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

41st Annual Scientific Meeting of the American Society of Retina Specialists
July 30, 2023 – Seattle, WA

Disclosures

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

Charles Wykoff has the following financial interests or relationships to disclose:

4DMT (C, R), Abbvie (C), Adverum (C,R), Aerie (C), AffaMed (R), AGTC (C), Alcon (C), Alexion (R), Alimera (R), Allgenesis (R), Amgen (R), Annexin (R), Annexon (C,R), Apellis (C, R), Arrowhead (C), Ascidian (C), Asclepix (R), Bausch + Lomb (C), Bayer (C, R), Boehringer Ingelheim (C,R), Chengdu Kanghong (R), Cholgene (C), Clearside (C,R), Curacle (C, R), Eyebiotech (C, R), EyePoint (C, R), Foresite (C), Frontera (C), Genentech (C,R), Gyroscope (C, R), IONIS (R), iRENIX (R), IVERIC Bio (C,R), Janssen (C, R), Kato (C), Kiora (C), Kodiak (C,R), LMRI (R), McMaster University (R), Merck (C), Nanoscope (C,R), Neurotech (C, R), NGM (C,R), Notal Vision (C), Novartis (C, R), Ocular Therapeutix (C, R), Ocuphire (C, R), OcuTerra (C, R), OliX (R), ONL (C, SO), Opthea (C,R), Oxurion (R), Oxular (C,R), Oyster Point (R), Palatin (C), PerceiveBio (C, R), PolyPhotonix (SO), Ray (C), RecensMedical (C, SO), Regeneron (C,R), RegenXBio (C,R), Resonance (C), Rezolute (R), Roche (C, R), SamChunDang (R), Sandoz (C,R), Sanofi (C), SciNeuro (C), Shanghai Henlius (R), Stealth (C), Surrozen (C), Suzhou Raymon (C), THEA (C), Therini (C), TissueGen (SO), UNITY (R), Valo (C), Verily, (R) Visgenx (SO), Vitranu (SO)

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

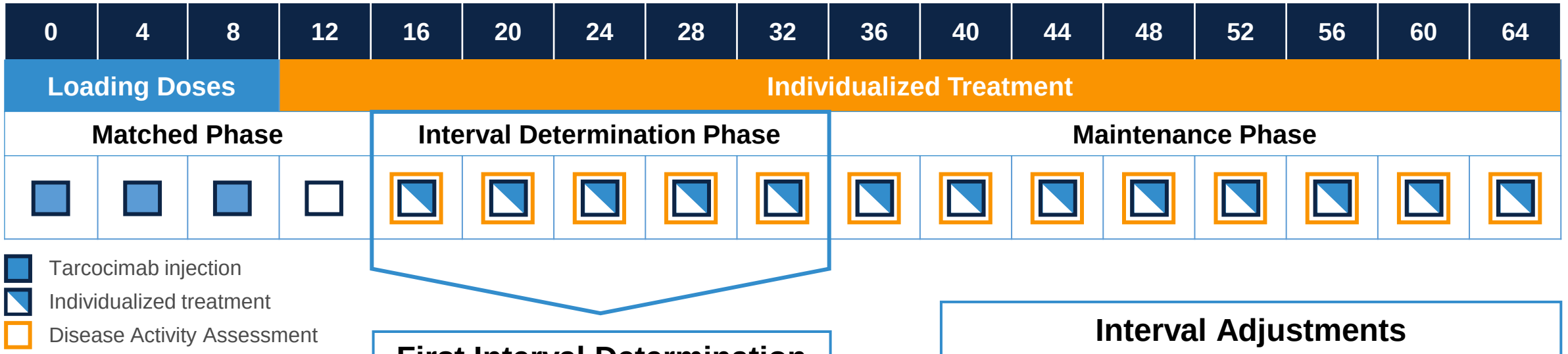
Key secondary endpoint

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

Disease <u>activity</u> criteria

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

Disease <u>stability</u> criteria:

- CST within 30 µm of lowest previous CST

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**

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)

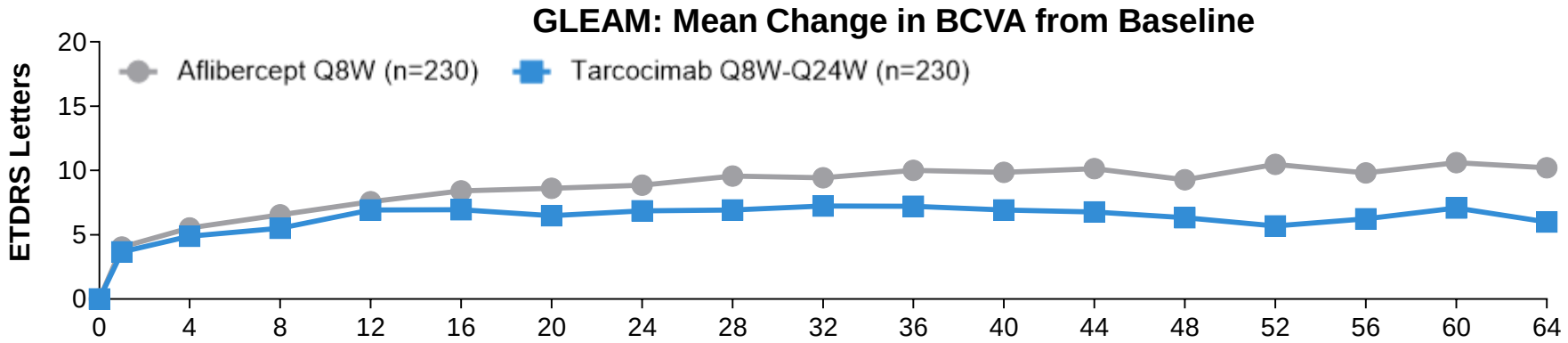
n = Number of participants treated; The denominator for percentages is the number of participants treated within each treatment arm. Snellen equivalent of 20/40 is 69 ETDRS letters and of 20/200 is 38 ETDRS letters.
Denominator for percentages of Diabetic Retinopathy Severity Score is the number of subjects 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.

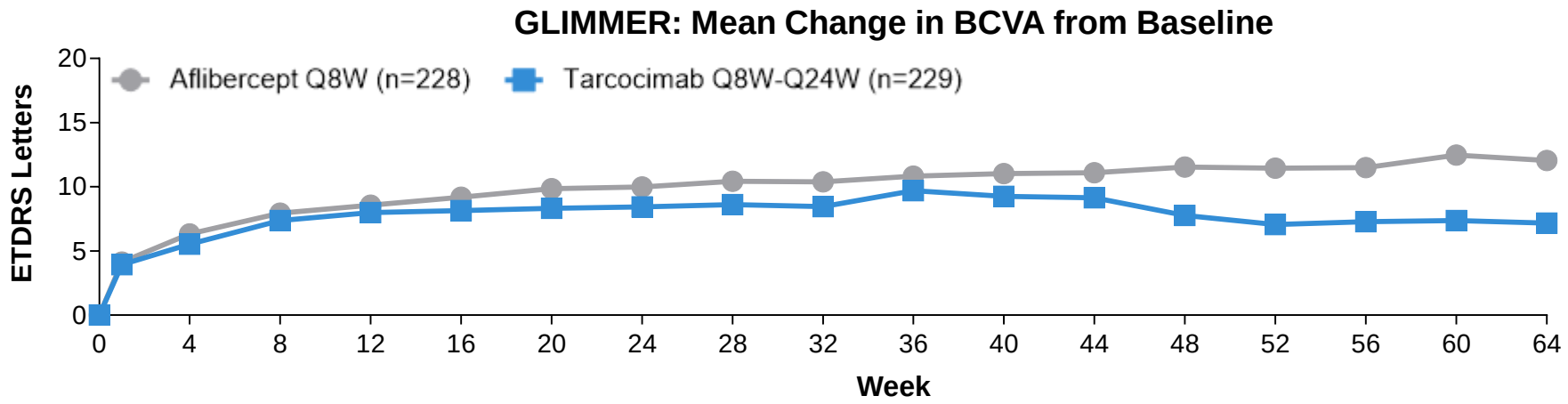
Primary endpoint: mean change in BCVA from baseline at average of weeks 60-64. Tarcocimab did not demonstrate non-inferiority to aflibercept in either GLEAM or GLIMMER



Avg of Weeks 60 & 64 (SD)

10.3 (8.1)

6.4 (8.8)



Avg of Weeks 60 & 64 (SD)

12.2 (10.1)

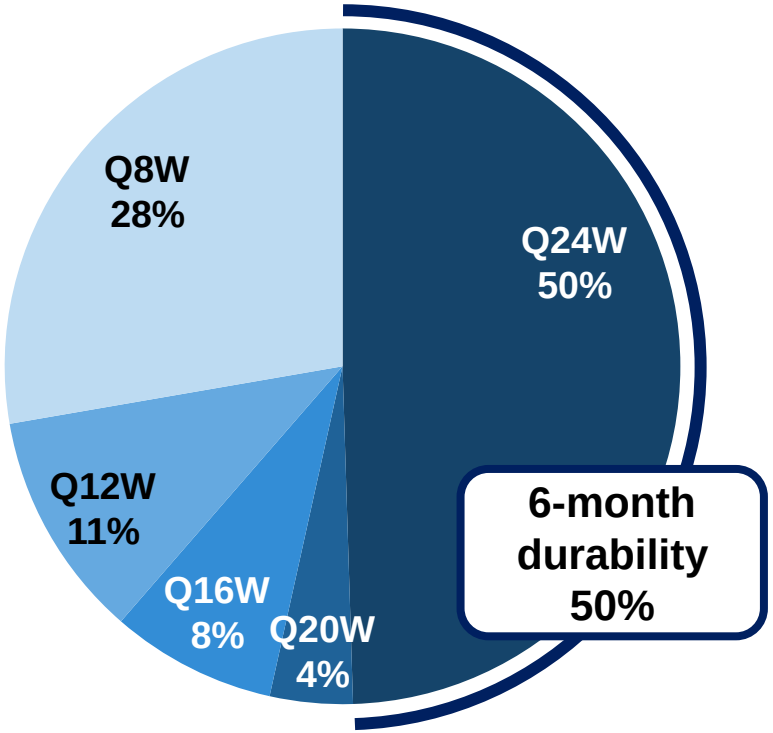
7.4 (11.2)

		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		

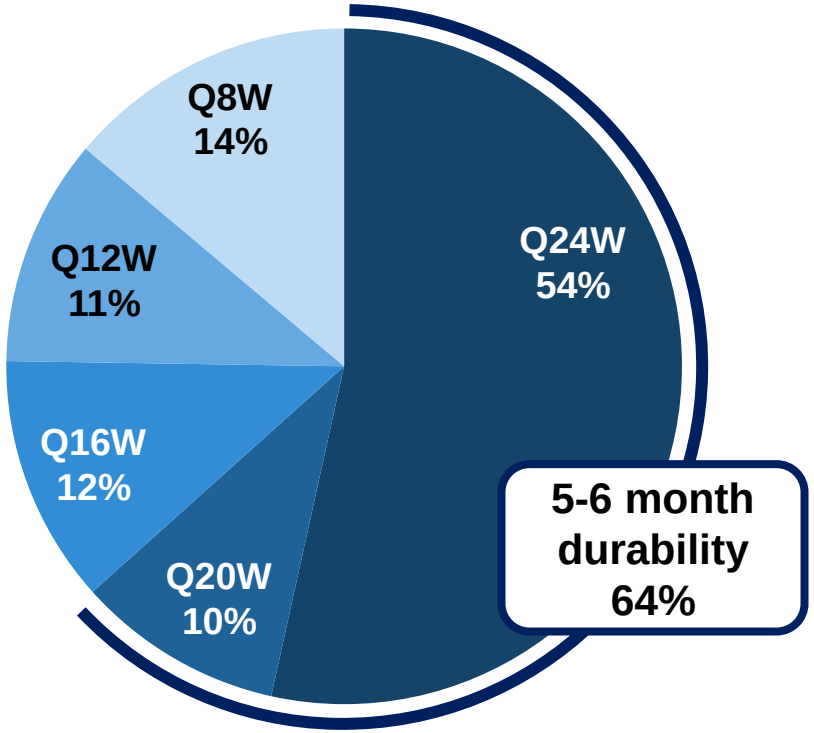
Observed values shown in graphs. LSM, least square mean; MMRM, mixed model for repeated measures. Non-inferiority margin = 4.5 ETDRS letters. BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study. [A] Results are based on a MMRM model including the change from baseline 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

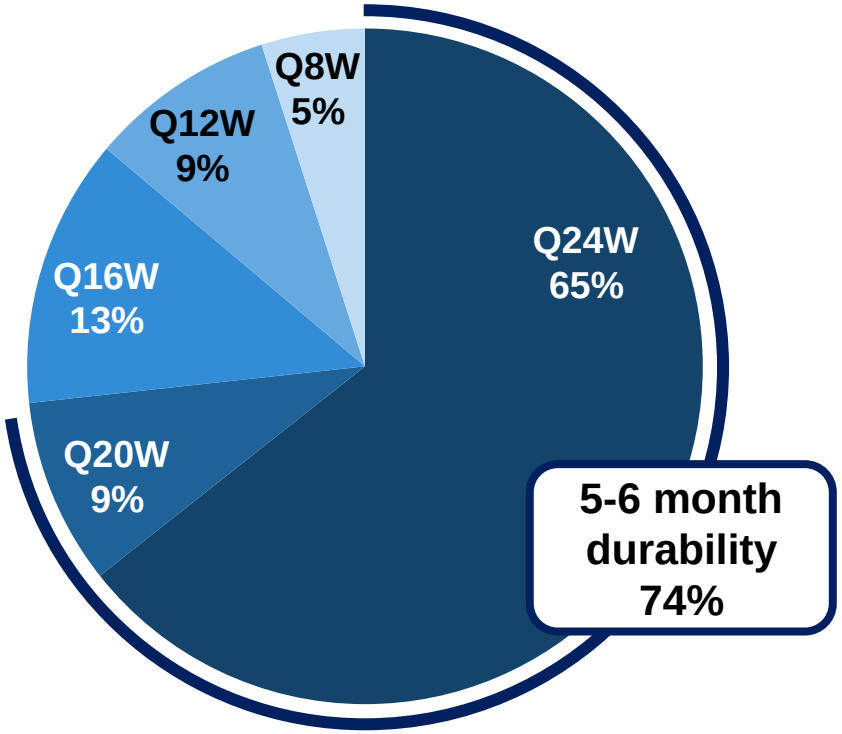
Interval at the Primary Endpoint[a]



First interval (after 3 loading doses)[b]



Longest interval achieved[b]

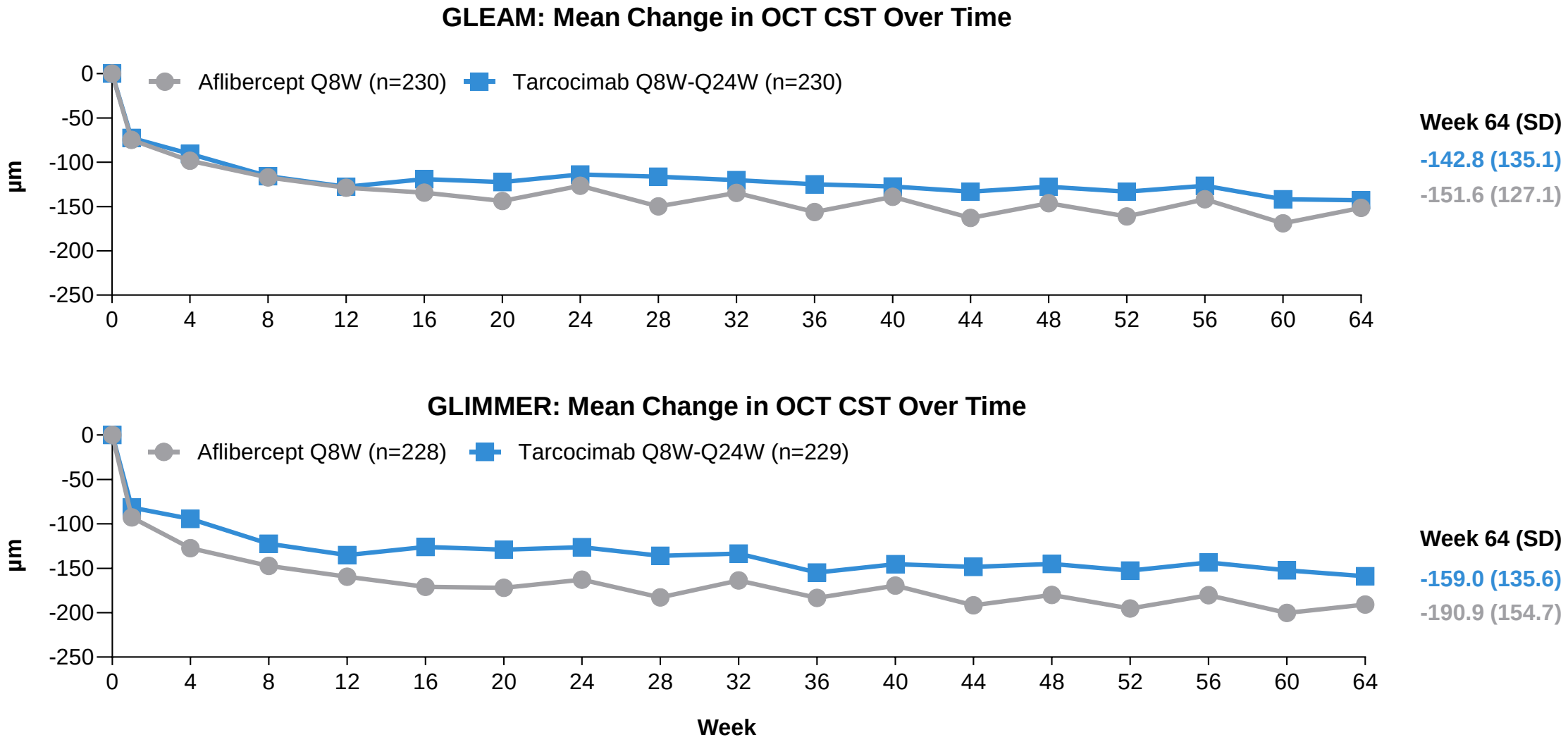


Median No. of Injections through Week 64

	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 (≥2.0% in either study arm) were low. An imbalance in cataracts was observed

Pooled GLEAM and GLIMMER

Common Ocular Adverse Events (AEs) up to Week 64	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	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 Week 64 Safety Population. Events are investigator reported. In upper table, patients can have more than one AE of the same AE category reported. Adverse events are events with start date ≥first study drug date and ≤last study drug date + 28 days.

Cataract imbalance in GLEAM and GLIMMER not observed with monthly dosing in DAYLIGHT. Mechanism underlying this observation is not yet understood & further analyses are warranted

	GLEAM + GLIMMER (DME)		DAYLIGHT (wAMD)		DAZZLE (wAMD)		BEACON (RVO)	
Duration of Follow-Up	**64 Weeks**		**48 Weeks**		**52 Weeks**		**24 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%)	7 (2.5%)	6 (2.1%)
Median number of doses	**5**	10	**12**	7	5	8	4	6

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

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.

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%)

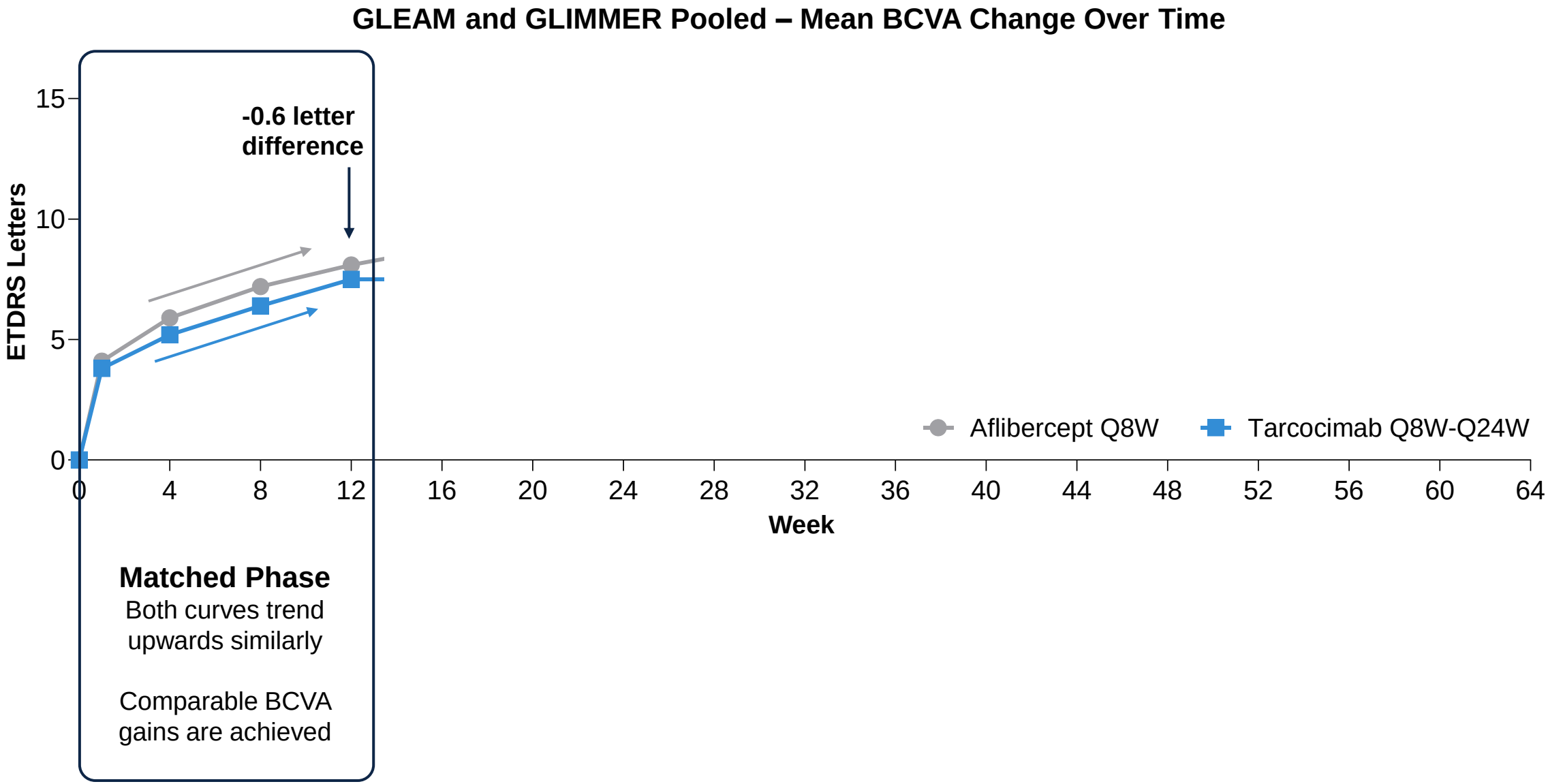
Endophthalmitis in Study Eye up to Week 64	**Tarcocimab Q8W-Q24W (n=458)**	**Aflibercept Q8W (n=459)**
Subjects with at Least 1 Endophthalmitis AE	1 (0.2%)	2 (0.4%)

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

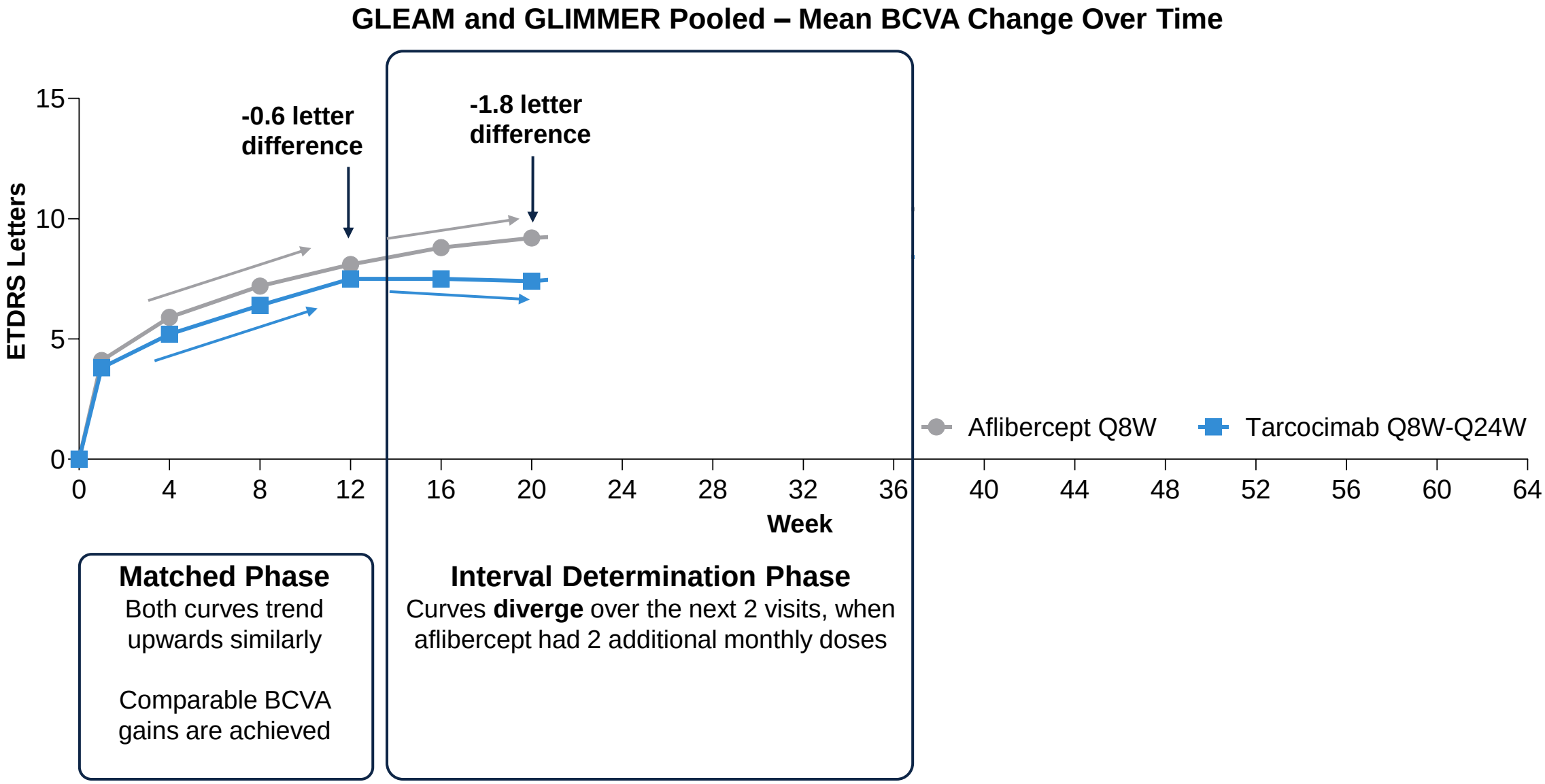
*Reported AE terms: keratic precipitates, iritis, eye inflammation, uveitis, vitreal cells, vitreous haze, vitritis
Results presented for the Week 64 Safety Population. Events are investigator reported. Adverse events are events with start date ≥first study drug date and ≤last study drug date + 28 days.

Why did tarcocimab not meet the primary endpoint?

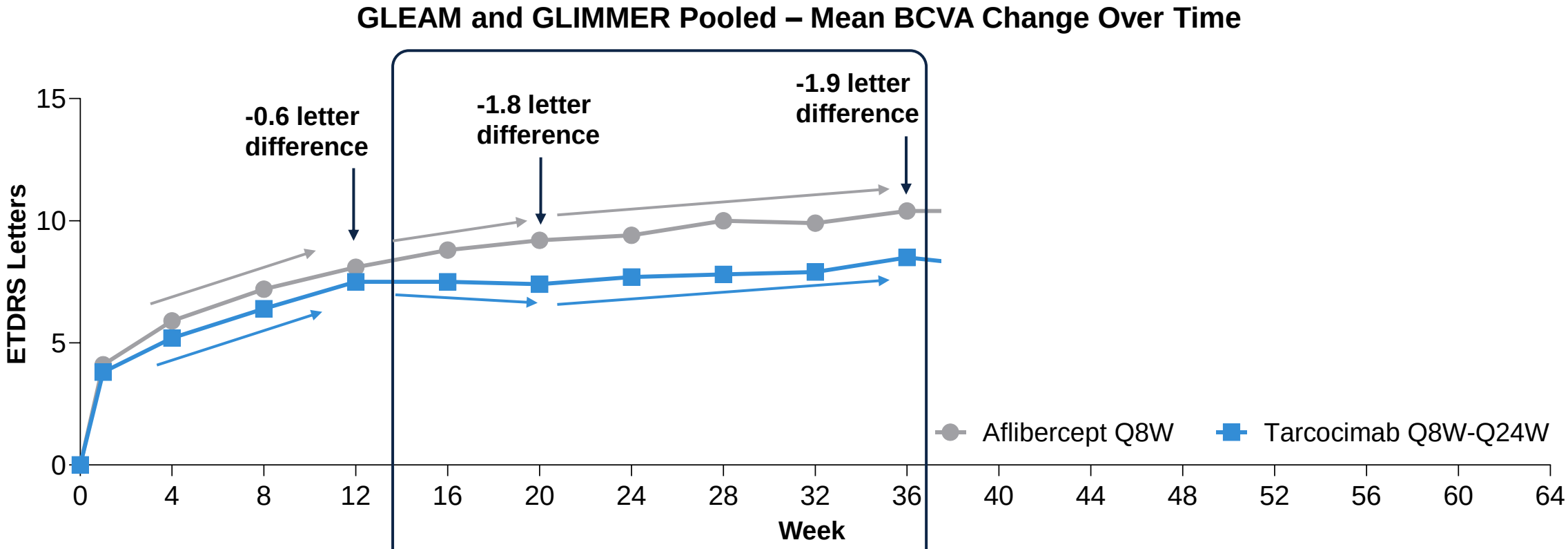
Insight #1: the matched phase was not the problem



Insight #2: having two fewer loading doses likely had an impact



Insight #3: individualized dosing with tarcocimab maintained initial BCVA gains, with ≥50% patients consistently on 6-month dosing



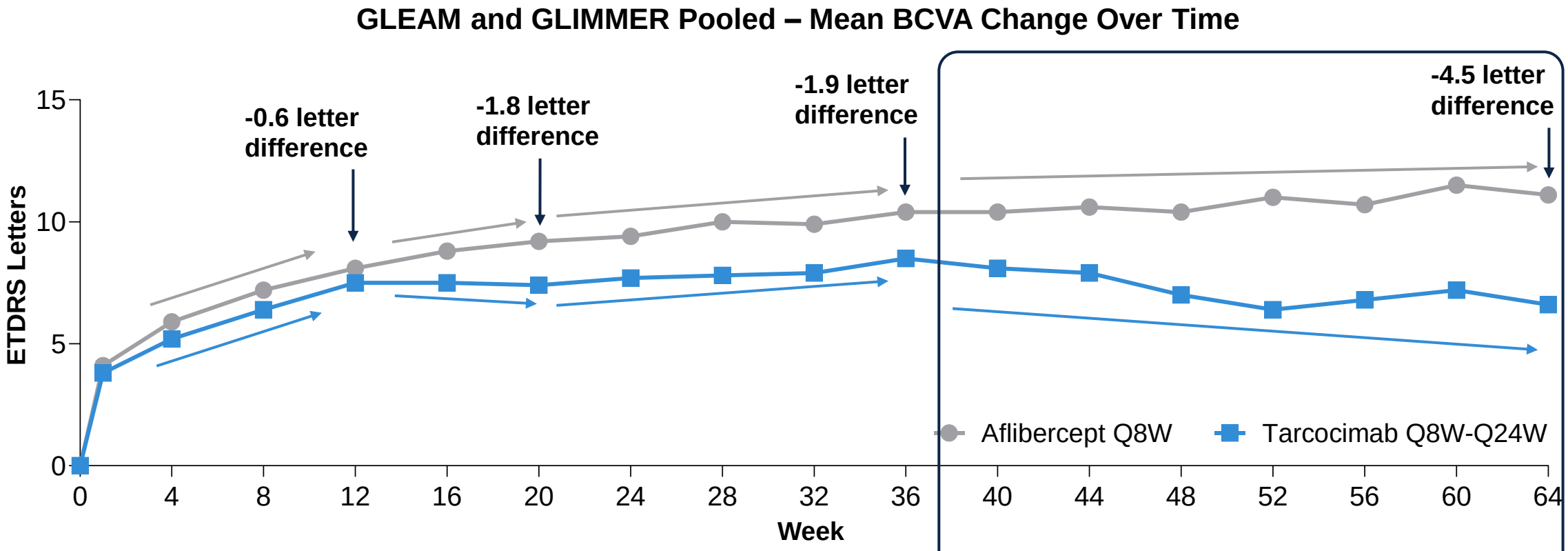
Matched Phase
Both curves trend upwards similarly

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

Insight #4: the main difference 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

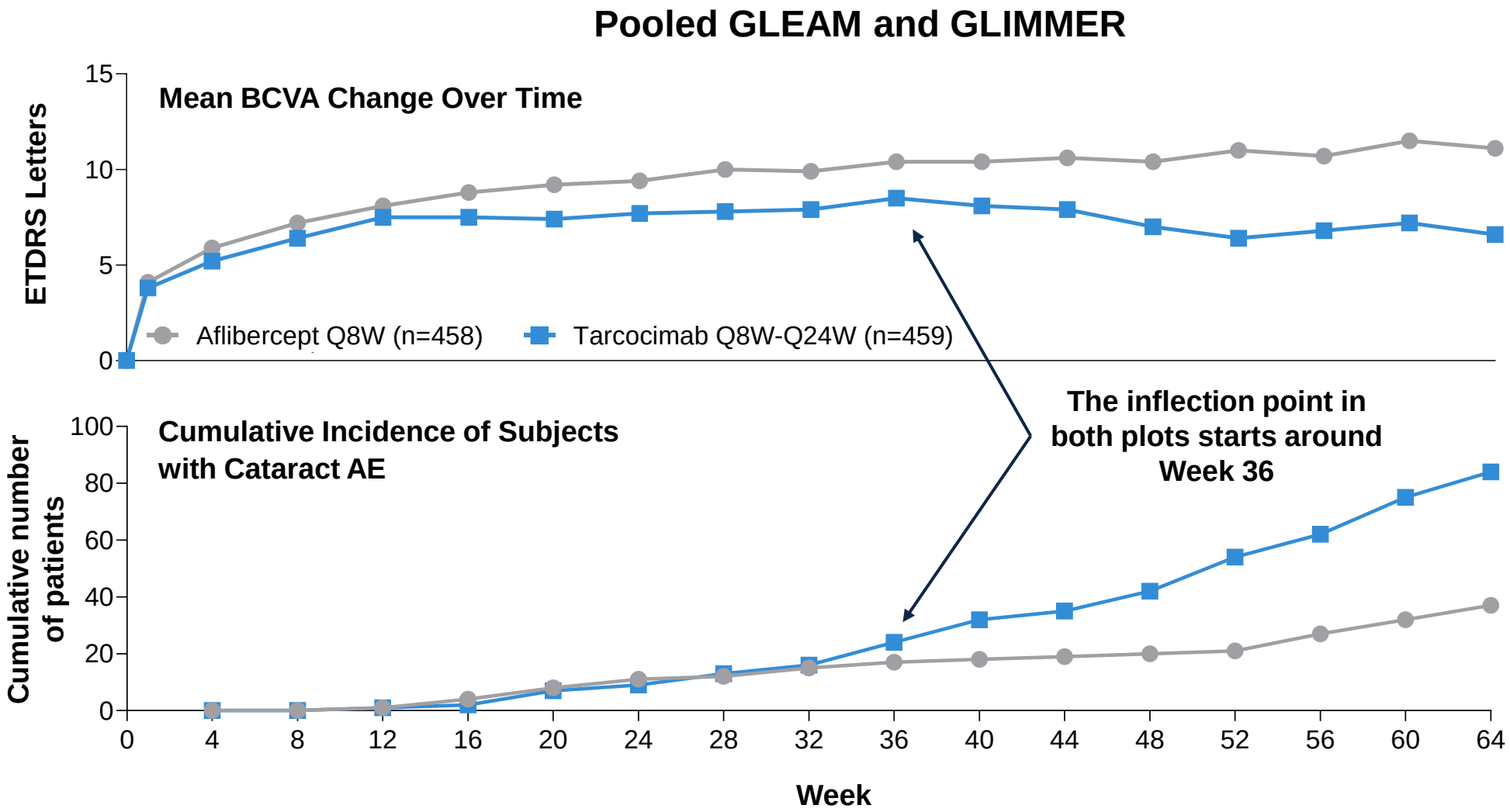
Both curves subsequently trend upwards, with ≥50% of tarcocimab patients initiating 6-month dosing

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:

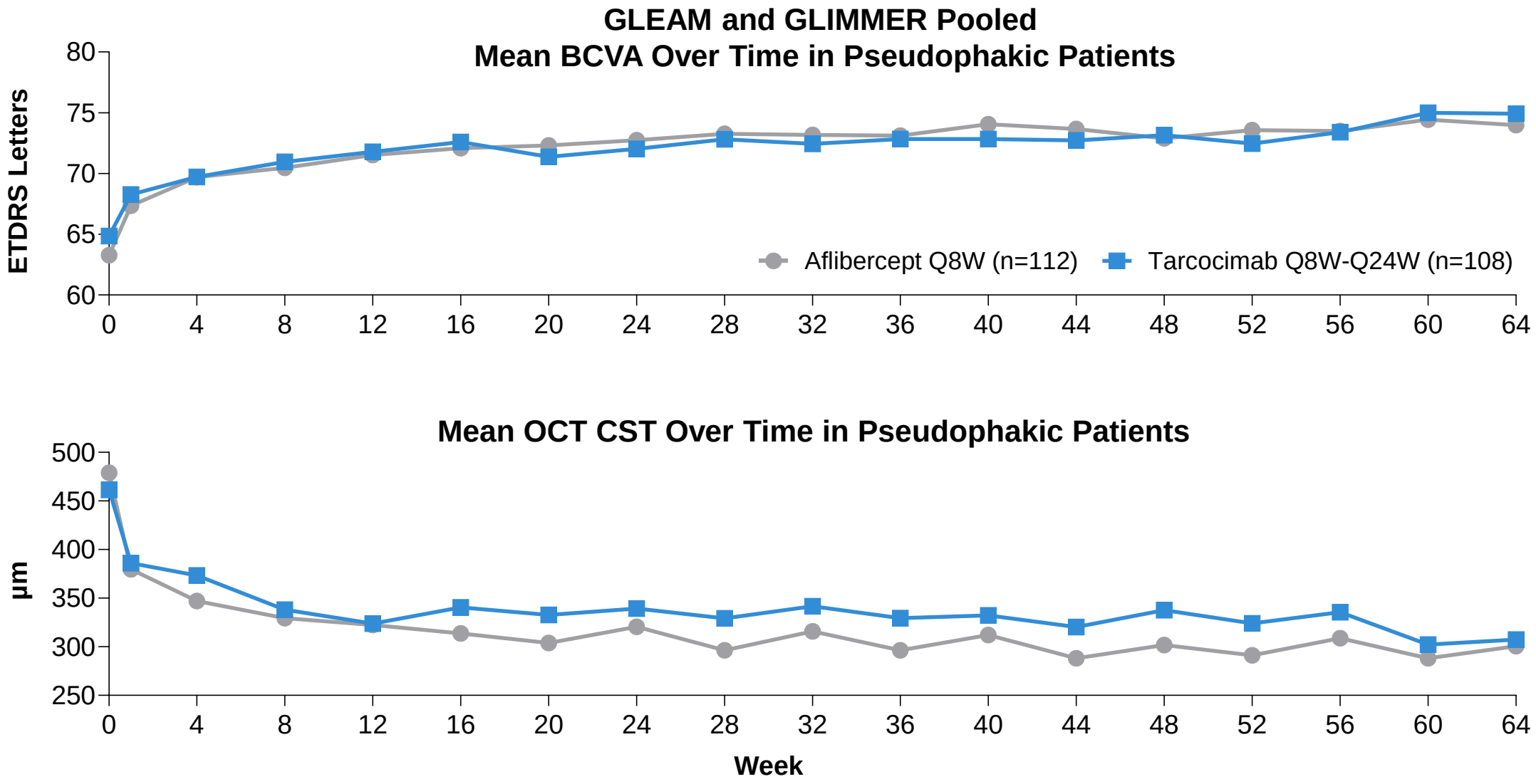
Tarcocimab: 89 (19.4%)

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

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 • Mechanism(s) behind this are being explored
Development of tarcocimab is being discontinued	• GLOW (NPDR) and Year 1 BEACON (RVO) data will be reported • Efforts underway to better understand increased incidence of cataracts
KSI-501, a clinical stage anti-IL-6/VEGF bispecific, is progressing	• KSI-501 program has a differentiated mechanism of action targeting both IL-6 mediated immune-inflammation as well as VEGF mediated angiogenesis and vascular permeability • Kodiak is advancing KSI-501 both as (i) its naked protein and (ii) an enhanced bioconjugate form

Thank you to all GLEAM and GLIMMER investigators, site staff and patients

Czech Republic: Axon Clinical, Oftex, Vseobecna Fakultni Nemocnice V Praze; **France:** Centre Paradis Monticelli, Centre Hospitalier Intercommunal de Créteil, Fondation Rothschild, CHRU Dijon Complexe Du Bocage, Hôpital de La Croix Rousse, Hôpital Lariboisière; **Germany:** St. Elisabeth Krankenhaus, Universitätsklinikum Freiburg, Universitätsklinikum Regensburg, St Franziskus Hospital, Dietrich Bonhoeffer Klinikum Neubrandenburg; **Hungary:** Jahn Ferenc Dél-Pesti Kórház és Rendelointézet, Bajcsy-Zsilinszky Korhaz es Rendelointezet, Budapest Retina Associates, Ganglion Medical Center, Semmelweis Egyetem, Szabolcs-Szatmar-Bereg Megyei Korhazak es Egyetemi Oktatokorhaz; **Israel:** Shamir Medical Center Assaf Harofeh, Tel Aviv Sourasky Medical Center, Hadassah University Hospital, Rambam Medical Center, Meir Medical Center, Rabin Medical Center, Kaplan Medical Center, Assuta HaShalom, Bnai Zion Medical Center; **Italy:** Ospedale San Raffaele, Fondazione PTV Policlinico Tor Vergata, Fondazione Policlinico Universitario A Gemelli, AOU dell'Università degli Studi della Campania Luigi Vanvitelli; **Latvia:** Pauls Stradins Clinical University Hospital, Riga Eastern Clinical University Hospital Clinic Bikernieki, Latvian American Eye Center, Signes Ozolinas Doctor Praxis In Ophthalmology; **Poland:** Dr. Nowosielska Okulistyka i Chirurgia Oka, Optimum Profesorskie Centrum Okulistyki, Uniwersytecki Szpital Kliniczny im. Jana Mikulicza Radeckiego we Wroclawiu, Oftalmika Sp., Specjalistyczny Szpital im. Alfreda Sokolowskiego, Uniwersyteckie Centrum Kliniczne Im. Prof. K. Gibinskiego Slaskiego Uniwersytetu Medycznego w Katowi; **Slovakia:** Nemocnica s Poliklinikou Trebisov, Fakultna Nemocnica Trencin, Fakultna Nemocnica s Poliklinikou Zilina, Hospital Ruzinov, Fakultna Nemocnica s Poliklinikou F. D. Roosevelta, Uvea Klinika; **Spain:** Hospital dos de Maig, Hospital Universitario Rio Hortega, Hospital Universitari General de Catalunya - Grupo Quironsalud, Hospital Universitario Puerta de Hierro – Majadahonda, Hospital Universitario Miguel Servet, Hospital Universitari i Politecnic La Fe de Valencia, Hospital Clinic de Barcelona, Hospital Clinico Universitario Lozano Blesa; **United States:** Northern California Retina Vitreous Associates, Retinal Research Institute, Retina Vitreous Associates Medical Group, Retina Research Institute of Texas, Retina Consultants of Texas - Houston, Retina Consultants of Texas - The Woodlands, Sierra Eye Associates, Retina Consultants of San Diego, Medical Center Ophthalmology Associates, Charleston Neuroscience Institute, NJ Retina - Teaneck, Retina Specialty Institute, Colorado Retina Associates, Retinal Consultants of Hawaii, Southeast Retina Center, Texas Retina Associates - Plano, Vitreoretinal Surgery PA, Cumberland Valley Retina Consultants, Retina Northwest, Austin Retina Associates - Austin, Palmetto Retina Center, Retina Vitreous Associates of Florida, Southeastern Retina Associates, Retina Associates PA, Ophthalmic Consultants of Boston, Tennessee Retina, Retina Associates of Florida, Envision Ocular, Foundation for Vision Research, Wolfe Eye Clinic, Strategic Clinical Research Group, Associated Retinal Consultants, National Ophthalmic Research Institute, Rand Eye Institute, Retina Consultants of Texas – Katy, Cascade Medical Research Institute, Retina Consultants of Orange County, Retina Associates of Kentucky, Retinal Consultants Medical Group Inc, Black Hills Regional Eye Institute, Vitreo Retinal Consultants and Surgeons, California Retina Consultants – Santa Maria, Florida Eye Associates, Springfield Clinic, Austin Retina Associates – Round Rock, Retina-Vitreous Surgeons of Central NY, Retina Group of New England, Retinal Specialists of Idaho, Emanuelli Research & Development Center, Long Island Vitreo Retinal Consultants, Retina Associates of Western New York, Retina Group of Florida, UCLA Doheny Eye Center, Charleston Neuroscience Institute, Vitreo Retinal Associates, Retina Consultants of Nevada – Henderson, Maine Eye Center, Connecticut Eye Consultants, Retina Consultants of Southern California, Center for Retina & Macular Disease, Retina Center Northwest, Talley Medical Surgical Aye Care Associates, Retina Institute of Virginia, Spokane Eye Clinic, Florida Retina Institute, Midatlantic Retina, Southern Vitreoretinal Associates, Western Carolina Retinal Associates, Ophthalmic Consultants of Long Island, Blue Ocean Clinical Research, Austin Research Center for Retina, Retina Vitreous Associates of Florida, Fort Lauderdale Eye Institute, Charles Retina Institute, Georgia Retina, The Lundquist Institute for Biomedical Innovation at Harbor – UCLA Medical Center, Texas Retina Associates – Fort Worth, Texas Retina Associates – Arlington, Florida Retina Consultants, Palmetto Retina Center, Retina Consultants of San Antonio, Star Vision Research, Charleston Neuroscience Center, Piedmont Eye Center.