PROTOCOL

STUDY TITLE:	Sirolimus in Conjunction with EYLEA® (aflibercept) versus EYLEA® Alone for Exudative AMD
PROTOCOL NUMBER:	RKM 009
STUDY DRUG:	Sirolimus
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Study Compound: Sirolimus

Phase: 2

Study Objective: To determine safety and efficacy of intravitreal injections of Sirolimus in subjects with exudative AMD with persistent intraretinal or subretinal edema due to neovascular AMD despite previous intravitreal Anti-VEGF treatment.

Clinical Hypothesis: Intravitreal Sirolimus, as used in the uveitis and diabetic trials, has shown to be long lasting and to significantly reduce macular edema. Additionally, the mechanism of action of intravitreal Sirolimus is distinct from that of Anti-VEGF treatment. Thus, there may be an additive effect on anatomic improvement when subjects with persistent edema despite previous Anti-VEGF treatment are exposed to Sirolimus and Eylea.

Study Design:

Structure: Single site, randomized, subject-masked study

Duration: 36 weeks

Study Treatment (Group 1):

- Intravitreal Sirolimus at baseline, week 4, 12, 20 and 28. EYLEA® (aflibercept) at week 1, 8, 16, 24 and 32
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Comparator (Group 2):

- Intravitreal EYLEA® (aflibercept) at baseline, week 8, 16, 24, and 32. Sham injection at week 1, 4, 12, 20 and 28.

Randomization: Subjects will be randomized to receive study medication in a 1:1 ratio.

Visit Schedule:

There will be 11 scheduled visits during the study. These include baseline (Day 0), week 1, 4, 8, 12, 16, 20, 24, 28, 32 and 36 (exit).

Study Population Characteristics

Number of subjects: 20 subjects will be randomized

Condition/Disease: Exudative Age-Related Macular Degeneration with Persistent Edema despite previous intravitreal Anti-VEGF treatment.

Key Inclusion Criteria:

- One eye will be selected and treated as the study eye. If both eyes are eligible, the eye with the best potential visual improvement as determined by the investigator will be selected for treatment.
- BCVA 5-75, inclusive, in study eye
- Presence of choroidal neovascularization (CNV) secondary to AMD
- Persistent fluid despite at least 3 previous intravitreal anti-VEGF injections in the past 6 months
- Injection of Anti-VEGF may be deferred for at least 4 weeks from randomization based on clinical assessment of AMD by the investigator.

Key Exclusion Criteria:

- Greater than 100 micron decrease in central subfield thickness on OCT since last standard of care visit
- History of major ophthalmic surgery in the study eye in the past 3 months and any ophthalmic surgery in the past 30 days.
- History of significant ocular disease or condition other than exudative AMD that may confound results
- Presence of significant epiretinal membrane
- Significant vitreoretinal traction
- Hypersensitivity to components of study medication

Response Measures

Efficacy:

- Change in intraretinal and subretinal fluid from baseline to week 36, as measured by CST on Heidelberg OCT
- Percent of subjects in each group found to be without intraretinal and/or subretinal fluid at week 36.
- Change in BCVA from baseline to week 36
- Number of treatments required to control CNV

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 week 36 as measured by CST on Heidelberg OCT

Secondary endpoints include the following:

- Change in BCVA from baseline to week 36
- Change in intraretinal and subretinal edema from baseline to week 36
- CNV lesions components: subretinal retinal hyper-reflective material (SRHM), PED thickness,
- Number of injections required to control CNV based on volume of subretinal fluid.

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1. 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. 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. When fluid is present in these structures, retreatment is generally necessary to stabilize vision – and subjects with persistent fluid generally have poorer visual gain. Intravitreal Sirolimus has shown to be long lasting and significantly reduce macular edema associated with uveitis and diabetic disease. Additionally, the mechanism of action of intravitreal Sirolimus is distinct from that of Anti-VEGF treatment as Sirolimus targets mTOR. This results in a number of biochemical anti-angiogenic effects that include modulation of kinase function, TOR, FKBP12 binding and ultimate regulation of cell cycle progression as well as inhibition of HOF, and VEGF production. Thus, there may be an additive or synergistic effect on anatomic improvement when subjects with persistent edema despite previous Anti-VEGF treatment are exposed to intravitreal Sirolimus.

Eylea is an anti-VEGF drug whose mechanism of action is to bind (trap) free VEGF-A. As VEGF-A is known to promote vascular growth, this treatment decreases the risk of choroidal neovascularization (CNV). EYLEA® is an approved drug for AMD and its recommended dose is every 8 wks (2mg/0.05 cc), after the first three doses of Anti-VEGF. The control/sham arm is receiving this drug at the recommended dosage. Since the inclusion criteria in the study requires at least 3 previous doses of anti-VEGF, the subjects would thus fall under this criteria.

2. Study Objectives

To determine safety and efficacy of intravitreal injections of Sirolimus with adjunct EYLEA® (aflibercept) in subjects with exudative AMD with persistent intraretinal or subretinal edema due to neovascular AMD versus treatment with EYLEA® (aflibercept) alone.

3. Study Design

This study is a single-center, masked, randomized, 36 week study, designed to evaluate the safety and treatment efficacy of intravitreal Sirolimus with adjunct EYLEA® (aflibercept) in patients with persistent edema due to neovascular AMD versus EYLEA® (aflibercept) alone. Twenty (20) patients will be randomized to receive study medication in a 1:1 ratio. Study treatment will be administered by intravitreal injections. The sham injections given in the EYLEA® alone group are needleless and they are given in order to help preserve the masking of those subjects in that treatment group.

There will be 11 possible scheduled visits during the study. See table 1.

4. Study Population and Entry Criteria

Number of Subjects: 20

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 eye with the best potential visual improvement as determined by the investigator will be selected for treatment.

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 (Study eye only):**
  3. BCVA 5 – 75 (20/800-20/30), inclusive, in study eye; if both eyes are eligible, the eye with the best potential visual improvement as determined by the investigator will be selected for treatment.
  4. Presence of choroidal neovascularization secondary to AMD
  5. At least 3 previous intravitreal anti-VEGF injections in the past 6 months
  6. Injection of Anti-VEGF may be deferred for at least 4 weeks from randomization based on clinical assessment of AMD by the investigator.
  7. Clear ocular media and adequate pupil dilation to permit good quality photographic imaging.

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 (Study eye only):**
  5. Decrease of greater than 150 microns in central subfield thickness as measured by OCT since the last intravitreal injection in the study eye
  6. Aphakia
  7. History of pars plana vitrectomy in the study eye

8. History of major ophthalmic surgery in the study eye in the past 3 months and any ophthalmic surgery in the study eye within the past 30 days
9. History of significant ocular disease or condition other than exudative AMD that may confound results
10. Uncontrolled glaucoma (defined as intraocular pressure >21mm Hg despite treatment with two or more ocular hypotensive medications at baseline)
11. No active ocular or periocular infections, or ocular malignancy including lymphoma
12. Presence of significant epiretinal membrane
13. Significant vitreoretinal traction

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.

Prohibited Medications/Treatments:

- Systemic anti-VEGF medications

5. Study Treatment

Group 1: Sirolimus 440ug for intravitreal injection will be provided by Santen in sterile single-use glass vials. One single-dose vial will be packaged in a box for each patient injection. Sirolimus injections will be given at baseline, week 4, 12, 20 and 28. EYLEA® (aflibercept) intravitreal injections will be given at week 1, 8, 16, 24 and 32.

Group 2: Intravitreal injection of EYLEA® (aflibercept) will be given at baseline, week 8, 16, 24 and 32. Sham injections will be given at week 1, 4, 12, 20, and 28 in order to maintain masking of patient to treatment assignment

Treatment Allocation Ratio: Subjects will be randomized to receive study medication in a 1:1 ratio.

Randomization: Prior to the start of the study non-study related personnel will prepare a set of sealed envelopes containing randomization assignments.

Administration: Subjects have a +/- 1 week window for visit. See Appendix A for detailed injection procedure.

Retreatment Criteria:
Subjects in both treatment groups will receive retreatment (or sham) at each scheduled visit as long as continued subretinal edema, intraretinal edema or active CNV is present.

6. Rescue Criteria/ Medications

Rescue Criteria:

- Subjects in either group 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 um 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 may be grounds for escape at the discretion of the investigator.
- Any other reason, at the discretion of the investigator

- **Note:** Subjects that escape to standard of care will continue to be followed for safety through week 36.

Rescue Medications:

- Subjects that escape to standard of care may receive treatment with medications at the investigator's discretion.

7. Safety Measures

Safety measures include the following:

- adverse events
- BCVA
- complete ophthalmic exam (consisting of an external examination of the eye, routine screening for eyelid/pupil responsiveness, , slit-lamp biomicroscopy, dilated fundus exam and IOP measurement)
- vital signs (blood pressure and pulse rate) and targeted physical examination
- optical coherence tomography (Heidelberg OCT)

8. 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 (SAEs), the participant will be followed until the event has been resolved or deemed medically stable by the investigator. SAEs will be reported to regulatory agencies as per their reporting requirements, including the FDA and IRB.

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 intravitreal Sirolimus or Anti-VEGF medication and will follow the progress of the pregnancy. The investigator will document the outcome of the pregnancy.

Other safety information to be reported includes medication errors, overdose, exposure to infants via breast milk, suspected observed or confirmed quality defect (medicinal product or provided syringe and needle)

9. Method of Analysis

The analysis of data from the study will be performed when all subjects have either completed the study at week 36 or discontinued early from the study. Once all of data through week 36 have been cleaned, verified, and placed in the database, it will be transferred to the personnel performing the analysis and unmasked.

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 in each group at week 36 (and at other time points), change in BCVA between baseline and week 36, and the number of anti-VEGF injections needed in each group will be measured. Based on the results of these tests, additional testing, as outlined below, may be performed.

Efficacy evaluation
Univariate Analysis: These will be exploratory in nature since they will be eye-specific with no correction for correlation between eyes. However the findings will aid in deciding which demographic/clinical covariates to include in the final multivariate model for each of the primary or secondary outcomes. Testing between randomization groups in difference of overall (and by subgroups) for week 36 mean change of VA and OCT central subfield thickness, will rely on both the parametric t-test and/or nonparametric Wilcoxon test. Similar univariate testing will also be conducted for other continuous secondary outcome measures (e.g., IOP change). Group testing of categorized outcomes (e.g., VA groups; change by more than 10 or 15 letters) will rely on Chi-square/Fisher exact methods.

Multivariate analysis: These will rely on constructing a model exploiting the generalized linear mixed techniques which encompasses a multitude of types of outcomes (binary, categorical and continuous).. For continuous outcomes the model will rely on specifying the distribution of the response (Gaussian or non-Gaussian). For binary (e.g., change by more than 10 or 15 letters) or categorical outcomes, the model will use the binary or polytomous logistic regression methods. Analysis will be performed using Procedure GLIMMIX in SAS version 9.3. All statistical tests will utilize an overall significance level of 0.05. To allow for subgroup testing (e.g., phakic and pseudophakic), interaction terms will be included in these models and adjustment for multiple comparisons will be sought. Additional analysis using Kaplan Meier and Cox Proportional Hazard model techniques will also be explored for the outcome of time to ten/fifteen letter improvement of BCVA by ETDRS. Area under curve analysis of visual acuity change, retinal volume, amount of intraretinal and subretinal fluid, and OCT CST between baseline and week 36, will be evaluated using either logistic regression principles or other linear models.

Analysis of the primary and secondary efficacy endpoints will be based on the intent-to-treat (ITT) approach. For those subjects exiting study, we will perform LOCF for both groups.

All sub
jects randomized (ITT population) will be included in the analysis, and subjects will be grouped according to their randomized treatment. Safety parameters will be evaluated in the patient population of all randomized patients.

10. Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the schedule of visits and procedures. The visit schedule includes 11 possible scheduled visits: baseline, week 1, 4, 8, 12, 16, 20, 24, 28, 32 and 36.

Baseline visit:

- obtain informed consent and authorization
- collect demographic information and medical and ophthalmic history
- collect information about concomitant medication and procedures
- targeted physical examination
- vital signs (blood pressure and pulse rate)
- pregnancy test for women of childbearing potential

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
- dilated fundus photography
- Heidelberg fluorescein angiography

Confirm eligibility and randomize
Perform assigned intravitreal injection.

Week 1 visit:

- query for adverse events
- query for medication changes and medical procedures
- standard BCVA, using ETDRS method following refraction, study eye only
- complete ophthalmic examination: slit-lamp biomicroscopy, indirect ophthalmoscopy and IOP, study eye only
- Heidelberg OCT imaging, study eye only
- Perform assigned intravitreal injection (or sham).

Week 4, 8, 12, 16, 20, 24, 28, and 32:

- query for adverse events
- query for medication changes and medical procedures
- Pregnancy test for women of childbearing potential

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

Perform assigned intravitreal injection per protocol (or sham).

Week 36:

- query for adverse events
- query for medication changes and medical procedures
- vital signs (blood pressure and pulse rate)
- Pregnancy test for women of childbearing potential
- Targeted physical examination

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
- dilated color fundus photography
- Heidelberg fluorescein angiography.

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.

11. 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.

12. References

1. Rein DB, Wittenborn JS, Zhang X, Honeyutt AA, Lesesne SB, Saaddine J, et al. Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. Arch ophthalmol. 2009;127;533-540.
2. Ferris FL 3rd. Senile macular degenertion: 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.

APPENDIX A

Study Drug Storage

Sirolimus will be received frozen. Sirolimus must be stored and should remain frozen in a secure, locked, dark, temperature controlled, -20ºC freezer (with allowable temperature range between -15ºC to -35ºC) 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 for a minimum of 5 minutes, or by setting the vial at room temperature for a minimum of 30 minutes. Care should be taken to protect the product from light. A sterile, single-use 250 µL syringe custom marked at 20 µL will be provided separately for intravitreal injection use. Study drug should be drawn into the provided single-use plastic syringe within 60 minutes after removing the vial from the freezer. Use separate needles for drawing and injecting the study drug. Study drug should be injected within 2 hours of being drawn up into the single-use syringe.

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 Sirolimus, 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 Sirolimus into the visual axis. The injection volume of 0.02 ml is then delivered. A different scleral site should be used with each subsequent injection.

If performing sham injection the tip of the syringe (without a needle or medication) will be pressed gently against the conjunctiva.

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. Confirm vision is at least hand motions before subject leaves the clinic. Instruct subject verbally on post injection instructions including signs of infection. In addition, patients should be monitored during the week following the injection to permit early treatment if an infection occurs.

Table 1

Table of Events/Visit Schedule

	visit										
procedure	Baseline (Day 1)	week 1	week 4	week 8	week 12	week 16	week 20	week 24	week 28	week 32	week 36
Informed consent	x										
Inclusion/exclusion	x										
Demographics	x										
Pregnancy Test	X		x	x	x	x	x	x	x	x	x
Targeted physical exam	x										x
Vitals (blood pressure, heart rate)	x										x
Med/Oph History	x										
AE query		x	x	x	x	x	x	x	x	x	x
Con meds/proc	x	x	x	x	x	x	x	x	x	x	x
BCVA	x	X*	x	x	x	x	x	x	x	x	x
IOP	x	X*	x	x	x	x	x	x	x	x	x
Biomicro w/lens grading	x	X*	x	x	x	x	x	x	x	x	x
Indirect Ophthalmoscopy	x	x*	x	x	x	x	x	x	x	x	x
Heidelberg-OCT	x	x*	x	x	x	x	x	x	x	x	x
FA and fundus photos	x										x
Subj Travel	x	x	x	x	x	x	x	x	x	x	x
study eye injection	x	x	x	x	x	x	x	x	x	x	x
Sirolimus(S) and Eylea(E) Arm	S	E	S	E	S	E	S	E	S	E	
Eylea(E) arm	E	SHAM	SHAM	E	SHAM	E	SHAM	E	SHAM	E	

10 subjects will receive Sirolimus with adjunct Eylea throughout study

10 subjects will receive Eylea throughout study

*study eye only