KSI-301 Phase 3 DME Studies GLEAM & GLIMMER

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 Secondary to Treatment-naïve Diabetic Macular Edema (DME)

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GLEAM & GLIMMER - Study Overview

Study Design

GLEAM and GLIMMER are two identical 2-year, prospective, randomized, double-masked, active-comparator-controlled, multi-center Phase 3 studies

- **Population:** Treatment-naïve DME, a single eye per participant. Approximately 450 subjects per study
- **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 visits in which no active treatment is indicated.

Study Objectives

Primary:

Demonstrate the non-inferiority of **KSI-301 dosed in a Q24W-flex dosing** regimen vs aflibercept Q8W on BCVA at Year 1

Secondary

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

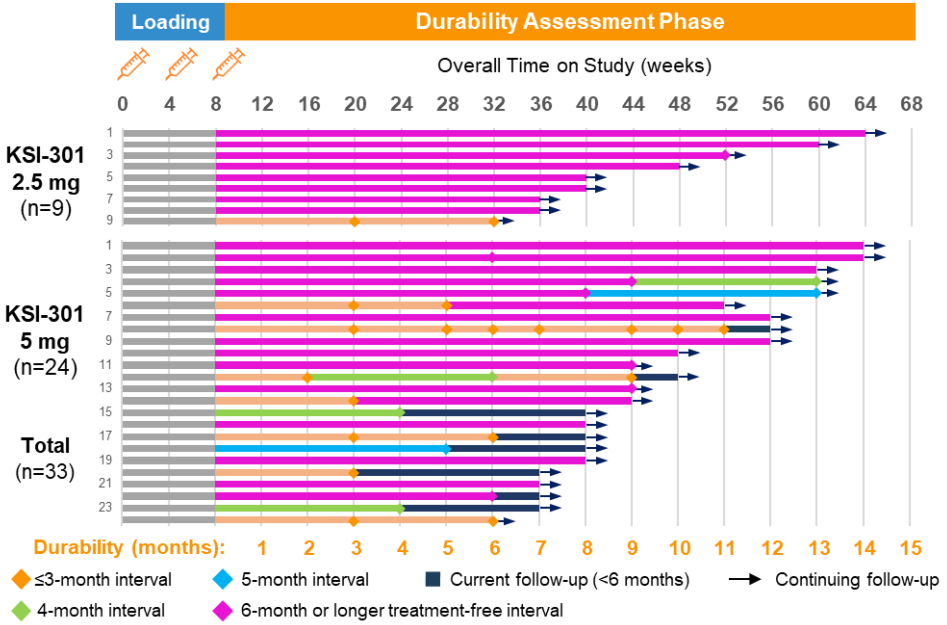
The study design for GLEAM & GLIMMER was informed by Phase 1b results and further optimized in Phase 3

Learnings from Phase 1b

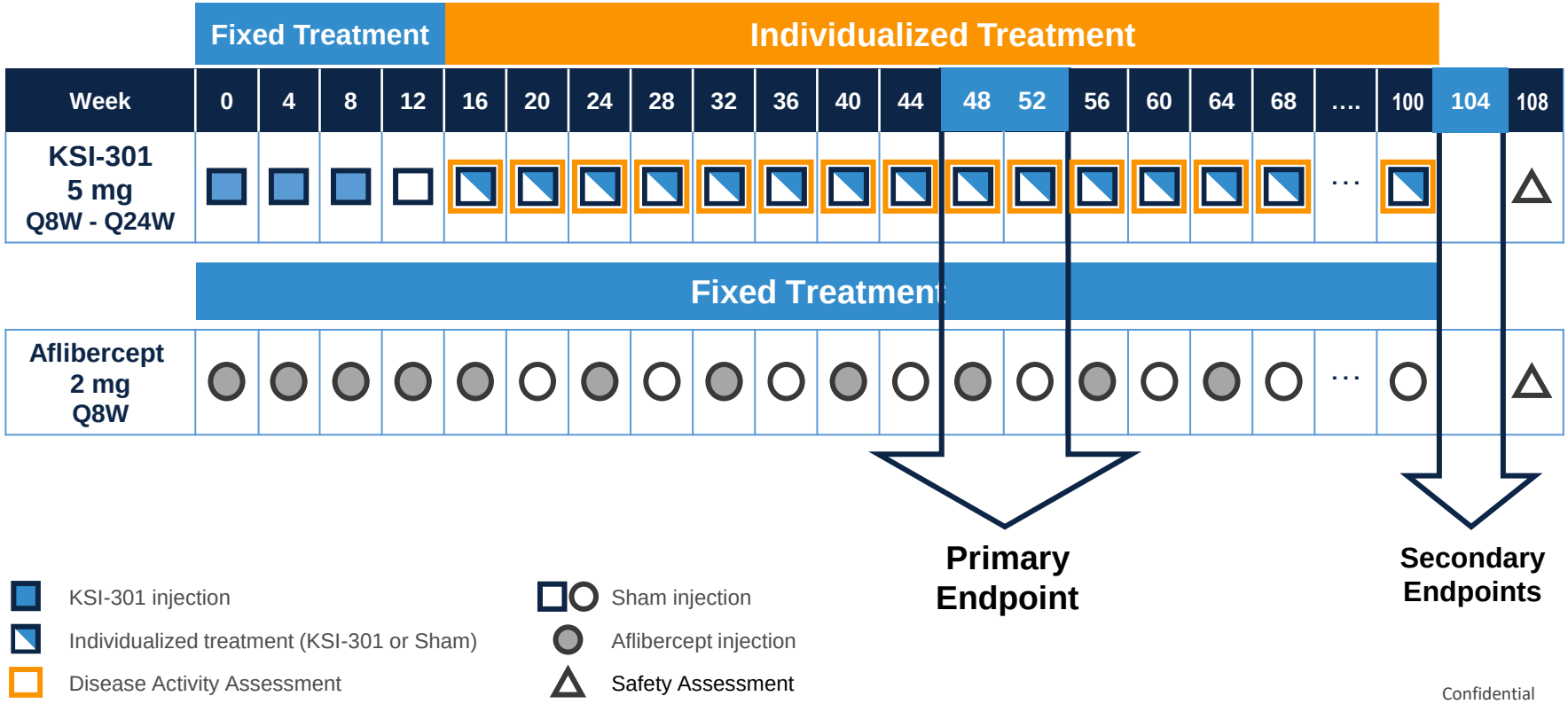
- Three loading doses of KSI-301 can provide a rapid *and* long-lasting effect
- 100% went 2 months or longer before the first retreatment
- 67% went 6 months or longer before the first retreatment
- 79% have achieved a 6-month or longer treatment-free interval at least once during follow-up

Optimization of Phase 3 Design

- Same population: treatment-naïve DME
- Tighter dosing interval: from every 8 to 24 weeks
- Tighter disease activity criteria to ensure best outcomes for patients
- Decreased subjectivity: IRT-driven treatment
- High statistical power for non-inferiority (>90%)



KSI-301 GLEAM & GLIMMER Study Design



Disease Activity Criteria for KSI-301 participants in the Individualized Treatment Period

- 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 DME disease activity, or
- Increase in OCT CST ≥75 µm compared to lowest previous measurement due to worsening of DME disease activity; or
- New or worsening proliferative DR (PDR): progression from NPDR to PDR, vitreous hemorrhage, iris neovascularization and/or new or worsening retinal neovascularization.

Disease activity assessments will be conducted by the masked Investigator and the IRT system will adjust the dosing schedule.

Pan-retinal photocoagulation (PRP) is allowed for the treatment of new, active retinal or iris neovascularization due to worsening diabetic retinopathy. PRP will be reported as a concomitant procedure.

IRT Data entry

Day 1 to Week 8

Quantitative

- BCVA
- CST

Week 12 to Week 100

Quantitative:

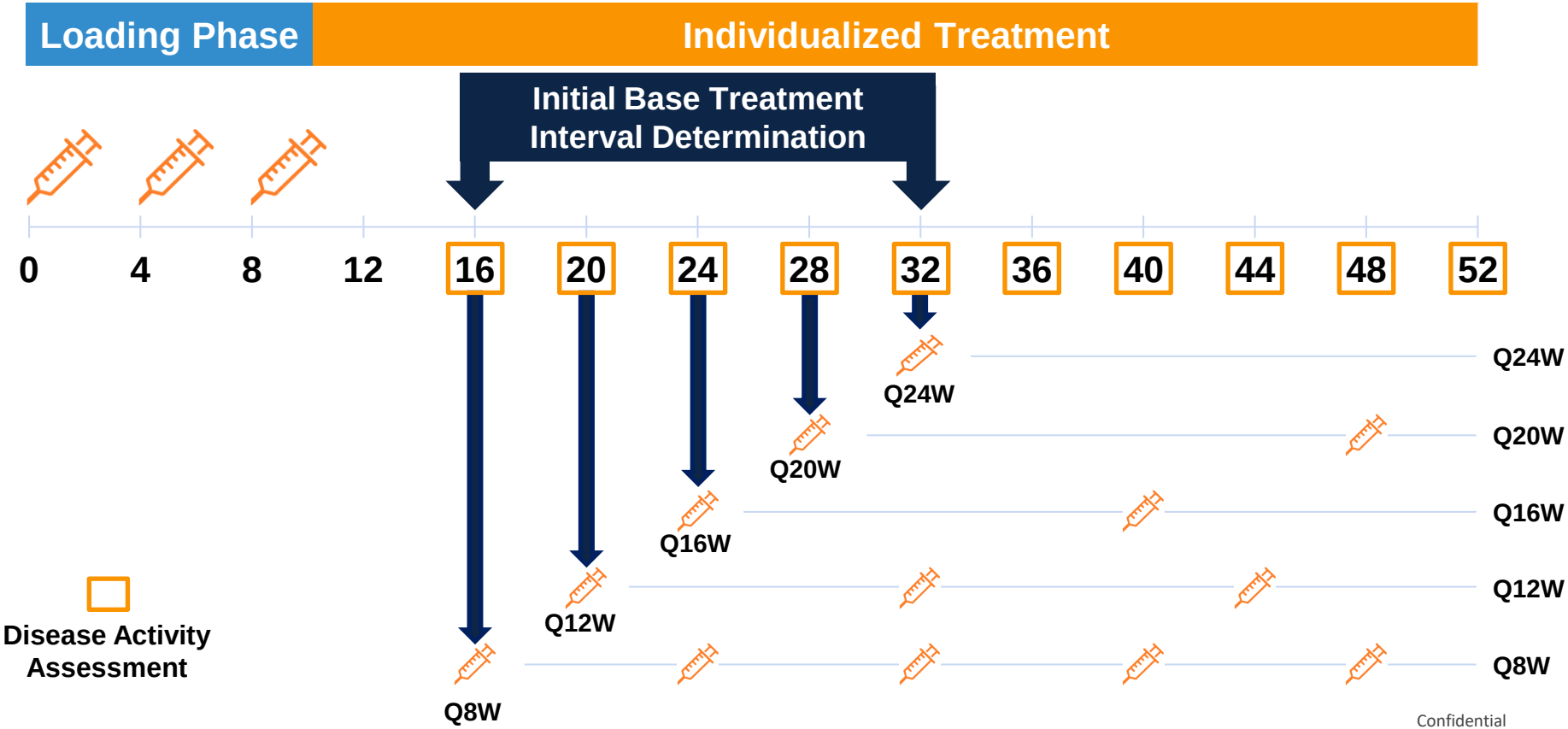
- BCVA
- CST

Qualitative (yes or no):

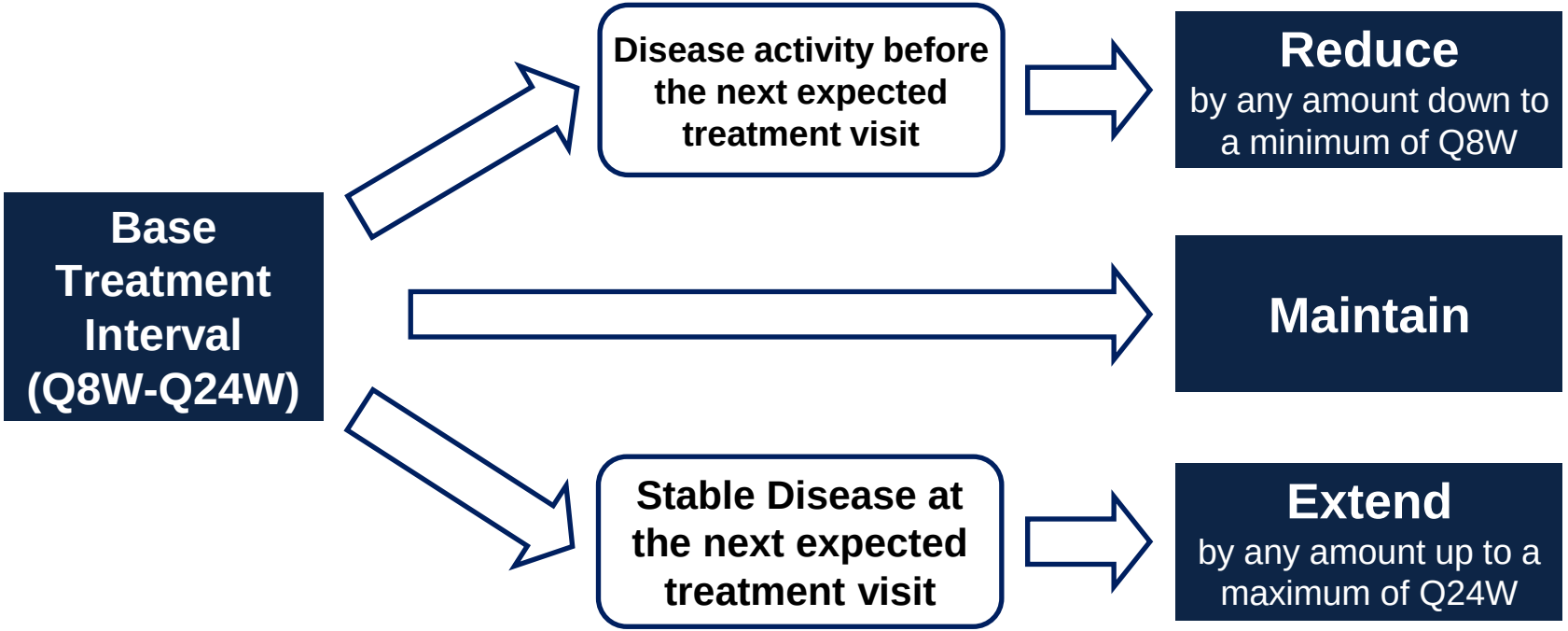
- Determining that changes (if any) are due to worsening disease activity
- Presence of new or worsening PDR

For masking purposes, the same data will be entered in the IRT system every month for all participants, but no modifications to the aflibercept treatment schedule will be made

KSI-301 Base Treatment Interval determination and subsequent dosing



Adjusting the Base Treatment Interval



If adjusted, the new interval will be considered the new base dosing interval and can be further adjusted throughout the individualized treatment period

Disease Stability Criterion for KSI-301 participants in the Individualized Treatment Period

- Disease stability criterion:
  - No increase in CST of >30 µm compared to the lowest previous measurement.
- Must be met in addition to the absence of any of the disease activity criteria
- This criterion must be met at each visit where the base treatment interval is being extended.

Key Inclusion Criteria

General

- Adult patients (≥18 years) with Type 1 or Type 2 diabetes
- HbA1c ≤12%
- Contraception

Ocular

- Treatment-naïve DME in study eye, diagnosed within 9 months
- **BVCA ≤78 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 DME

If both eyes are eligible, the eye with the worse BCVA at the Screening Visit will be selected as the Study Eye. If both eyes are eligible and have the same BCVA, the decision of which eye to select as the Study Eye will be made by the Investigator.

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
- Kidney failure requiring or expected to require transplant or dialysis during the study
- Participation in an investigational study within 30 days of screening

Ocular

- Macular edema due to causes other than DME
- Iris or angle neovascularization or neovascular glaucoma
- High-risk PDR (VH, NVD ≥1/3 DAs, NVE ≥1/2 DAs)
- Structural damage to center of macula (e.g. significant macular ischemia, foveal hard exudates)
- Cataract surgery, MIGS, YAG capsulotomy within 2 months
- PRP within 3 months
- Tractional retinal detachment or history of retinal detachment
- Uncontrolled glaucoma (IOP ≥25 on treatment)
- History of uveitis either eye
- Significant media opacities
- Cataract expected to require surgery within 12 months
- Aphakia or prior vitrectomy
- Active/suspected ocular or periocular infection in either eye
- 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).

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 DME
- High-risk PDR (VH, NVD ≥1/3 DAs, NVE ≥1/2 DAs)
- 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 DME

For Consideration

- Presence of PRP
- 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

- **GLEAM and GLIMMER** are two identical 2-year, prospective, randomized, double-masked, active-comparator-controlled, multi-center Phase 3 studies in patients with treatment-naïve macular edema secondary to DME, designed to evaluate KSI-301's efficacy and durability with a potentially significant reduction in treatment burden

- The primary objective is to demonstrate the non-inferiority of KSI-301 dosed in a 6-month flex dosing regimen after only 3 loading doses vs aflibercept every 8 weeks after 5 loading doses
  - Mean change in BCVA from Day 1 to Year 1

- During KSI-301's Individualized Treatment Period, Disease activity assessments will define the optimal treatment interval for each patient (IRT based)

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