KSI-301 Phase 3 RVO Study BEACON

A Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Due to Treatment-naïve Macular Edema Secondary to Retinal Vein Occlusion (RVO)

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BEACON Study Overview

Study Design

BEACON is a 1-year, prospective, randomized, double-masked, active-comparator-controlled, multi-center Phase 3 study

- **Population:** Treatment-naïve macular edema due to RVO (BRVO, HRVO and CRVO), single eye per participant. Approximately 550 subjects.
- **Treatment arms:** KSI-301 5 mg or aflibercept 2 mg (randomized 1:1)
- **Masking:**
  - Two investigators required to maintain masking.
  - Sham injections are administered at monthly visits in which no active treatment is indicated

Study Objectives

Primary:

Demonstrate the non-inferiority of **KSI-301 dosed Q8W** after 2 monthly injections vs aflibercept Q4W on BCVA at Week 24

Secondary

- Evaluate the efficacy of KSI-301 on visual and anatomical parameters
- Evaluate the durability of KSI-301
- Evaluate the safety of KSI-301

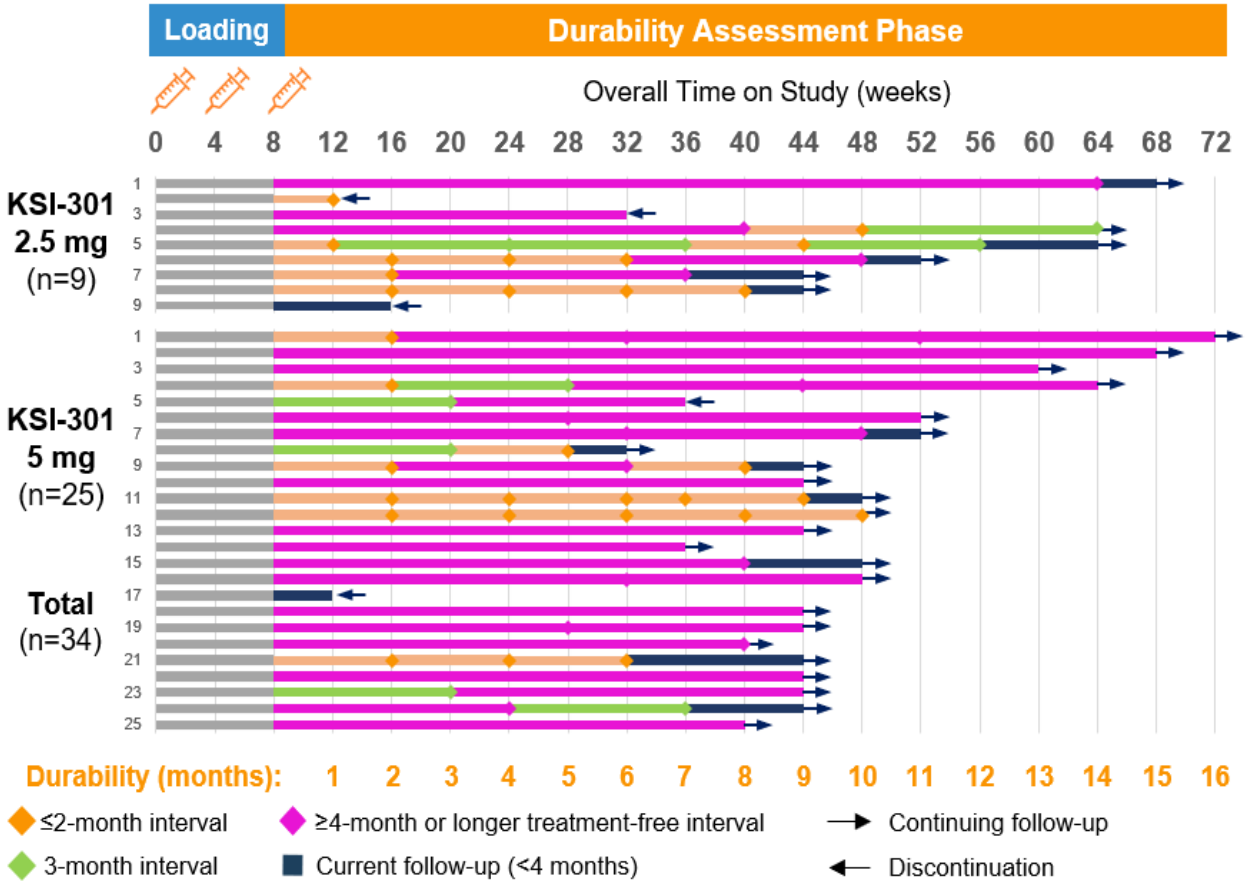
BEACON study design: informed by Phase 1b results with additional optimizations implemented

Learnings from KSI-301 Phase 1b - RVO

- 100% required 4 or fewer treatments during the first 20 weeks of the study
- 94% went 2 months or longer before the first retreatment
- 55% have achieved a 6-month or longer treatment-free interval at least once during follow-up

Optimization of Phase 3 Design

- Same population: treatment-naïve RVO
- Tighter dosing interval: fixed Q8W until primary endpoint
- Tighter disease activity criteria to ensure best outcomes for patients
- Decreased subjectivity: IRT-driven treatment
- High statistical power for non-inferiority (>90%)



KSI-301 Phase 3 RVO BEACON Study Design

n = 550

KSI-301 injection
KSI-301 individualized treatment/Sham
Sham injection
Aflibercept injection
Aflibercept individualized treatment/Sham
Disease Activity Assessment

PE= Primary endpoint
SE= Secondary endpoints
SA= Safety assessment

Disease Activity Criteria in the Individualized Treatment Period – both KSI-301 & Aflibercept groups

- Increase in OCT CST ≥50 µm compared to lowest previous measurement *AND* a decrease in BCVA of ≥ 5 letters compared to the average of the 2 best previous BCVA assessments, due to worsening of RVO disease activity, or
- Increase in OCT CST ≥75 µm compared to lowest previous measurement due to worsening of RVO disease activity

On visits when *either* of these criteria are met, the participant is treated with KSI-301 or aflibercept as per their assigned treatment arm.

On visits when these criteria are not met, the participant is treated with sham.

Disease activity assessments will be conducted by the masked Investigator and the IRT system will adjust the dosing schedule based on disease activity data entered by the study site.

IRT Data Entry

Day 1 to Week 20

Quantitative

- BCVA
- CST

Week 24 to Week 44

Quantitative:

- BCVA
- CST

Qualitative (yes or no):

- Determining that changes (if present) are due to worsening disease activity

The same data will be entered in the IRT system every month for all participants. Starting at Week 24, decision for active treatment is derived from the IRT calculation and the qualitative assessment from the PI.

Key Inclusion Criteria

General

- Adult patients (≥18 years)
- Contraception

Ocular

- Treatment-naïve ME secondary to RVO (BRVO, CRVO, HRVO) in study eye, diagnosed within 6 months
- **BVCA 80 to 25 letters (20/25 to 20/320)**
- **CST ≥320 microns on OCT Heidelberg (≥310 in Zeiss/Topcon)**
- Vision loss in study eye due to RVO

Key Exclusion Criteria

General

- Uncontrolled blood pressure
  - Systolic ≥ 180
  - Diastolic ≥ 100
- Recent history (within 6 months) of myocardial infarction, stroke, TIA, acute CHF or acute coronary event
- Participation in an investigational study within 30 days

Ocular

- Macular edema due to causes other than RVO
- Active iris or angle neovascularization or neovascular glaucoma
- Uncontrolled glaucoma (IOP ≥ 25)
- History of Glaucoma-filtering surgery
- History of retinal detachment or treatment for RD
- History of uveitis in either eye
- Significant media opacities
- Any history or evidence of a concurrent ocular condition that could require medical or surgical intervention or affect macular edema or alter visual acuity during the study
- Prior vitrectomy
- Active/suspected ocular or periocular infection in either eye on Day 1

Vienna Reading Center Eligibility Assessment

Inclusion

- Sufficient image quality
- CST ≥320 microns on OCT Heidelberg (≥310 in Zeiss/Topcon)

Exclusion

- Macular edema due to causes other than RVO
- Structural damage to center of macula (e.g., significant macular ischemia, hard exudates in the foveal center)
- Tractional retinal detachment or history of retinal detachment
- Significant media opacities
- Active retinal disease other than RVO

For Consideration

- Concurrent ocular condition that in the opinion of the Investigator could require either medical or surgical intervention or affect macular edema (e.g., vitreomacular traction, epiretinal membrane)

Conclusions

- **BEACON** is a 1-year, prospective, randomized, double-masked, active-comparator-controlled, multi-center Phase 3 study in patients with treatment-naïve macular edema secondary to RVO, designed to evaluate KSI-301's efficacy/durability with a reduced treatment burden

- The primary objective is to demonstrate the non-inferiority of KSI-301 dosed every 8 weeks **(**after 2 monthly injections) vs aflibercept every 4 weeks.
  - Mean change in BCVA from Day 1 to Week 24

- During the Individualized Treatment Period, Disease activity assessments will define the need for additional treatment (IRT based)

- Inclusion/Exclusion criteria thoughtfully defined to allow for a clinically relevant population to be studied.

Masking Guidelines

Masking

- BEACON, GLEAM and GLIMMER are all **double-masked studies**.
  - Subjects and masked staff at investigational sites must remain unaware to which treatment arms subjects have been assigned and which treatment was administered.

- Why do we have sham injections?
  - Treatment frequency is not identical in the KSI-301 and aflibercept arms, so sham injections are used on non-treatment visits to mask the regimens.

- A minimum of two investigators are required per site
  - Evaluating Physician, who will remain masked
  - Treating (Injecting) Physician (and designated unmasked assistants, as needed) who will be unmasked to subjects' treatment assignments and will administer all injections (KSI-301, aflibercept and sham). Also responsible for the immediate post-injection assessments vision check for counting fingers and post-injection IOP check.

Masking Status by Roles and Responsibilities of Site Personnel

- Unmasked Personnel
  - Injecting Physician
  - Unmasked Assistant(s)

- Masked Personnel
  - Evaluating Physician
  - Study Coordinator
  - Photographer
  - Visual Acuity Examiner (VAE)
  - Monitor/CRA
  - Pharmacist

- Masking takes effect as of patient randomization.
  - Pre-randomization assessments include Screening as well as Day 1 pre-injection assessments and are therefore unmasked.

Masking Grid

(all the details will be reviewed at your SIV)

Assessment/Activity	Study Team Member					
	Same Rules Apply to All				Same Rules Apply to Both	
	Masked Investigator	Coordinator	Photographer	VAE	Unmasked Injector	Unmasked Assistant
Consent	Y	Y	Y	N	Y	Y
Medical and Ocular History	Y	Y	Y	N	Y	Y
Vital Signs	Y	Y	Y	Y	Y	Y
BCVA	Y	Y	Y	Y	Y	Y
Ophthalmic Exam (including Tonometry)	Y	Y	Y	Y	Y	Y
Imaging (FA/OCT/CFP)	Y	Y	Y	Y	Y	Y
Blood draw and processing	Y	Y	Y	Y	Y	Y
Access EDC	Y	Y	Y	N	Y	Y
Register/Randomize subject in IRT	Y	Y	Y	N	Y	Y
↑ Before Randomization						
↓ After Randomization						
BCVA	N	N	N	Y	N	N
Pre-injection Ophthalmic Exam	Y	Y	Y	N	N	N
Pre-Injection Tonometry	Y	Y	Y	Y	N	N
Injection or Sham Procedure	N	N	N	N	Y	N
Post- Injection assessments (vision check, IOP)	N	N	N	N	Y	Y
Imaging (FA/OCT/CFP)	Y	Y	Y	N	N	N
Assess AE/SAE relationship (study drug/inj. procedure)	Y	N	N	N	N	N
Blood draw and processing	Y	Y	Y	Y	Y	Y
Vital Signs	Y	Y	Y	Y	Y	Y
Access EDC	Y	Y	Y	N	*N	N
Allocate Drug in IRT	Y	Y	Y	N	Y	Y
Receive drug and confirm in IRT	Y	Y	Y	N	Y	Y

**If PI is the Unmasked Injector, they can access EDC for final data review & signature.*

Subject-specific Masking Log

PPD

Subject-specific Masking Log
Protocol Number: KS301PXXX

KODIAK

Investigator Name:	Site Number:

Subject Number	Subject Initials	Masked Physician	Unmasked Physician

_____ Signature of Principal Investigator

_____ Date (DD-Mon-YYYY)