Cover Page for Protocol

NCT04895293

Title: Evaluation of RBM-007 in subjects with treatment naïve exudative age-related macular degeneration (TEMPURA Study)

Study: RKM-011

Date: 11 April 2021

Statistical plans contained within protocol

Clinical Study Protocol
RKM-011

Evaluation of RBM-007 in subjects with treatment naïve exudative age-related macular degeneration

Protocol Number:	RKM-011
Investigational Product:	RBM-007 Injectable Solution
Indication:	Treatment of exudative age-related macular degeneration
Phase:	Phase 2
Sponsor:	Raj K. Maturi, M.D., P.C. [redacted] Phone [redacted]
Medical Monitor	Raj K. Maturi, M.D., P.C.
Protocol Date:	11 April 2021
Protocol Version:	Initial
Replaces:	N/A/

Contact Information and Protocol Authorization

Clinical Study Protocol

RKM-011
Phase 2

Protocol Title: Evaluation of RBM-007 in subjects with treatment naïve exudative age-related macular degeneration

Protocol Number: **RKM-011**

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory:

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Raj K. Maturi, M.D., P.C.

_____
Date:

TABLE OF CONTENTS

1 Protocol Summary

Study Compound: RBM-007

Phase: 2

Study Objective: To determine safety and efficacy of intravitreal injections of RBM-007 in subjects with treatment naïve exudative AMD in the study eye.

Clinical Hypothesis: RBM-007, as used in previous trials of neovascular AMD, has shown an improvement in vision as well as an improvement in subretinal fibrosis in a cohort of subjects with chronic wet AMD. The mechanism of action of RBM-007 is distinct from that of Anti-VEGF treatments. RBM-007 has a powerful fibroblast growth factor-2 inhibition which serves to reduce both VEGF expression as well as inhibit FGF based neovascular response and fibroblast-proliferation. Having both mechanisms of action active early in the disease process will reduce the development of fibrosis in naïve wet-AMD subjects and potentially provide an improved and sustained visual function and favorable anatomic change.

Structure: Single site, open label study

Duration: 4 months

Study Treatment group:

- RBM-007 treatment at baseline, month 1and month 2. Safety evaluations at week 2, months 3 and 4.

Randomization: all study subjects will receive study drug and those non-responsive to study drug will be treated with rescue anti-VEGF drug, in addition to continuing RBM-007

Visit Schedule:

There will be 6 scheduled visits during the study. These include baseline (Day 0), week 2, and months 1, 2,3, 4/exit.

Primary endpoint one month after the last RBM-007 injection (month 3)

Study Population Characteristics

Number of subjects: Up to 5 subjects will be enrolled

Condition/Disease: Naïve exudative Age-Related Macular Degeneration with associated visual loss.

Key Inclusion Criteria:

- Aged 50 or older, diagnosed with exudative AMD.
- BCVA 5-73, inclusive, in study eye
- Presence of choroidal neovascularization (CNV) secondary to AMD, in study eye

Key Exclusion Criteria:

- History of major ophthalmic surgery in the past 3 months, and any ophthalmic surgery in study eye in the last 30 days
- History of significant ocular disease other than exudative AMD that many confound results
- Hypersensitivity to components of study medication

Response Measures

Efficacy:

- Change in BCVA from baseline to month 3
- Change in intraretinal and subretinal fluid from baseline to month 3, as measured by CST on Heidelberg OCT
- Change in OCT-angiography in study eye from baseline to month 3
- Number of subjects escaping to standard of care
- Change in measured area of intraretinal/subretinal fibrosis

Safety: adverse events, BCVA, complete ophthalmic examination, physical examination and vital signs.

All adverse events and serious adverse events will be continually assessed throughout the study. The investigator will assess safety throughout the study to determine appropriateness of continuing dosing and enrollment.

General Statistical methods and Types of Analyses:

The primary efficacy endpoint is:

- Change in edema from baseline to month 3 (one month after the last injection) as measured by CST on Heidelberg OCT

Secondary endpoints include the following:

- Change in BCVA from baseline to month 3
- Change in intraretinal and subretinal edema from baseline to month 3
- CNV lesions components: subretinal hyper-reflective material (SRHM), PED thickness
- Number of subjects escaping to standard of care treatment
- Change in size of OCT-angiography leakage from baseline to month 3

2 Background and Clinical Rationale

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people over the age of 65 in the United States.[1] The majority of severe vision loss due to advanced AMD is related to the onset of choroidal neovascularization (CNV).[2,3] Neovascular AMD is characterized by the growth of choroidal vessels into the subretinal space. These vessels have a tendency to leak fluid and blood, causing retinal edema and central vision loss.

The CATT study data demonstrates that it is difficult to achieve anatomic flattening of the macula in patients with neovascular AMD.[4] After one year of required monthly treatment in both the bevacizumab and ranibizumab groups, approximately 50% of subjects continued to have intraretinal and/or subretinal fluid on optical coherence tomography.[4] When fluid is present in these structures, retreatment is generally necessary to stabilize vision – and subjects with persistent fluid generally have poorer visual gain. RBM-007 has shown, in a previous clinical trial (see attached SUSHI Study CSR) evidence of bioactivity, reducing macular edema associated with choroidal neovascularization in wet AMD. Additionally, the mechanism of action of RBM-007 is more expansive than that of Anti-VEGF treatment alone as RBM-007, a novel oligonucleotide-based aptamer, has potent anti-FGF2 activity, which leads to reduced VEGF expression.[5,6] In the rat and mouse models of laser-induced choroidal neovascularization, RBM-007 showed activity after intravitreal injection at doses as low as 5 μg/eye[7]. In the laser-induced choroidal neovascularization fibrosis model in rats, it showed activity after intravitreal injection at doses as low as 15 μg/eye[7] (see Ribomic Investigator Brochure for RBM-007, 2020).

3 Study Objectives

To determine safety and efficacy of intravitreal injections of RBM-007 in subjects with naïve exudative AMD.

4 Study Design

This study is a single-center, open label, 4-month study, designed to evaluate the safety and treatment efficacy of RBM-007 in patients with intraretinal or subretinal edema due to previously untreated neovascular AMD. Up to 5 subjects will be randomized to receive study medication. Study treatment will be administered by intravitreal injections.

There will be 5 scheduled visits during the study. See table 1.

5 Study Population and Entry Criteria

5.1 Number of Subjects:

5

Study Population Characteristics: If both eyes meet all of the inclusion/exclusion criteria the eye with the worse BCVA at baseline will be selected as the study eye. If both eyes meet all of the

inclusion/exclusion criteria and BCVA values are identical for both eyes, the right eye will be selected as the study eye.

5.2 Inclusion Criteria:

- **General Inclusion Criteria:**
  1. Male or female patients, 50 years of age or older at baseline
  2. Patient has completed/signed an informed consent prior to any study-related procedures and is able to follow study instructions and likely to complete all required visits.

- **Ocular Inclusion Criteria:**
  3. BCVA 5 – 73 ETDRS letters (20/800-20/40 Snellen equivalent), inclusive, in study eye
  4. Presence of choroidal neovascularization secondary to AMD
  5. Clear ocular media and adequate pupil dilation to permit good quality photographic imaging.

5.3 Exclusion Criteria:

- **General Exclusion Criteria:**
  1. Females who are pregnant, nursing, planning a pregnancy or who are of childbearing potential not using a reliable method of contraception.
  2. History or current evidence of hypersensitivity to any components of the study medication or fluorescein, as assessed by the investigator.
  3. Participation in any investigational drug or device study within 30 days prior to baseline
  4. History or current evidence of a medical condition that may, in the opinion of the investigator, preclude the safe administration of study medication or affect the results of the study.

- **Ocular Exclusion Criteria:**
  5. Active ocular or periocular infections, malignancy
  6. Aphakia
  7. History of pars plana vitrectomy in the study eye
  8. History of major ophthalmic surgery in the past 3 months in the study eye, or minor surgery in the past 30 days
  9. History of significant ocular disease other than exudative AMD that may confound results
  10. Uncontrolled glaucoma (defined as intraocular pressure >21mm Hg despite treatment with ocular hypotensive medications at baseline).

5.4 Permissible Medications/Treatments:

- Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. Therapies for the non-study eye are permissible at any time.

5.5 Prohibited Medications/Treatments:

Systemic anti-VEGF medications, or systemic anti-fibroblast growth factor mediations.

6 Escape Criteria/ Medications

6.1 Escape Criteria:

- Subjects with a 10 letter decrease at two consecutive visits or a 15 letter decrease at any visit may be escaped to standard of care.
- Central retinal thickness increase by 50 μm or more associated with at least a 5-letter decrease may be escaped to standard of care
- Presence of new hemorrhage, worsening hemorrhage, new extra foveal fluid, or at the discretion of the investigator.
- **Note:** Subjects that escape to standard of care will continue to be followed for safety through the four-month study period.

6.2 Escape Medications:

- Subjects that escape to standard of care may receive treatment with medications at the investigator's discretion, which in most cases would be an intravitreal Anti-VEGF drug (Eylea, or another drug as determined by the investigator).

7 Study Treatment

RBM-007 injectable solutions (20 mg/mL) 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. Three single use vials will be placed in a carton, and the labeling will include protocol number, kit number, drug concentration and storage conditions. RBM-007 injectable solutions will be provided by RIBOMIC/Representative and will be stored in an appropriate secure area at the investigational site. RBM-007 vials should be protected from light, stored upright, and kept at -20°C.

7.1 Randomization:

Not applicable for this open-label, single-treatment study.

7.2 Administration

Once investigational drug kit numbers have been assigned to the subject, the vial of investigational drug with the assigned kit number will be removed from the freezer. The contents should be thawed by rotating the vials between the palms of the hands, or by setting the vial at room temperature. Care should be taken to protect the product from light.
Investigational drug should be used for intravitreal injection in the study subject within 1 hour after removing the vial from the freezer.

Study drug preparation should be performed by the designated 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 injection, vials should be placed in the plastic bag provided by the sponsor, write the subject number and kit number clearly and robustly using a permanent marker, seal and store the bag in a secure area.

7.3 Investigational drug: RBM-007:

Loading the syringe

1. A sterile, single-use 250 µL syringe with several custom marking 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.
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.
6. Ensure that the 30-gauge x 0.5-inch needle is affixed tightly to the syringe.
7. 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.
8. 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.

8 Safety Measures

Safety measures include the following:

- adverse events recording
- BCVA
- complete ophthalmic exam (consisting of an external examination of the eye, routine screening for eyelid/pupil responsiveness, confrontation visual field, slit-lamp biomicroscopy, dilated fundus exam and IOP measurement)
- vital signs (blood pressure and pulse rate) and general physical examination
- optical coherence tomography (OCT), with OCT-A determination
- Fluorescein angiography
- Fundus autofluorescence

9 Adverse Events

All adverse events throughout the course of the study will be monitored and reported on the adverse event form including seriousness, severity, action taken and relationship to study drug. If adverse events occur, the first concern will be the safety of the study participants. For serious adverse events, the participant will be followed until the event has been resolved or deemed medically stable by the investigator.

If a female of childbearing potential becomes pregnant during the study, the subject will be exited from the study. The investigator will notify the subject's physician that the subject has been treated with RBM-007 and will follow the progress of the pregnancy. The investigator will document the outcome of the pregnancy.

10 Method of Analysis

The analysis of data from the study will be performed when all subjects have either completed the visit at Month 4 or discontinued early from the study. Once all of data through Month 4 have been cleaned, verified, and placed in the database, it will be transferred to the personnel performing the analysis.

10.1 General Data Summaries

Continuous variables will be summarized with means and standard deviations and medians with min and max values and categorical variables with frequencies and percentages. Standard parameters and statistical tests will be performed to evaluate for the primary and secondary end points. Specifically, mean change in the CST, manual determination for the presence of subretinal fluid and intraretinal fluid at month three (and at other time points), change in BCVA between baseline and month three, and the number of anti-VEGF injections needed will be measured. Based on the results of these tests, additional testing, as outlined below, may be performed.

10.2 Efficacy evaluation

Descriptive statistics will be performed on all subjects with special care taken to carefully analyze the change in OCT-A, OCT determined macular thickness, visual acuity (BCVA), fundus autofluorescence and fluorescein angiography. All subjects randomized (ITT population) will be included in the analysis, and subjects will be grouped according to the number of study treatments received (if less than 3). Safety parameters will be evaluated in the patient population.

11 Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the schedule of visits and procedures. The visit schedule includes 5 scheduled visits: baseline, month 1, 2, 3, and 4.

<u>*Baseline visit*</u>*:*

- obtain informed consent and authorization
- collect demographic information and medical and ophthalmic history
- collect information about concomitant medication and procedures
- physical examination
- vital signs (blood pressure and pulse rate)
- Pregnancy Test (if indicated)

Perform the following procedures in both eyes:

- standard BCVA, using ETDRS method following refraction

- complete ophthalmic examination: slit-lamp biomicroscopy, indirect ophthalmoscopy and IOP
- Heidelberg OCT imaging
- Angiovue OCT-A imaging
- dilated fundus photography (Heidelberg)
- fluorescein angiography (Heidelberg)
- autofluorescence fundus photography (Heidelberg)
- confirm eligibility
- perform intravitreal injection in study eye (treat fellow eye as standard of care, as indicated)
- query for adverse evets

Week 2 Safety Assessment Visit

- query for adverse events
- query for medication changes and medical procedures
- if rescue criteria met, treat with anti-VEGF at this visit.

Perform the following procedures in both eyes:

- standard BCVA, using ETDRS method following refraction
- complete ophthalmic examination: slit-lamp biomicroscopy, indirect ophthalmoscopy and IOP
- Heidelberg OCT imaging
- Angiovue OCT-A imaging

Month 1, and 2 visits

- query for adverse events
- query for medication changes and medical procedures
- if rescue criteria met, treat with RBM-007 then, standard of care anti-VEGF at that visit. An anterior chamber paracentesis will be performed at the visit as well for intraocular pressure control. Treatment with RBM-007 may be withheld per investigator discretion.

Perform the following procedures in both eyes:

- standard BCVA, using ETDRS method following refraction
- complete ophthalmic examination: slit-lamp biomicroscopy, indirect ophthalmoscopy and IOP
- Heidelberg OCT imaging
- Angiovue OCT-A imaging
- dilated fundus photography (Heidelberg)
- Perform assigned intravitreal injection per protocol in study eye

Month 3 visit: (primary endpoint)

- query for adverse events
- query for medication changes and medical procedures

Perform the following procedures in both eyes

- standard BCVA, using ETDRS method following refraction
- complete ophthalmic examination: slit-lamp biomicroscopy, indirect ophthalmoscopy and IOP

- Heidelberg OCT imaging
- Angiovue OCT-A imaging
- dilated fundus photography (Heidelberg)
- autofluorescence fundus photography (Heidelberg)

Month 4 (exit):
- query for adverse events
- query for medication changes and medical procedures
- vital signs (blood pressure and pulse rate)
- physical examination
- Pregnancy Test (if indicated)

Perform the following procedures in both eyes:
- standard BCVA, using ETDRS method following refraction
- complete ophthalmic examination: slit-lamp biomicroscopy, indirect ophthalmoscopy and IOP
- Heidelberg OCT imaging
- Angiovue OCT-A imaging
- fluorescein angiography (Heidelberg)
- dilated fundus photography (Heidelberg)
- autofluorescence fundus photography (Heidelberg)

Unscheduled visits:
Additional examinations may be performed at the investigator's discretion to ensure the safety and well-being of the subject during the study.

12 Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines.

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study.

This study is to be conducted in accordance with IRB regulations. The investigator will obtain approval from a properly constituted IRB prior to initiating the study and re-approval or review at least annually.

13 References

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2. Ferris FL 3rd. Senile macular degeneration: review of epidemiologic features. Am J Epidemiol. 1983;118(2)132-151.
3. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt JC et al. Racial differences in the cause-specific prevalence of blindness in East Baltimore. N Engl J Med. 1991;14(20):1412-1417.
4. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. 5-Year Outcomes with Anti-VEGF Treatment of Neovascular Age-related Macular Degeneration (AMD): The Comparison of AMD Treatments Trials. Ophthalmology. 2016 August; 123(8): 1751–1761.
5. Jin L, Nonaka Y, Miyakawa S, Fujiwara M, Nakamura Y. Dual Therapeutic Action of a Neutralizing Anti-FGF2 Aptamer in Bone Disease and Bone Cancer Pain. Mol Ther 2016; 24:1974-86.
6. Belgore F, Lip GYH, Blann AD. Basic fibroblast growth factor induces the secretion of vascular endothelial growth factor by human aortic smooth muscle cells but not by endothelial cells. European Journal of Clinical Investigation 2003; 33:833-839.
7. Matsuda Y, Nonaka Y, Satoshi Futakawa, et al. Anti-Angiogenic and Anti-Scarring Dual Action of an Anti-Fibroblast Growth Factor 2 Aptamer in Animal Models of Retinal Disease. Mol Ther 2019; 17: 819-832.

Investigator Brochure for RBM-007 Injectable Solution (Ribomic USA, Version 3.0, 9 September 2020).

Appendix A: Injection Procedure for All Subjects

The following procedures will be implemented to minimize the risk of potential adverse events associated with serial intravitreal injections. Aseptic technique will be observed by clinic staff involved in the anesthetic preparation, study drug preparation and administration.
Assemble the supplies. Supplies include gloves, eyelid speculum, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, ophthalmic antimicrobial solution and injection supplies.

Instill at least 2 drops of 0.5% proparacaine into the study eye.

The investigator will glove. Optional: place a speculum underneath the eyelids of the study eye.

Instill 2 drops of 5% povidone iodine ophthalmic solution in the study eye, making sure the drops cover the planned injection site on the conjunctiva. Wait 15-30 seconds.

Investigator performs intravitreal injection of RBM-007 into study eye.

Remove lid speculum (if placed) and irrigate eye with eyewash solution.

Instruct subject verbally on post injection instructions including signs of infection.

Confirm vision is at least hand motions before subject leaves the clinic.

Study Drug Storage

RBM-007 will be received frozen. RBM-007 must be stored and should remain frozen in a secure, locked, dark, temperature-controlled freezer at -20 ºC with restricted access.

Study Drug Preparation

The vial of study drug will be removed from the freezer and 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.
A sterile, single-use 250 µL syringe custom marked at 100 µL will be provided separately for intravitreal injection use. Study drug should be drawn into the provided single-use plastic syringe. Use separate needles for drawing and injecting the study drug. Study drug should be used for intravitreal injection in the study subject within 1 hour after removing the vial from the freezer.
Each vial contains enough study drug to inject one subject. Each vial will be used one time only.

Method of administration

Pre-injection antibiotic eye drops may be administered at the discretion of the treating doctor.

Proper aseptic injection techniques must always be used when administering RBM-007. which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, a sterile eyelid speculum (or equivalent). The periocular skin, eyelid and ocular surface should be disinfected and adequately anesthetized, and a broad-spectrum topical microbicide should be administered prior to the injection according to standard medical practice.

Inferior temporal injection site is recommended. The intravitreal injection site may be modified at the physician's discretion. The injection needle should be inserted 3.5-4.0 mm posterior to the limbus aiming towards the center of the globe, avoiding the horizontal meridian. Care should be taken to avoid injecting RBM-007 into the visual axis. The injection volume of 0.1 mL is then delivered. A different scleral site should be used with each subsequent injection.

Post-injection antibiotic eye drops may be administered at the discretion of the treating doctor

Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately after injection. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs.

Table 1: Schedule of Visits and Events

Procedure	Baseline	Week 2 (± 7days)	Month 1 (± 7days)	Month 2 (± 7days)	Month 3 (± 7days)	Month 4 (± 7days)
Informed consent	X					
Inclusion/exclusion	X					
Demographics	X					
Pregnancy Test[1]	X					X
Vital signs	X					X
Med/Ophthalmic History	X					
AE query	X	X	X	X	X	X
Con meds/proc	X	X	X	X	X	X
BCVA & IOP	X	X	X	X	X	X
Biomicroscopy w/lens grading	X	X	X	X	X	X
Indirect Ophthalmoscopy	X	X	X	X	X	X
Heidelberg-OCT	X	X	X	X	X	X
Optovue OCT-A	X	X	X	X	X	X
Fluorescein Angiography	X					X
Fundus Photos	X		X	X	X	X
Autofluorescence Fundus Photography	X				X	X
Physical Examination	X					X
RBM-007 injection	X		X	X		
Injection of Anti-VEGF agent (SOC + Anterior chamber paracentesis) [1]		X	X	X	X	X

[1] If indicated