KSI-301 Anti-VEGF Antibody Biopolymer Conjugate for Diabetic Macular Edema: Primary Endpoint Efficacy and Safety Outcomes of the GLEAM and GLIMMER Phase 3 Pivotal Studies

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on behalf of the GLEAM and GLIMMER Study Groups

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Disclosures

This presentation will discuss IRB/IEC approved research of an investigational medicine.

Dr. Robert Wong has the following financial interests or relationships to disclose:

Ashvattha Therapeutics (R), Bayer (R), DRCR.net (R), Eyebio (R), Genentech (R), Ionis (R), Iveric (R), **Kodiak (R),** Novo Nordisk (R), Ocuterra (R), Opthea (R), RCTX (R,O), and Roche (R).

C= Consultant | R= Research Support | O= Ownership/Stock Options

KSI-301 (tarcocimab tedromer) and Antibody Biopolymer Conjugates (ABCs)

ANTIBODY

IgG1 Anti-VEGF Antibody

BIOPOLYMER

Branched, Optically Clear,
High Molecular Weight
Phosphorylcholine Polymer

CONJUGATE

KSI-301 (tarcocimab tedromer) is an anti-VEGF ABC that blocks all VEGF-A isoforms

GLEAM and GLIMMER – identically-designed Phase 3 studies

Two identically-designed, randomized, double-masked, multi-center Phase 3 non-inferiority studies of tarcocimab tedromer 5 mg vs aflibercept 2 mg in treatment-naïve DME

Tarcocimab individualized dosing every 2 to 6 months after only 3 monthly loading doses

Aflibercept dosed every 2 months after 5 monthly loading doses

Primary endpoint

Mean BCVA change from baseline over average of Weeks 60 and 64
non-inferiority tested at 4.5 letter margin

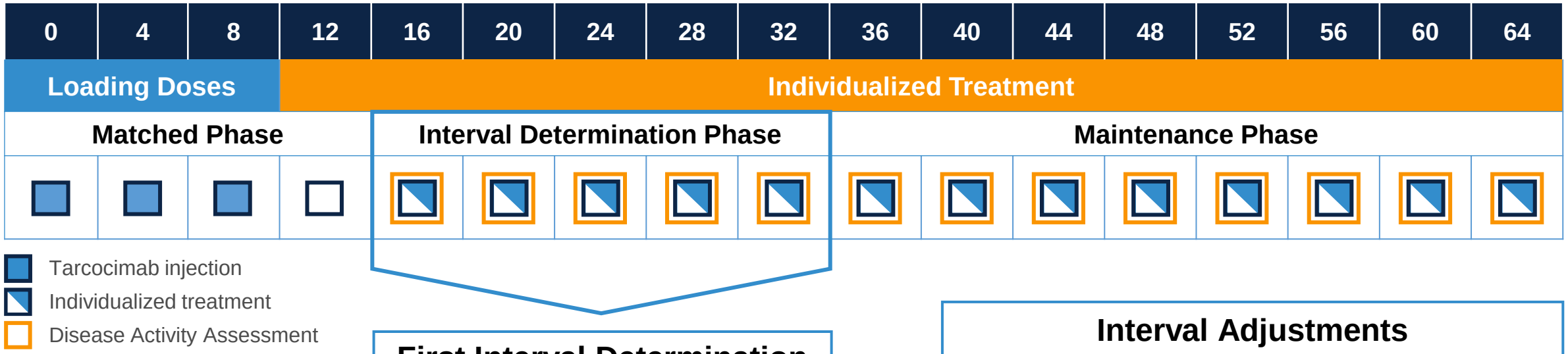
Key secondary endpoint

Proportion of patients with ≥2-step worsening in DRSS at Week 52
non-inferiority tested at 10% margin

End of Study at Week 104

DME: diabetic macular edema; BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; CST: central subfield thickness; DRSS: diabetic retinopathy severity scale
Q8W: every 8 weeks; Q24W: every 24 weeks. GLEAM, Study KS301P104, NCT04611152; GLIMMER, Study KS301P105, NCT04603937. Tarcocimab tedromer also referred to as tarcocimab in this presentation.

Tarcocimab individualized dosing based on patient-specific disease activity assessments, allowing for dynamic interval adjustments between Q8 and Q24 week dosing



First Interval Determination

Based on disease activity, patients assigned to Q8W to Q24W

Interval Adjustments

Extended: if disease stability achieved, dosing was *deferred.*
Longest interval allowed: 24 weeks

Reduced: if disease activity present before the base interval visit.
Shortest interval allowed: 8 weeks

Otherwise, interval **maintained**

Disease activity criteria

- Increase in CST ≥40 µm compared to lowest previous CST; or
- CST ≥350 µm; or
- New or worsening proliferative DR (PDR)

Disease stability criteria:

- CST within 30 µm of lowest previous CST

Baseline ocular characteristics well-matched between groups in each study and between studies, and typical of treatment-naïve DME patients

	GLEAM		GLIMMER	
	Tarcocimab Q8W-Q24W n=230	**Aflibercept Q8W n=230**	**Tarcocimab Q8W-Q24W n=229**	**Aflibercept Q8W n=228**
BCVA, ETDRS Letters, mean (SD)	**66.4 (9.78)**	**66.6 (9.6)**	**64.2 (11.43)**	**64.3 (11.21)**
Snellen equivalent				
≥20/40 Snellen equivalent, n (%)	118 (51.3%)	122 (53.0%)	101 (44.1%)	102 (44.7%)
≤20/200 Snellen equivalent, n (%)	3 (1.3%)	3 (1.3%)	11 (4.8%)	12 (5.3%)
OCT Central Subfield Thickness (CST), µm, mean (SD)	**465.9 (115.46)**	**458.8 (117.55)**	**476.2 (124.65)**	**477.5 (130.66)**
Lens Status, n (%)				
Phakic	177 (77.0%)	178 (77.4%)	174 (76.0%)	168 (73.7%)
Pseudophakic	53 (23.0%)	52 (22.6%)	55 (24.0%)	60 (26.3%)
DR severity (ETDRS DRSS score)				
Mild to moderate NPDR (Better or equal to level 43)	95 (44.2%)	97 (44.3%)	115 (52.8%)	116 (53.2%)
Moderately severe or severe NPDR (47 or 53)	117 (54.4%)	117 (53.4%)	99 (45.4%)	98 (45.0%)
PDR (61, 65, 71/75)	3 (1.4%)	5 (2.3%)	4 (1.8%)	4 (1.8%)
Missing or Ungradable	15	11	11	10
Intraocular Pressure, mmHg, mean (SD)	14.91 (3.07)	15.54 (3.13)	15.59 (2.96)	15.31 (3.14)

n = Number of participants treated; The denominator for percentages is the number of participants treated within each treatment arm. Snellen equivalent of 20/40 is 69 ETDRS letters and of 20/200 is 38 ETDRS letters.
Denominator for percentages of Diabetic Retinopathy Severity Score is the number of subjects with gradable results at baseline. Subjects with ungradable results are not included in the denominator.
BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; DRSS: diabetic retinopathy severity scale; OCT: optical coherence tomography; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy

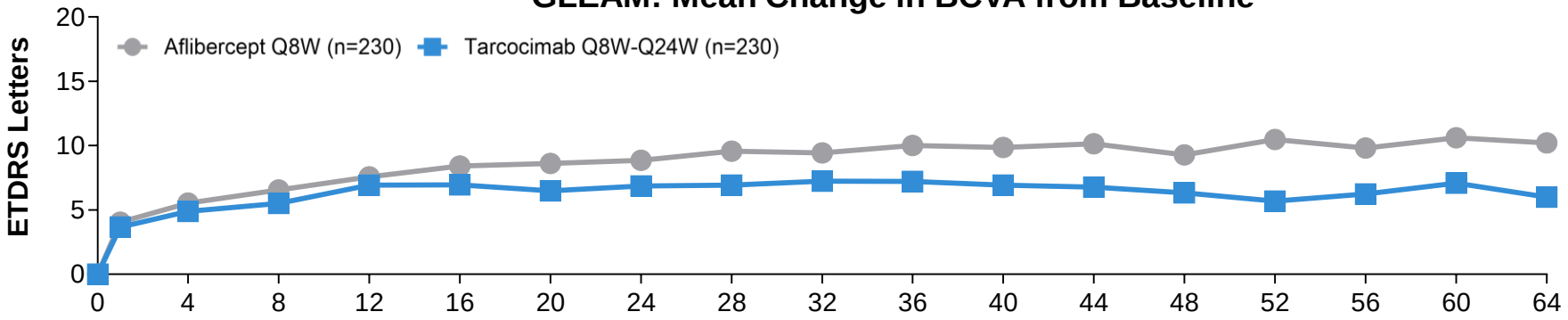
Patient disposition

	GLEAM		GLIMMER	
	Tarcocimab Q8W-Q24W n=230	**Aflibercept Q8W n=230**	**Tarcocimab Q8W-Q24W n=231**	**Aflibercept Q8W n=228**
Patients treated	**230 (100%)**	**230 (100%)**	**229 (99.1%)**	**228 (100%)**
Patients completing Week 64	204 (88.7%)	211 (91.7%)	210 (90.9%)	204 (89.5%)
Discontinuations prior to Week 64	26 (11.3%)	19 (8.3%)	21 (9.1%)	24 (10.5%)
Reasons for discontinuation				
Adverse events	9 (3.9%)	8 (3.5%)	9 (3.9%)	10 (4.4%)
Withdrew consent	5 (2.2%)	6 (2.6%)	7 (3.0%)	6 (2.6%)
Lost to follow-up	11 (4.8%)	2 (0.9%)	5 (2.2%)	6 (2.6%)
Non-compliance	1 (0.4%)	3 (1.3%)	0	0
Physician decision	0	0	0	1 (0.4%)
Other	0	0	0	1 (0.4%)

n = Number of participants randomized; Q8W every 8 weeks; Q8W-Q24W: every 8 to every 24 weeks; The denominator for percentages is the number of participants randomized within each treatment arm.
Two subjects were randomized but not treated in the tarcocimab arm of GLIMMER.

Primary endpoint: mean change in BCVA from baseline at average of weeks 60-64. Tarcocimab did not demonstrate non-inferiority to aflibercept in GLEAM or GLIMMER

GLEAM: Mean Change in BCVA from Baseline

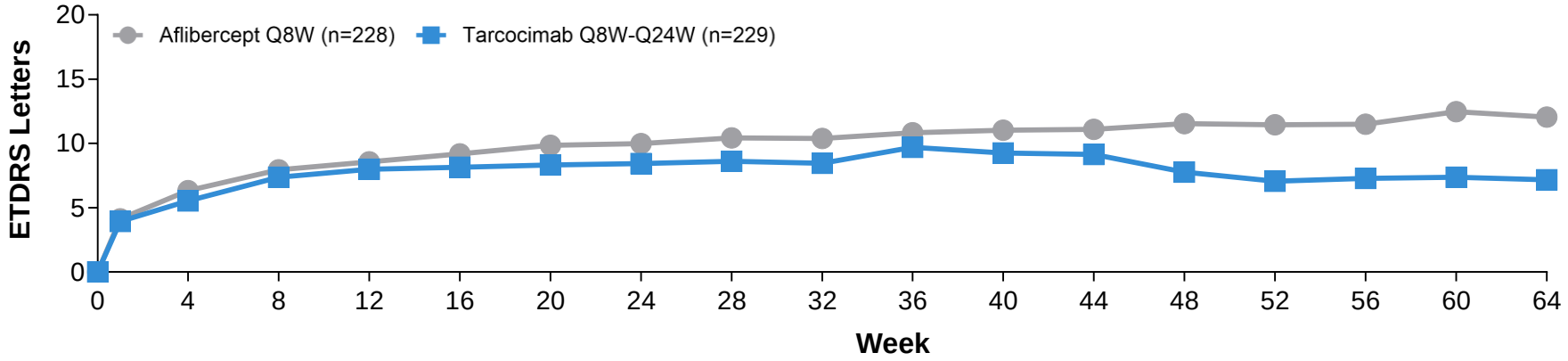


Avg of Weeks 60 & 64 (SD)

10.3 (8.1)

6.4 (8.8)

GLIMMER: Mean Change in BCVA from Baseline



Avg of Weeks 60 & 64 (SD)

12.2 (10.1)

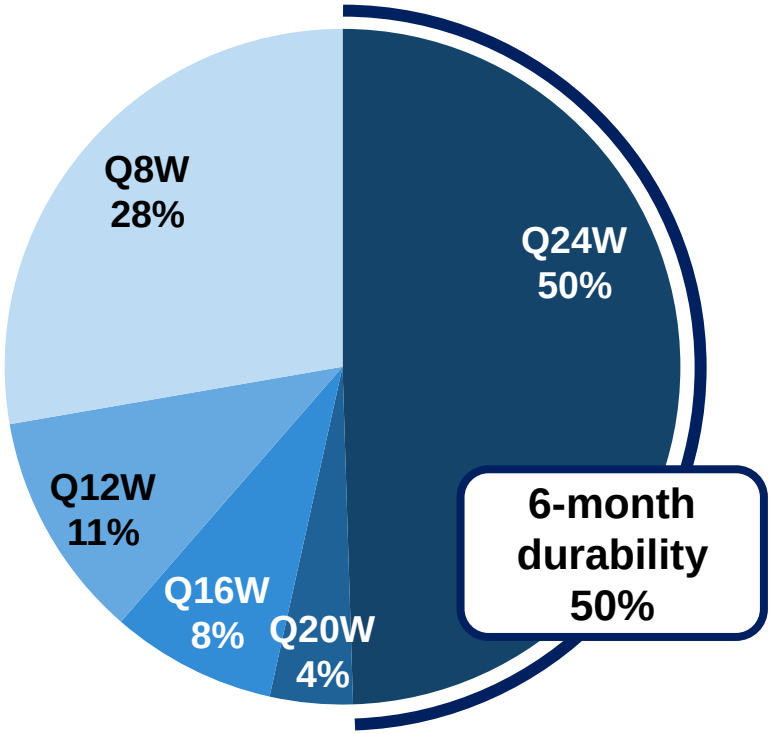
7.4 (11.2)

		LSM change from BL BCVA (MMRM)[a]	95.04% CI for LSM difference	P-value for non-inferiority[a]
GLEAM	Aflibercept Q8W	9.5	-5.47, -2.17	0.4162
	Tarcocimab Q8W-Q24W	5.6		
GLIMMER	Aflibercept Q8W	11.5	-6.61, -2.78	> 0.9999
	Tarcocimab Q8W-Q24W	6.8		

Observed values shown in graphs. LSM, least square mean; MMRM, mixed model for repeated measures. Non-inferiority margin = 4.5 ETDRS letters. BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study.
a. Results are based on a MMRM model including the change from baseline value as the dependent variable; treatment, visit (Week 1 through Week 64), and treatment by visit interaction, and the randomization stratification variables [baseline BCVA (78-69, 68-49, and 48 or worse letters), OCT CST (≤420 and >420 microns), and geographical location (North America and Rest of World)], as well as continuous covariates of baseline BCVA value and OCT CST value, as fixed effects; and subject as a random effect.

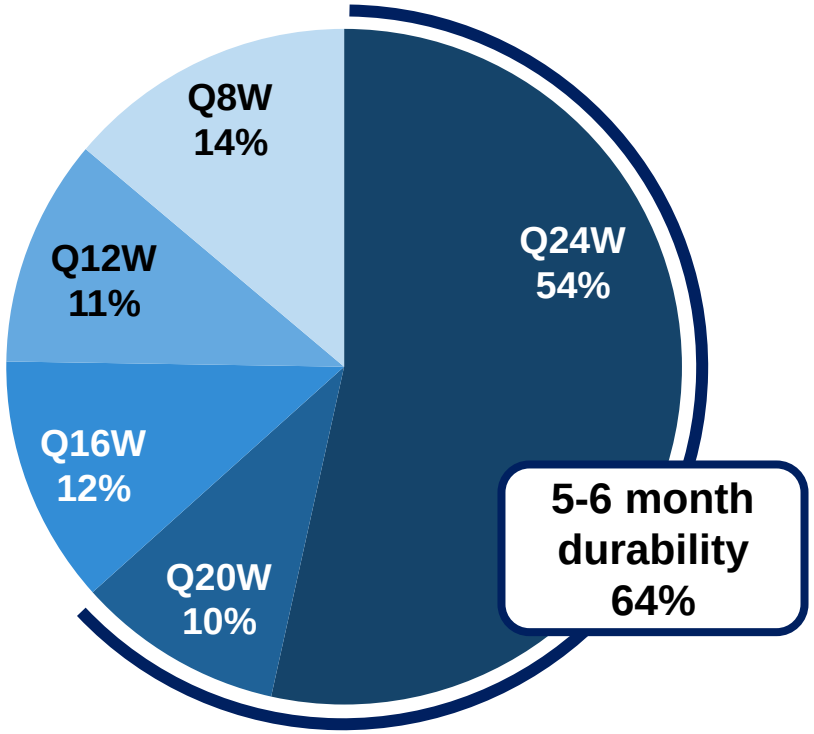
Durability: ≥50% of tarcocimab patients consistently achieved 6-month dosing
Three in every 4 tarcocimab patients successfully completed at least one 5 to 6-month interval

Interval at the Primary Endpoint[a]



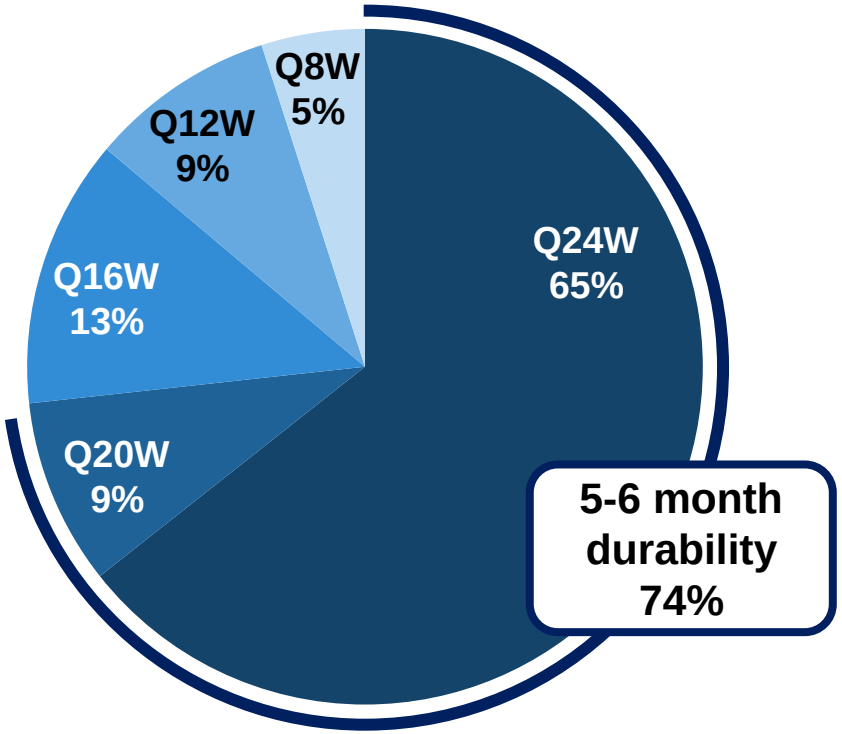
Half achieved 6-month durability at the primary endpoint

First interval (after 3 loading doses)[b]



2/3 achieved 5 and 6-month durability immediately after the loading phase

Longest interval achieved[b]



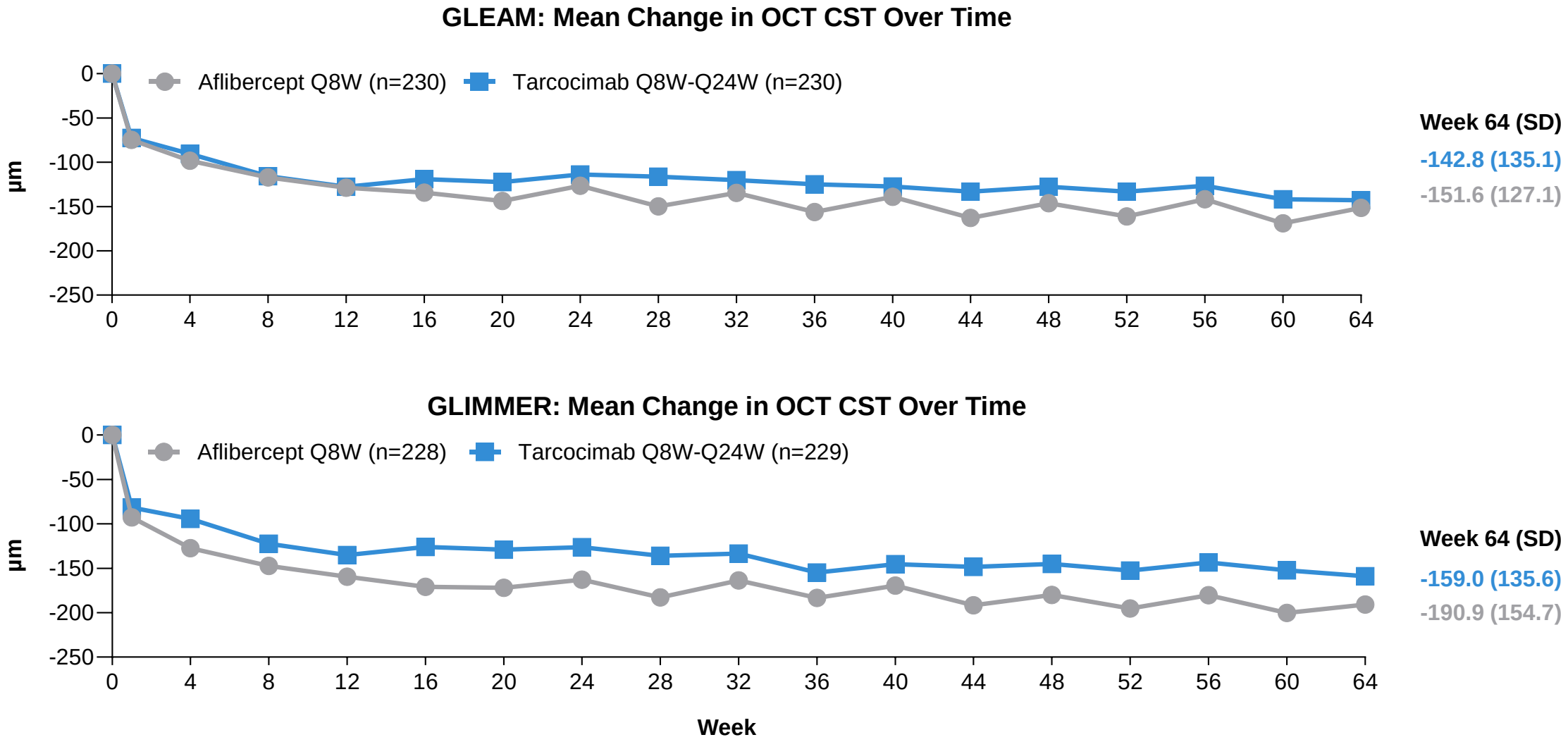
3/4 achieved 5 and 6-month durability at least once

Median No. of Injections through Week 64

	GLEAM	GLIMMER
Tarcocimab	5	5
Aflibercept	10	10

[a] Analyses include tarcocimab patients who completed a treatment interval from Week 56 onwards (pooled GLEAM and GLIMMER, n= 418).
[b] Percentages are based on tarcocimab patients who completed at least one treatment interval after the loading doses (pooled, n= 429).
Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; Q20W, every 20 weeks; Q24W, every 24 weeks.

Tarcocimab dosed Q8W-Q24W and aflibercept dosed Q8W resulted in similar improvements in retinal thickness by Week 64, achieved with half the doses (median of 5 vs 10 doses, respectively)



Observed values. OCT: optical coherence tomography; CST: central subfield thickness.

Rates of common ocular adverse events were low. An imbalance in cataracts was observed

Pooled GLEAM and GLIMMER

Common Ocular Adverse Events (AEs) up to Week 64[a]	Tarcocimab Q8W-Q24W (n=458)	Aflibercept Q8W (n=459)
Subjects with any AE in the Study Eye	220 (48.0%)	160 (34.9%)
Total number of AEs		
Cataract	69 (15.1%)	32 (7.0%)
Conjunctival haemorrhage	40 (8.7%)	23 (5.0%)
Cataract subcapsular	23 (5.0%)	4 (0.9%)
Diabetic retinal oedema	21 (4.6%)	7 (1.5%)
Vitreous detachment	20 (4.4%)	19 (4.1%)
Dry eye	19 (4.1%)	13 (2.8%)
Vitreous floaters	17 (3.7%)	7 (1.5%)

Pooled GLEAM and GLIMMER

Cataract in Study Eye up to Week 64[b]	Tarcocimab Q8W-Q24W (n=458)	Aflibercept Q8W (n=459)
Subjects with Cataract AE in the Study Eye	89 (19.4%)	40 (8.7%)

Results presented for the Safety Population (≥2.0% in either study arm). Events are investigator reported. Adverse events are events with start date ≥first study drug date and ≤last study drug date + 28 days.

a. Includes all adverse events (AE) reported. A single patient can have multiple events of the same AE term reported.

b. Total number of patients with one or more events of cataract. A patient with multiple events of the same AE term reported are only counted once.

Rates of intraocular inflammation were low in both treatment groups

Pooled GLEAM and GLIMMER

Intraocular Inflammation in Study Eye up to Week 64	**Tarcocimab Q8W-Q24W (n=458)**	**Aflibercept Q8W (n=459)**
Subjects with at Least 1 Intraocular Inflammation AE*	6 (1.3%)	1 (0.2%)

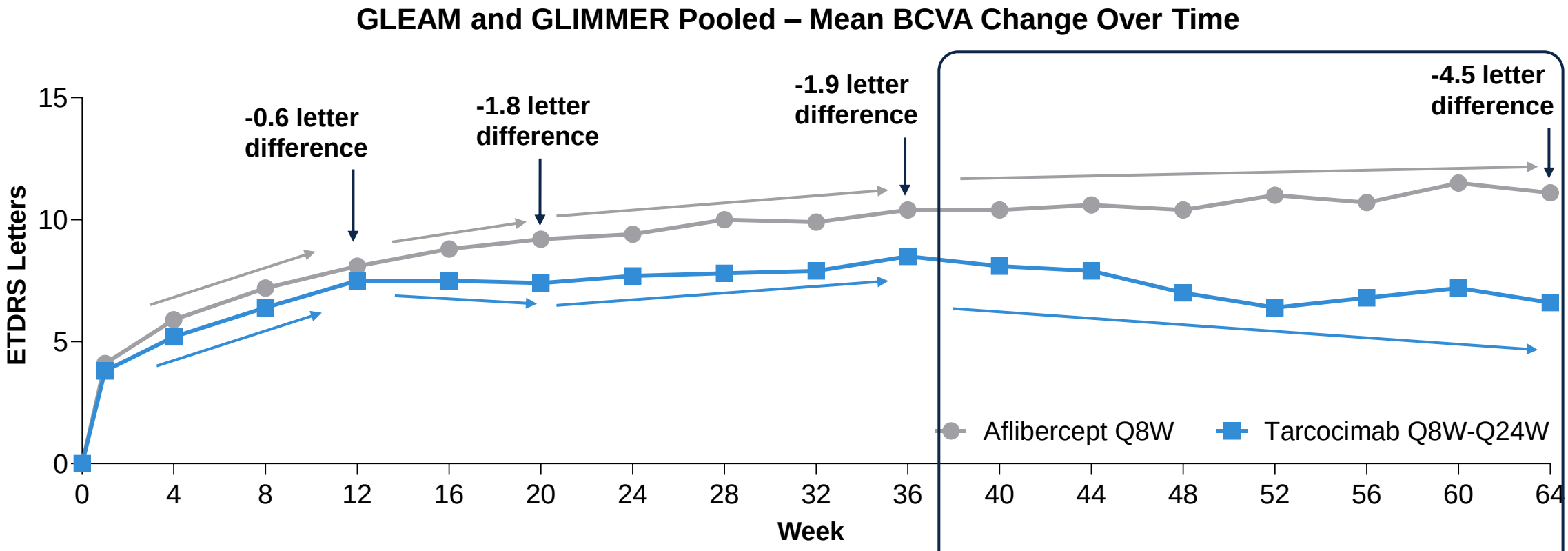
Endophthalmitis in Study Eye up to Week 64	**Tarcocimab Q8W-Q24W (n=458)**	**Aflibercept Q8W (n=459)**
Subjects with at Least 1 Endophthalmitis AE	1 (0.2%)	2 (0.4%)

No cases of intraocular inflammation with vasculitis or vascular occlusion were observed

*Reported AE terms: keratic precipitates, iritis, eye inflammation, uveitis, vitreal cells, vitreous haze, vitritis
Results presented for the Week 64 Safety Population. Events are investigator reported. Adverse events are events with start date ≥first study drug date and ≤last study drug date + 28 days.

Why did tarcocimab not meet the primary endpoint?

The main difference in BCVA was noted in the maintenance phase
An unexpected cataract finding was the main driver



Matched Phase
Both curves trend upwards similarly

Comparable BCVA gains are achieved

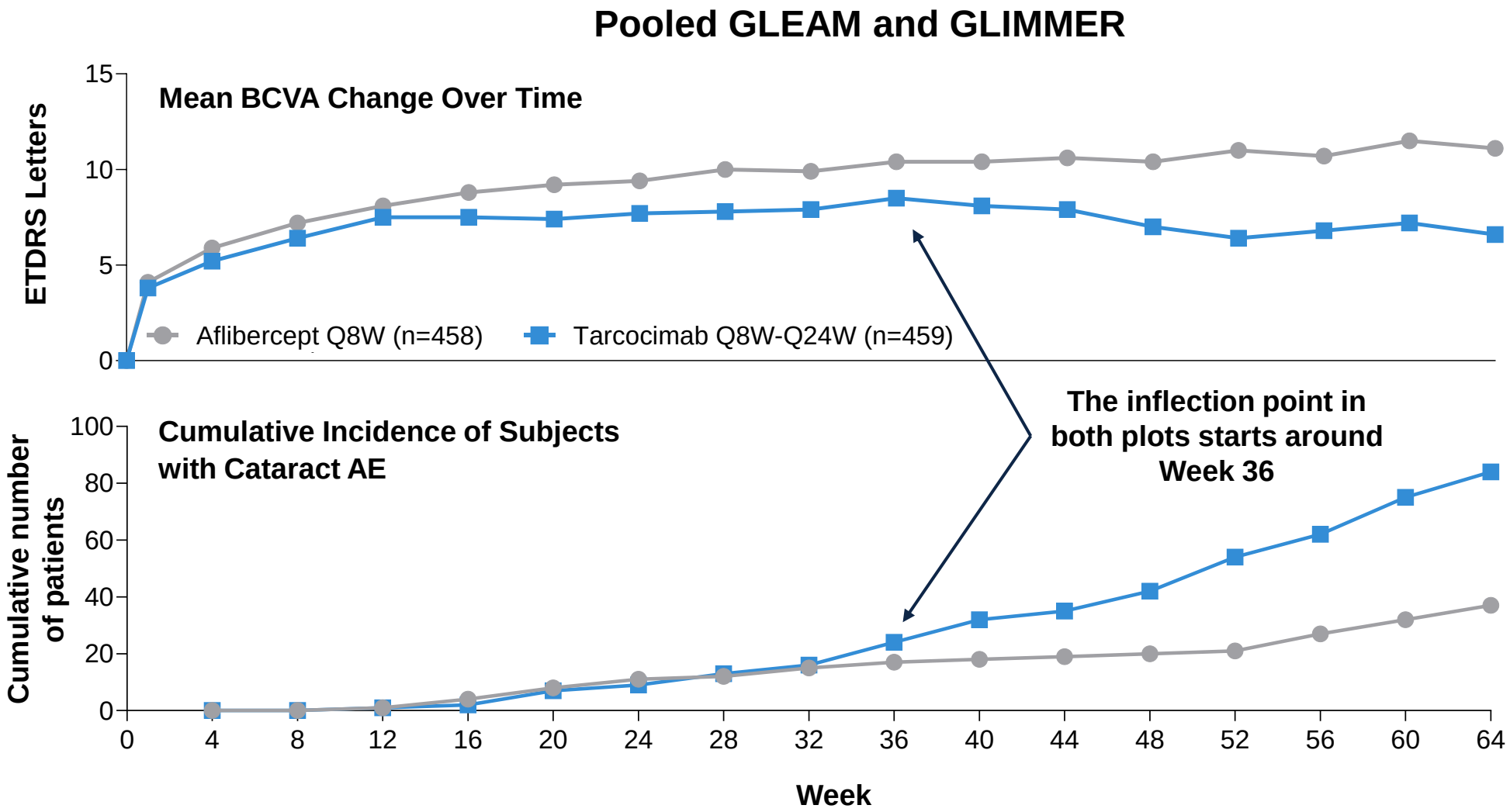
Interval Determination Phase
Curves **diverge** over the next 2 visits, when aflibercept had 2 additional monthly doses

Both curves subsequently trend upwards, with ≥50% of tarcocimab patients initiating 6-month dosing

Maintenance Phase
The curve trajectories **diverge** further, with tarcocimab patients losing vision on average.

A higher incidence of cataract AEs was noted with tarcocimab in this period

The divergence of the BCVA curves between groups coincides with a relative increase in cataract adverse events in the tarcocimab group



Subjects with Cataract AE in the study eye at Week 64:

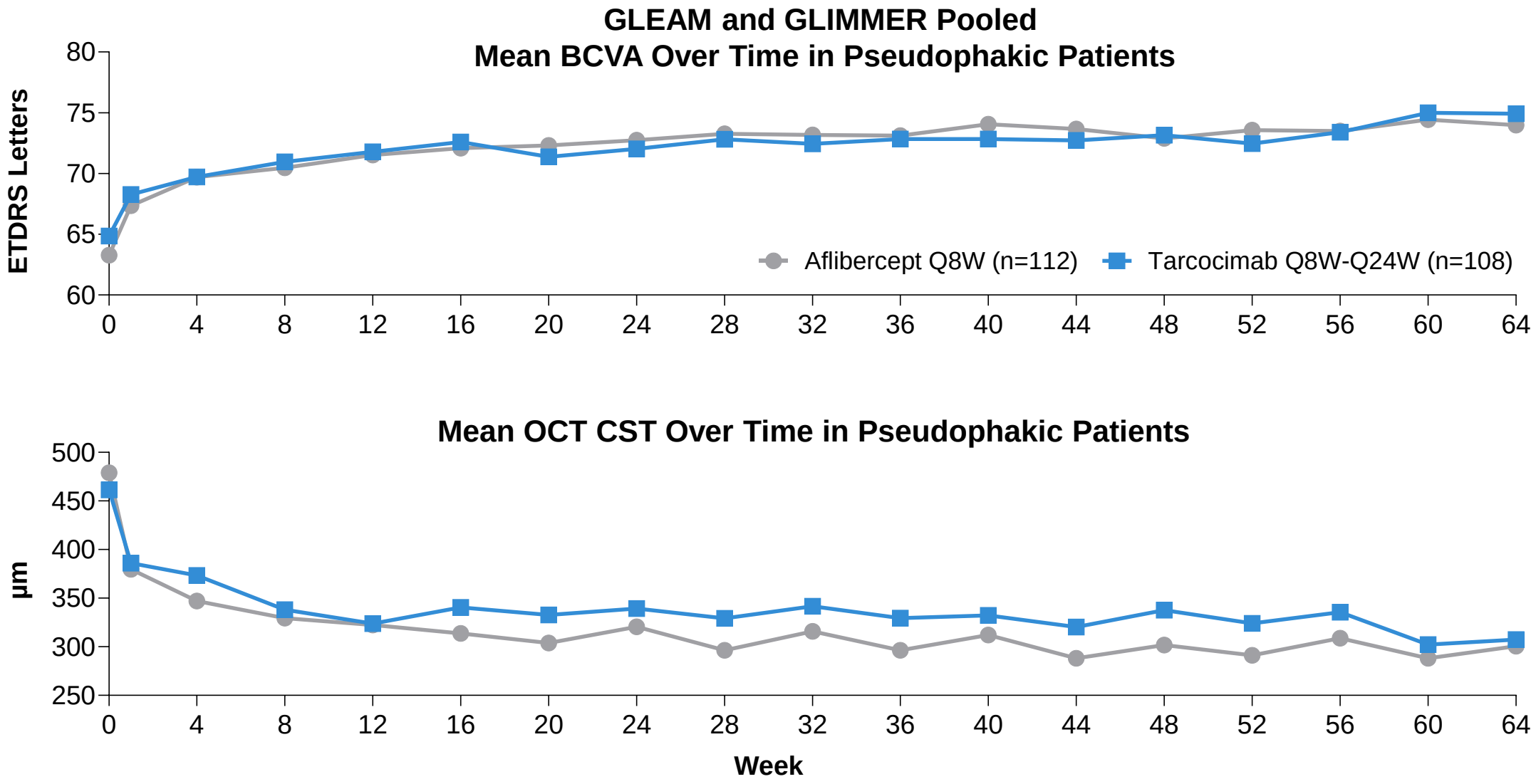
Tarcocimab: 89 (19.4%)

Aflibercept: 40 (8.7%)

Cumulative incidence of cataract AE is reported for the safety population (tarcocimab: 458, aflibercept: 459)

How did the pseudophakic patients do?

Pseudophakic patients in both groups did well and improved over time, while receiving the same median doses as the overall groups (5 tarcocimab vs 10 aflibercept)



Observed values. BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study. OCT: optical coherence tomography; CST: central subfield thickness

What have we learned about the increased incidence of cataracts?

Cataract imbalance in GLEAM and GLIMMER not observed with monthly dosing in DAYLIGHT, which indicates that exposure or accumulation does not play a significant role

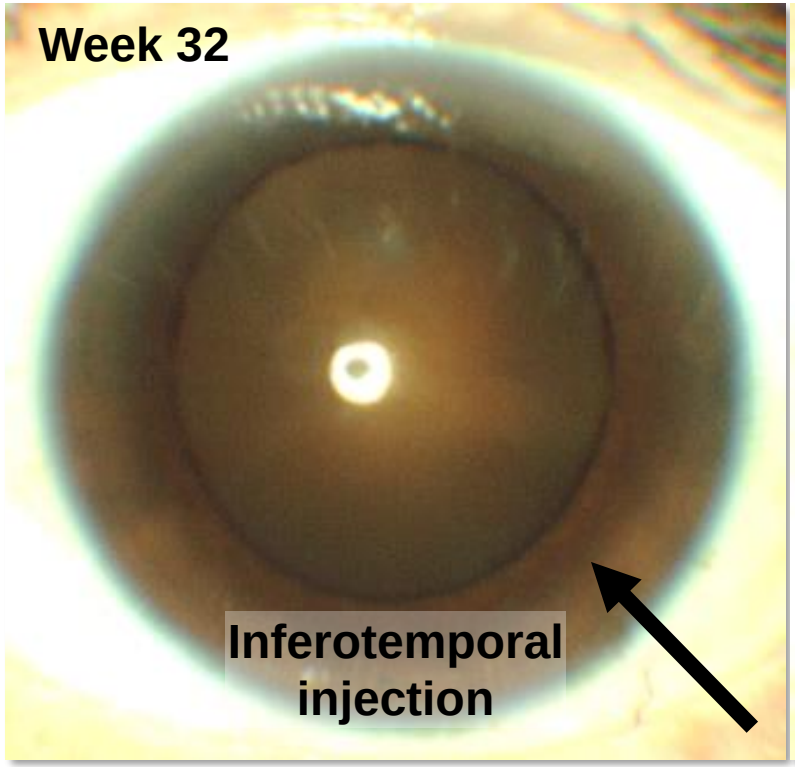
	GLEAM + GLIMMER (DME)		DAYLIGHT (wAMD)		DAZZLE (wAMD)		BEACON (RVO)	
Duration of Follow-Up	**64 Weeks**		**48 Weeks**		**52 Weeks**		**48 Weeks**	
Cataract in Study Eye up to Primary Endpoint	**Tarcocimab Q8W-Q24W (n=458)**	**Aflibercept Q8W (n=459)**	**Tarcocimab Q4W (n=276)**	**Aflibercept Q8W (n=281)**	**Tarcocimab Q12W-Q20W (n=277)**	**Aflibercept Q8W (n=280)**	**Tarcocimab Q4W (n=284)**	**Aflibercept Q8W (n=284)**
Subjects with Cataract AEs in the Study Eye, n (%)	**89 (19.4%)***	40 (8.7%)	**9 (3.3%)**	13 (4.6%)	19 (6.9%)	12 (4.3%)	14 (4.9%)	8 (2.8%)
Median number of doses	**5**	10	**12**	7	5	8	5	7

In DAYLIGHT, the Phase 3 **monthly dosing** study in wAMD patients, an imbalance in cataracts is **not** seen, even though patients received 7 more injections compared to tarcocimab patients in GLEAM and GLIMMER

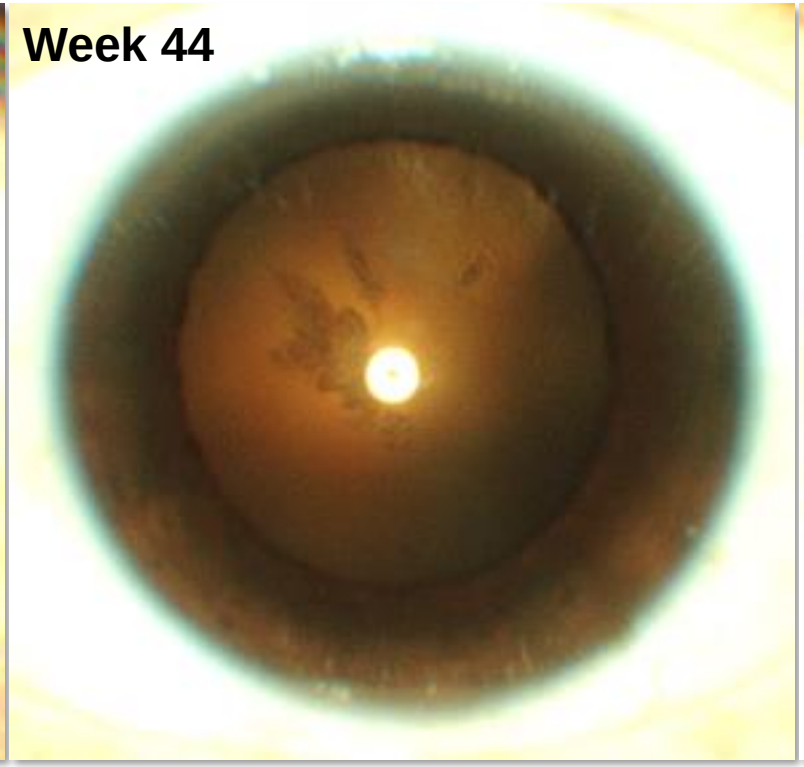
*One patient had a reported AE term of worsening secondary cataract, which coded to the preferred term of cataract
Results presented for the primary endpoint Safety Populations. Events are investigator reported. Adverse events are events with start date ≥first study drug date and ≤last study drug date + 28 days.

Tarcocimab has a higher cataract incidence. What do we believe it *is* related to?

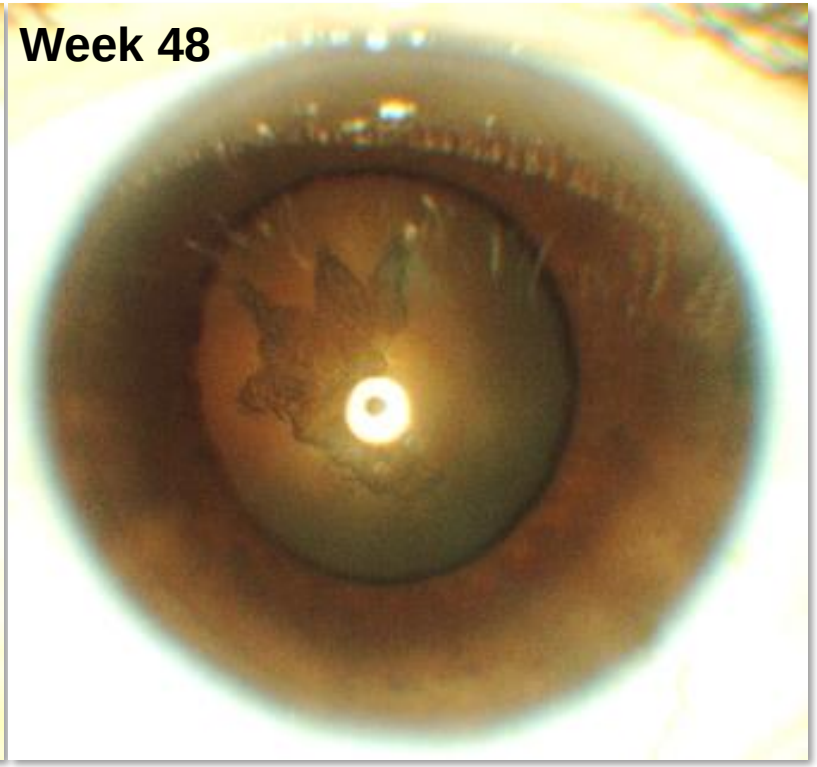
- **The triggering insult seems to be localized to the back of the lens.** A progressive posterior subcapsular cataract is a noticeable finding.



Diabetic patient treated with tarcocimab at Week 32. No posterior cataract is noted. This is the last injection the patient received prior to the cataract event



12 weeks later, a noticeable posterior cataract with sharp edges has developed.



4 weeks after, the cataract has progressed significantly

Tarcocimab has a higher cataract incidence. What do we believe it *is* related to?

- **Seems to be highly specific to diabetic patients *with* diabetic eye disease (retinopathy).**
  - wAMD patients receiving 12 monthly doses in DAYLIGHT over one year did not show an increased cataract incidence.
  - RVO patients had low, comparable rates of cataract over 1 year.

	Tarcocimab across 5 Kodiak pivotal trials (wAMD, DME and RVO patients combined) 1,312 patient-years of experience			Aflibercept across 5 Kodiak pivotal trials (wAMD, DME and RVO patients combined) 1,342 patient-years of experience		
	Medical history of diabetes WITH retinopathy N=471	Medical history of diabetes WITHOUT retinopathy N=159	No medical history of diabetes N=665	Medical history of diabetes WITH retinopathy N=470	Medical history of diabetes WITHOUT retinopathy N=165	No medical history of diabetes N=669
Phakic at baseline	351 (74.5%)	92 (57.9%)	387 (58.2%)	350 (74.5%)	86 (52.1%)	422 (63.1%)
Cataract event*	88 **(25.1%)**	8 (8.7%)	33 (8.5%)	40 **(11.4%)**	5 (5.8%)	27 (6.4%)

Diabetic patients ***without*** retinopathy treated with tarcocimab have similar cataract event incidence as non-diabetics

*Includes patients with medical history of diabetic retinopathy and/or DME.
wAMD: wet age-related macular degeneration; DME: diabetic macular edema; RVO: retinal vein occlusion.

The higher cataract incidence seen with tarcocimab seems to be a relationship between *a local insult in a susceptible environment*

Diabetic patients with retinopathy are the susceptible population

The lens in diabetics is under metabolic duress

- Sorbitol accumulates intracellularly, leading to a hyperosmotic effect that damages lens fibers.[1,2]
- Free radical formation, reactive oxygen species and advanced glycation end products all generate oxidative stress.[2-4]

The posterior lens capsule is more fragile in diabetics *with* diabetic retinopathy (DR)

Diabetics with DR have a significantly increased risk of posterior capsule rupture during cataract surgery, whereas diabetics without DR do not have an increased risk.[5]

Local insult due to injection procedure

Intravitreal injections are known to cause microtrauma in the posterior lens capsule

Intravitreal injections are a risk factor for posterior capsule rupture during cataract surgery.[5-7]

Local insult due to gel-like consistency

Expression of the gel-like medication in close proximity to the posterior lens capsule

The gel-like consistency of tarcocimab requires a 5x–10x increase in injection force & injection time, which results in variability in where and how tarcocimab is expressed

Cataract Formation

A tangential microtrauma due to the expression of a gel-like medication in close proximity to a susceptible posterior lens capsule seems to be the triggering insult

1. Kador PF, et al. Prog Retin Eye Res. 2016;54:1–29. 2. Kiziltoprak, H, et al. World J Diabetes. 2019 Mar 15; 10(3): 140–153. 3. Mulhern ML, et al. Mol Vis. 2007;13:1397–1405. 4. Stitt AW. Ann N Y Acad Sci. 2005;1043:582–597. 5. Dawson VJ, et al. Acta Ophthalmol. 2022 Nov;100(7):813-818. 6. Khalifa YM, et al. J Cataract Refract Surg. 2011 Jul;37(7):1364. 7. Bjerager J, et al. Acta Ophthalmol. 2022 Sep;100(6):614-623

The gel-like consistency of tarcocimab results in a higher cataract incidence in diabetic patients with retinopathy. Can it be solved?

An improved formulation for all antibody biopolymer conjugates is a plausible solution

Improved formulations combine ‘naked’ and conjugated antibody

Tarcocimab clinical formulation is 100% antibody-biopolymer-conjugate.

Enhancing the formulation of the ABC’s by maintaining a proportion of ‘naked’ antibody together with conjugated antibody results in a liquid-like consistency while keeping the same formulation strength of antibody.

Liquid-like consistency

Improved injection procedure (decreased injection time and force needed)

Average time to inject 100µl

Tarcocimab clinical formulation:	**7 seconds**
Tarcocimab commercial formulation:	**2-3 seconds**
KSI-501 enhanced formulation:	**1-2 seconds**

Significantly less or no insult from medication

Additional benefits for dose preparation and commercial manufacturing

Tarcocimab commercial formulation was manufactured as part of pivotal program development. KSI-501 enhanced formulation is expected to be ready for clinical use in 1H 2024.

Tarcocimab has higher cataract incidence. What do we believe it is *not* related to?

Patient Characteristics

Not related to mid-term metabolic control

Mean (SD) HbA1c at baseline was 8.0 (1.6) vs 8.0 (1.4), in tarcocimab patients with vs without cataract development.

Not related to diabetes duration

Mean (SD) diabetes duration at baseline was 16.0 (9.7) vs 16.5 (10.3) years, in tarcocimab patients with vs without cataract development.

Not related to age

Mean (SD) age at baseline was 62.2 (9.4) vs 62.0 (9.6) in tarcocimab patients with vs without cataract development.

Injectors

Not site related

The cataract events occurred across 59 different sites in the US and Europe.

Animal Toxicology

Not seen in non-clinical studies

In monkeys dosed with 7 monthly doses, no cataracts were observed. Nor is drug access to the lens observed with KSI-301, KSI-501 or radiolabeled biopolymer alone. Not seen in rabbits either.

Molecule Characteristics

Not related to the anti-VEGF effect

The imbalance is in diabetic patients with retinopathy; further, is not seen in RVO (the highest VEGF load retinal vascular disease).

Not due to the biopolymer alone

Not seen in any animal model, not seen outside of diabetic patients, and importantly not seen in wAMD patients dosed with 12 monthly doses.

Not related to tarcocimab's biophysical properties

pH, osmolality, water solubility, and other properties are consistent with intravitreal biologics, with the notable exception of the gel-like consistency.

Exposure

Not related to cumulative drug exposure

Cataract events occurred from one active tarcocimab dose ("insult") prior to the event (median of 5, range 1-8).

In wAMD patients, maximal (monthly) exposure resulted in a lower cataract incidence compared to aflibercept.

Manufacturing

Not related to a specific manufac-turing lot

Drug supply was pooled across the BEACON, DAYLIGHT, GLEAM and GLIMMER studies.

Conclusions

GLEAM and GLIMMER did not meet the primary endpoint	• The initial matched phase demonstrated robust efficacy • Individualized dosing with tarcocimab maintained initial BCVA gains, with half or more of the patients consistently on 6-month dosing
Tarcocimab continues to demonstrate strong durability	• 1/2 of patients achieved 6-month dosing at the primary endpoint • 2/3 of patients on 5- or 6-month dosing at first interval after the loading doses • 3/4 of patients successfully completed a 5- to 6-month dosing interval at least once
Cataracts compromised vision outcomes with tarcocimab	• Increased cataracts with tarcocimab correlated with deterioration of BCVA vs aflibercept • Pseudophakic patients did well on tarcocimab with similar BCVA to aflibercept, while receiving half the median number of doses compared to aflibercept (5 vs 10, respectively)
Cataracts seem to be a relationship between a localized insult in a susceptible environment **A plausible solution is available**	• The higher cataract incidence seems **specific to diabetic patients *with* retinopathy** • The usability of tarcocimab (**extended injection time and force) results in a tangential microtrauma due to the expression of a gel-like medication in close proximity to a susceptible posterior lens capsule, which seems to be the triggering insult** • An improved formulation with a liquid-like (non-gel) consistency and with the same strength of bioactive antibody **may be a plausible solution**
Data across tarcocimab program provides support for ABC Platform-derived medicines	• Analysis of clinical data across the tarcocimab Phase 3 pivotal program, including the GLEAM and GLIMMER studies, provides supportive evidence for the development of Kodiak's ABC Platform and platform-derived medicines. • Kodiak is advancing KSI-501, a clinical stage anti-IL-6/VEGF bispecific, both as (i) its naked protein and (ii) an enhanced bioconjugate formulation

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