17.2 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.

17.3 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 IRB 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.

18 DATA HANDLING AND RECORDKEEPING

18.1 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, eCRFs, 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 eCRF data, and compliance with GCP guidelines and applicable regulatory requirements.

18.2 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.

18.2.1 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 USA Inc.
- 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

18.2.2 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 into eCRFs. Review of the eCRFs 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 eCRF against source documents at the study site. RIBOMIC (or designee) will review and evaluate eCRF 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 eCRFs will be sent to the site to be maintained as study records.

19 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.

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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21 APPENDICES

21.1 Appendix A - 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.
- Submitting the following records and reporting to the Sponsor.

I. Prior to the Beginning of the Study

- A current curriculum vitae (CV) if not submitted to RIBOMIC previously or if updated.
- CVs for all sub-Investigators.
- 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 medical 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, as well as documentation of all drug accountability.

21.2 Appendix B - Elements of Informed Consent

21.2.1 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.

1. State that the study involves RESEARCH.
2. Explain the PURPOSE of the research.
3. Trial treatments and the probability for random assignment to each treatment.
4. State the expected DURATION of the subject's participation.
5. Describe the PROCEDURES to be followed.
6. Identify any EXPERIMENTAL procedures.
7. Describe any reasonably foreseeable RISKS OR DISCOMFORTS to the subject.
8. Describe any BENEFITS to the subject and responsibility for the subject or to others that may reasonably be expected from the research.
9. Note appropriate ALTERNATIVE procedures or courses of treatment, if any, that might be advantageous to the subject.
10. 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.
11. 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.
12. 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.
13. State that:

    A. Participation is VOLUNTARY,

    B. Refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled

    C. The subject MAY DISCONTINUE participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

21.2.2 Additional Elements of Informed Consent

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

1. 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.
2. Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. 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.
6. 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.

21.3 Appendix C - Declaration of Helsinki

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

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 practice and 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 individuals 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

21.4 Appendix D - Procedures for Examinations

21.4.1 Demographics/Eligibility, Medical/Surgical History and Concomitant Medication

Demographics/Eligibility, medical/surgical history and concomitant medication will be obtained through subject interviews at Screening (Day -28 to Day -1). Medical history and concomitant medications will be obtained through subject interviews at each visit.

21.4.2 Physical Examination

A full body systematic physical examination will be conducted during Visit1 (Baseline (Day1)). 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, neck, thyroid, ears, nose, throat, mouth, tongue, respiratory, cardiovascular, abdomen, and neurological.

The Clinical Investigator will assess subject's overall condition to determine qualification for study entry considering possible class effects of RBM-007.

21.4.3 Vital Signs

Blood pressure and heart rate will be measured at Visit 0/Screening (Day - 28 to Day -1) 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).

In accordance with the recommendations of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (US_Dept_Health_and_Human_Services, 2004), the following measurement procedure will be used to measure vital signs:

- Subject should not smoke or ingest caffeine within the 30-minute period immediately before the measurement.
- 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.

21.4.4 Urine Pregnancy Test

A urine pregnancy test will be conducted before IVT injection at *Visit 1 (Baseline (Day 1))* and Visit 6 for all females of childbearing potential. A female is considered of childbearing potential unless she is postmenopausal (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 obtain the pregnancy test, the subject should follow instructions provided by the manufacturer of the urine pregnancy test kit.

21.4.5 Best Corrected Visual Acuity

ETDRS chart will be used to examine and record BCVA at each study visit.

21.4.6 External Ocular Examination

External ocular examination will be done evaluating lid and lashes as normal and abnormal with notes if abnormal.

21.4.7 Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be used to examine eye structures at each study visit. Slit-lamp biomicroscopy will be performed prior to the injection and then again within 30 minutes after the injection. This will be also applied for the post IVT injection of Rescue treatment. The conjunctiva, cornea, and lens will be observed with the slit-lamp beam approximately 0.3 mm in width and 1.0 mm in length. Conjunctiva, Sclera and Cornea will be described as normal / abnormal with notes if abnormal.

Lens

The lens will be noted as normal/abnormal, phakic, aphakic, or pseudophakic. Phakic lens will be graded for cataract as nuclear, posterior subcapsular, and cortical as described below:

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

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 (Sun Working, 2005). The iris and the pupil will be evaluated for the presence of clinically significant abnormalities.

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) = Fain

(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.

21.4.8 Intraocular Pressure

IOP will be measured by applanation tonometry at each study visit. Procedures in each visit are described in Section 7.5.1.

For Rescue IVT injection, IOP will be measured as follows:

- IOP will be measured at 30 (±10) minutes post-injection.
- If post-injection IOP is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 60 (±10) minutes post-injection.
- If post-injection IOP at 60 (±10) minutes is > 21 mmHg after eye massage and/or aqueous tap performed per investigator discretion, IOP measurement will be repeated at 90 (±10) minutes post-injection.
- If there is an increase of ≥ 10 mmHg at 90 (±10) minutes post-injection compared to pre-injection IOP, the subject should 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).
- On the other hand, a subject with IOP measurement of > 21 mmHg will be managed according to the discretion of the Clinical Investigator.
- The IOP increase of ≥ 10 mmHg from pre-injection AND IOP measurement of > 21 mmHg will be reported as an AE.

• Aqueous tap can be performed at any time per the Clinical Investigator`s discretion for treatment or prevention of increasing in the IOP.

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 following IOP measurement procedure is in accordance with the procedure used in the Ocular Hypertension Treatment Study (Gordon et al., 2001) at each visit:

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 eCRFs.

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

21.4.9 Indirect Ophthalmoscopy

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

Indirect ophthalmoscopy will be used to examine the retina at each study visit. Indirect ophthalmoscopy will be performed prior to the injection and then again within 30 minutes after the injection. Areas to be assessed include cup to disc ratio, peripheral retina, macula, choroid, and vitreous. This will be also applied for the post IVT injection of Rescue treatment.

Cup/Disc Ratio

The cup/disc ratio will be determined by the examiner and recorded using two decimal places (e.g., 0.80).

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.

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

21.4.10Spectral Domain Optical Coherence Tomography

Spectralis, Cirrus or 3D OCT will be utilized to take optical images at each study visit. The images may be stored in the Egnyte server and sent to the central reading center at a later date at Sponsor discretion.

21.4.11Optical Coherence Tomography Angiography

OCT Angiography images will be taken at selected sites at study Visit 1 (Baseline Day1) and Visit 5 (Month 4) in all subjects. The images may be stored in the Egnyte server.

21.4.12Fundus Photography

Digital color fundus photography will be taken at each study visit. The images may be stored in the Egnyte server and sent to the central reading center at a later date at Sponsor discretion.

21.4.13Fundus Autofluorescence

Fundus autofluorescence will be performed at Visit 1 (Baseline (Day 1)) and Visit 5 (Month 4). The images may be stored in the Egnyte server and sent to the central reading center at a later date at Sponsor discretion.