Efficacy, durability and safety of KSI-301 antibody biopolymer conjugate in wet AMD

Primary results of the Phase 2b/3 DAZZLE study

Carl Regillo, MD
Retina Service
Wills Eye Hospital
Thomas Jefferson University
Philadelphia, PA

Same presentation was given at ARVO and RWC.
Unabridged version (includes slides 19, 22, 24 not presented due to time constraints)

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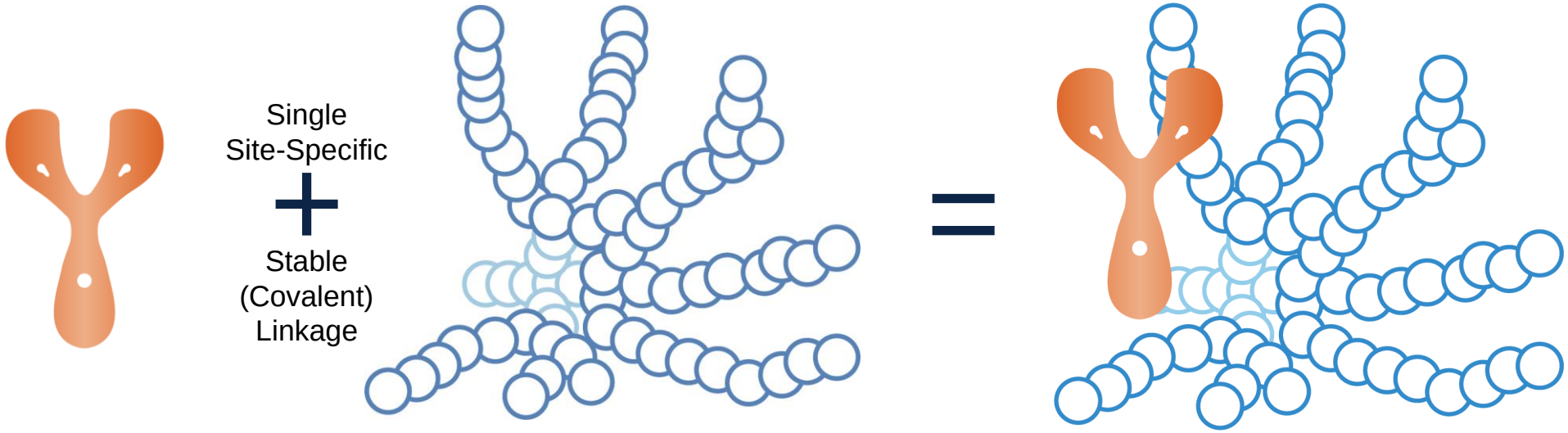
Disclosures

- Financial Disclosures:
  - *Consultant*: Adverum, Aldeyra, Allergan, Annexon, Apellis, Chengdu Kanghong, EyePoint, Genentech, GrayBug, Iveric Bio, Kodiak, Lineage, Merck, NGM, Novartis, Ocugen, Regenxbio, Stealth, Takeda, Thea, Zeiss
  - *Independent Research Contractor*: Adverum, Allergan, Annexon, Apellis, Astellas, Chengdu Kanghong, EyePoint, Genentech, Iveric Bio, Kodiak, Lineage, NGM, Notal, Novartis, Opthea, Regeneron, Regenxbio

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

KSI-301: Antibody Biopolymer Conjugates (ABCs)

Biologic engineered for increased durability and efficacy



ANTIBODY

IgG1 Antibody
Immunologically inert

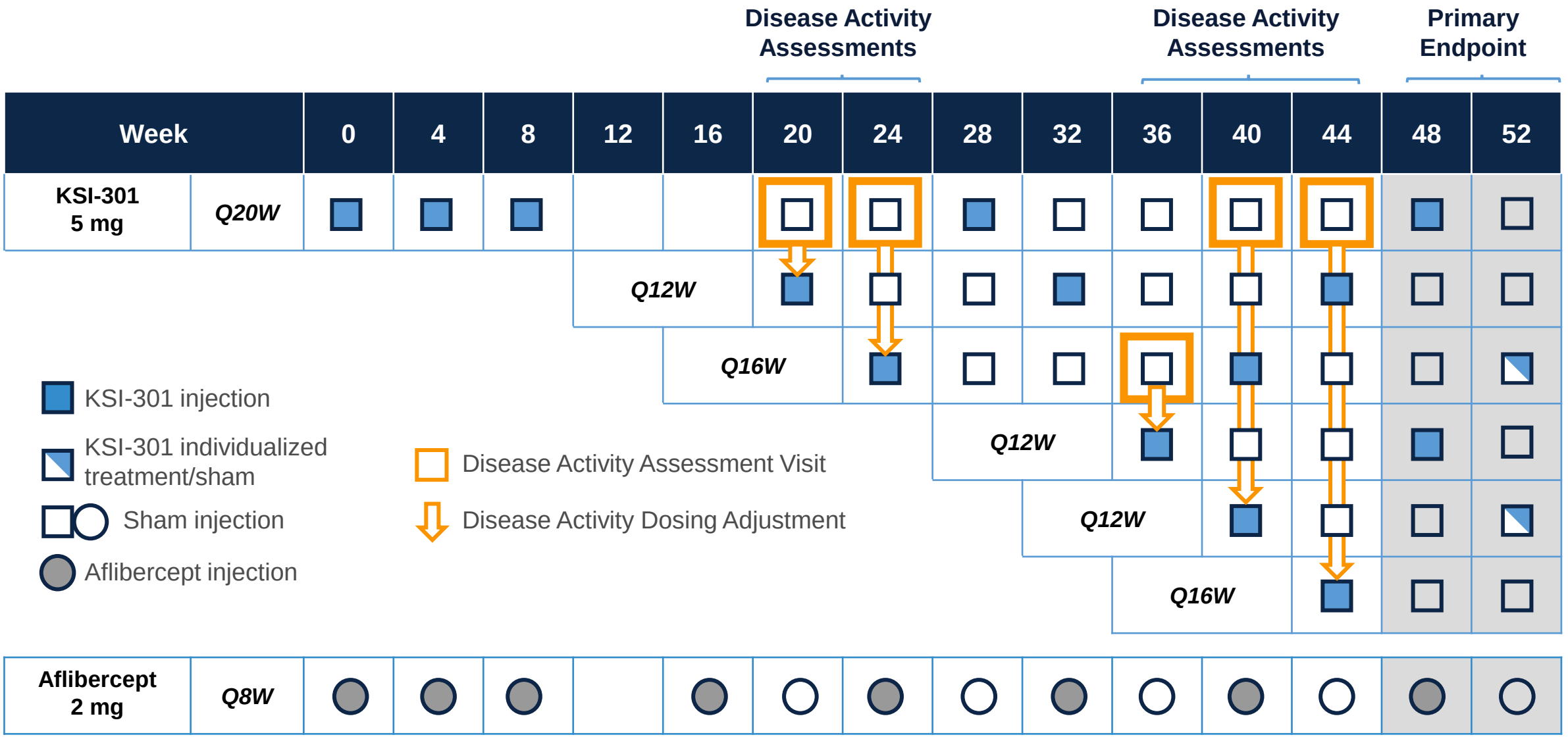
BIOPOLYMER

Branched, Optically Clear,
High Molecular Weight
Phosphorylcholine Polymer

CONJUGATE

A new set of integrated properties

DAZZLE Study Design: Randomized, double-masked non-inferiority study of KSI-301 every 3 to 5 months vs aflibercept every 2 months in treatment-naïve wet AMD patients



Clinicaltrials.gov, study identifier: NCT04049266
AMD: age-related macular degeneration; Q8W: every 8 weeks, Q12W: every 12 weeks; Q16W; every 16 weeks; Q20W: every 20 weeks.

Patient eligibility criteria

Key Ophthalmic Inclusion Criteria

- Active treatment-naïve CNV secondary to wet AMD
- BCVA of 80 to 25 ETDRS letters (≈20/25 to 20/320 Snellen)
- Any CNV lesion type with a CNV component affecting the central subfield
- Lesion area <12 disc areas
- CNV of at least 50% on the total lesion size
- Intraretinal fluid and/or subretinal fluid and/or subretinal hyperreflective material affecting the central subfield

Key Ophthalmic Exclusion Criteria

- CNV secondary to other causes
- Any history of macular pathology unrelated to AMD but affecting vision or contributing to subretinal or intraretinal fluid, such as central serous chorioretinopathy
- Fibrosis or atrophy of >50% of the lesion size and/or involving the foveal center Subretinal blood affecting the foveal center of the Study Eye and/or more than 50% of the lesion size
- History or evidence of a concurrent intraocular condition in the Study Eye that could require either medical or surgical intervention during the study to prevent or treat visual loss.
- Uncontrolled glaucoma

AMD: age-related macular degeneration; CNV: choroidal neovascularization; BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study;

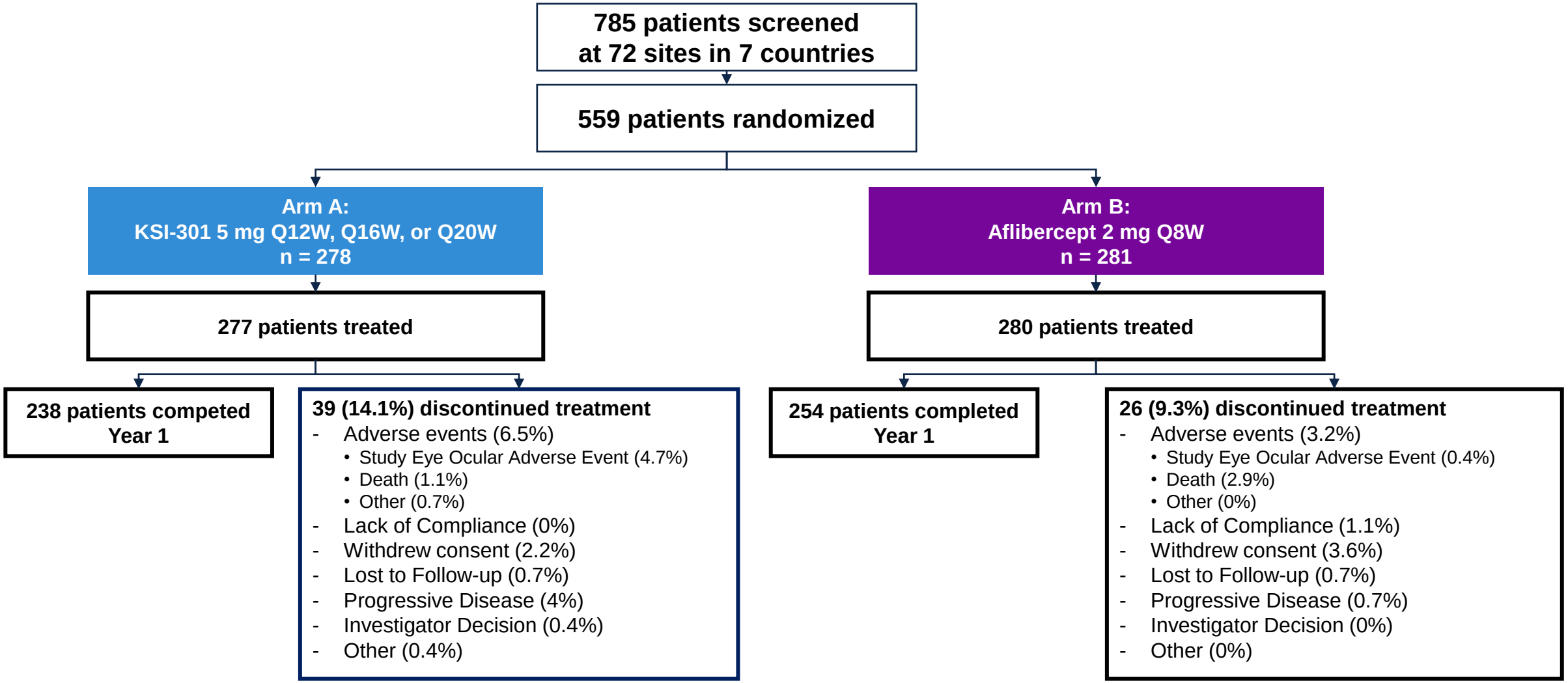
Disease activity assessment criteria for determining KSI-301 treatment intervals - based on functional and anatomical changes

Dosing interval for KSI-301 would be reduced from every 20 weeks to every 16 or 12 weeks, or from every 16 to every 12 weeks, if any of the following criteria were met at a disease activity assessment visit:

- Decrease in BCVA of ≥ 5 letters compared to Week 12 and an increase in Optical Coherence Tomography (OCT) central subfield thickness (CST) ≥50 µm compared to Week 12.
- Increase in OCT CST ≥75 µm compared to Week 12.
- Decrease in BCVA of ≥ 10 letters compared to the highest BCVA since Day 1 (inclusive) due to wet AMD disease activity (e.g. increased intraretinal fluid, increased subretinal fluid, new intraretinal hemorrhage, new subretinal hemorrhage).
- New macular hemorrhage (documented with color fundus photograph).

AMD: age-related macular degeneration; BCVA: best-corrected visual acuity; OCT: optical coherence tomography; CST: central subfield thickness

Patient Disposition – a greater number of discontinuations occurred in the KSI-301 group, mainly driven by events associated with undertreatment



Q8W: every 8 weeks; Q12W: every 12 weeks; Q16W; every 16 weeks; Q20W: every 20 weeks.

Baseline Key Demographics – Comparable Between Groups

Parameter	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
Gender		
Female	178 (64.3%)	168 (60.0%)
Age at Randomization, years		
Mean (SD)	76.6 (7.35)	76.2 (8.27)
Ethnicity		
Hispanic or Latino	17 (6.1%)	9 (3.2%)
Not Hispanic or Latino	260 (93.9%)	271 (96.8%)
Race		
American Indian or Alaska Native	1 (0.4%)	1 (0.4%)
Asian	4 (1.4%)	5 (1.8%)
Black or African American	1 (0.4%)	1 (0.4%)
Other	0	1 (0.4%)
White	271 (97.8%)	272 (97.1%)
Geographical Region		
Europe	48 (17.3%)	45 (16.1%)
USA	229 (82.7%)	235 (83.9%)

N = Number of participants treated; The denominator for percentages is the number of participants treated within each treatment arm
Q8W: every 8 weeks; Q12W: every 12 weeks; Q20W: every 20 weeks.

Baseline Ocular Characteristics

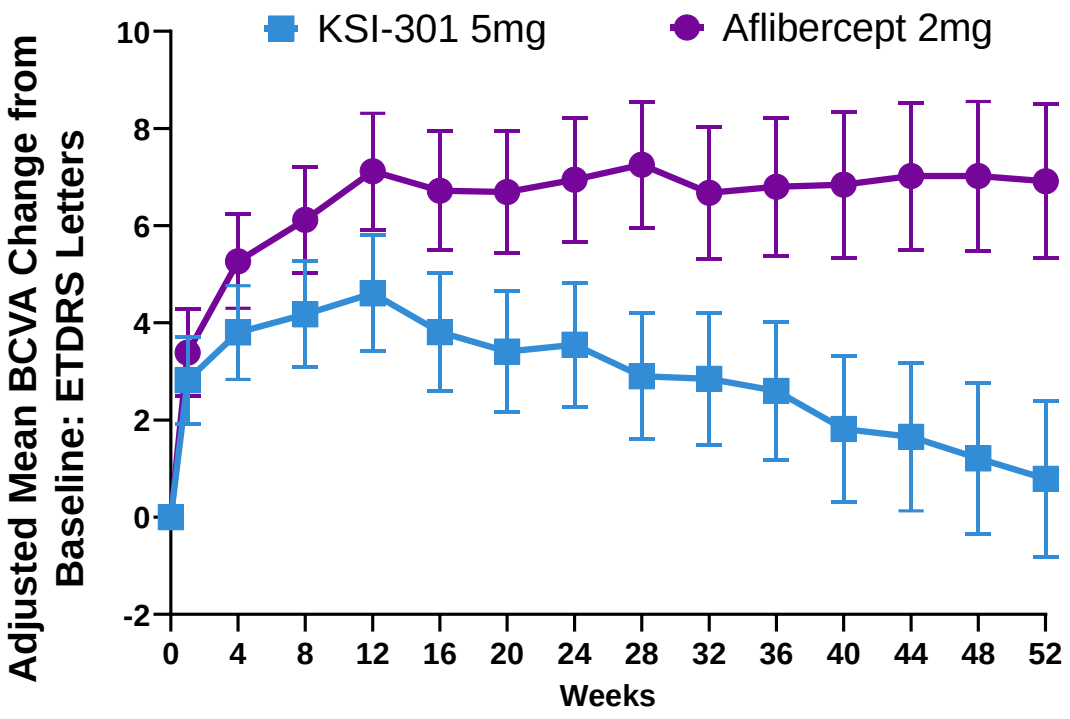
Parameter	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
BCVA, ETDRS Letters		
Mean (SD)	**63.6 (12.23)**	**63.6 (12.34)**
Snellen equivalent	≈20/50	≈20/50
BCVA Category		
≤ 49 ETDRS Letters	33 (11.9%)	33 (11.8%)
50 – 69 ETDRS Letters	133 (48.0%)	136 (48.6%)
70 – 80 ETDRS Letters	111 (40.1%)	111 (39.6%)
BCVA - Low Luminance VA Difference		
< 33	186 (67.1%)	187 (66.8%)
≥ 33	91 (32.9%)	93 (33.2%)
OCT Central Subfield Thickness from ILM to RPE, µm		
Mean (SD)	350.4 (110.90)	359.5 (112.81)
OCT Intraretinal fluid visible in Central 1 mm		
Present	121 (43.7%)	109 (38.9%)
OCT Subretinal fluid visible in Central 1 mm		
Present	224 (80.9%)	231 (82.5%)
Intraocular Pressure, mmHg		
Mean (SD)	15.1 (3.14)	14.6 (3.08)

N = Number of participants treated; The denominator for percentages is the number of participants treated within each treatment arm.
AMD: age-related macular degeneration; BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography; ILM: internal limiting membrane; RPE: retinal pigment epithelium; Q8W: every 8 weeks; Q12W: every 12 weeks; Q20W: every 20 weeks.

BCVA and OCT Outcomes

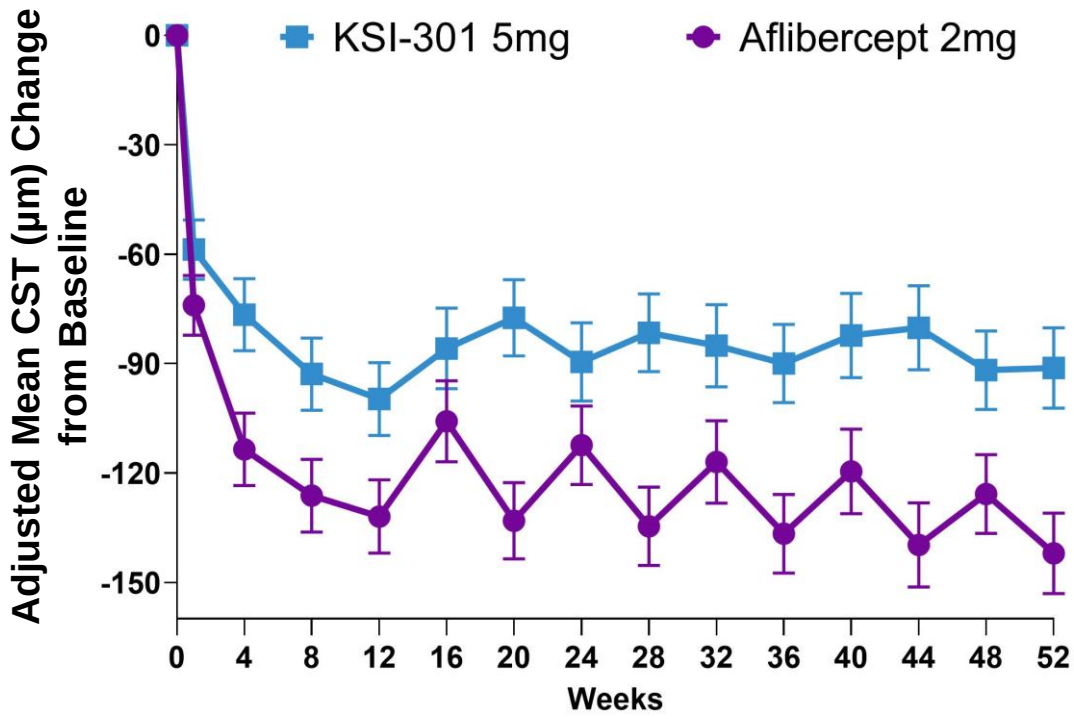
The study did not meet its primary endpoint of non-inferiority in BCVA

BCVA Change Over Time



	Average of weeks 48 & 52
KSI-301 5mg	1.0 (-0.5, 2.5)*
Aflibercept 2mg	7.0 (5.5, 8.5)*

OCT / CST Change Over Time



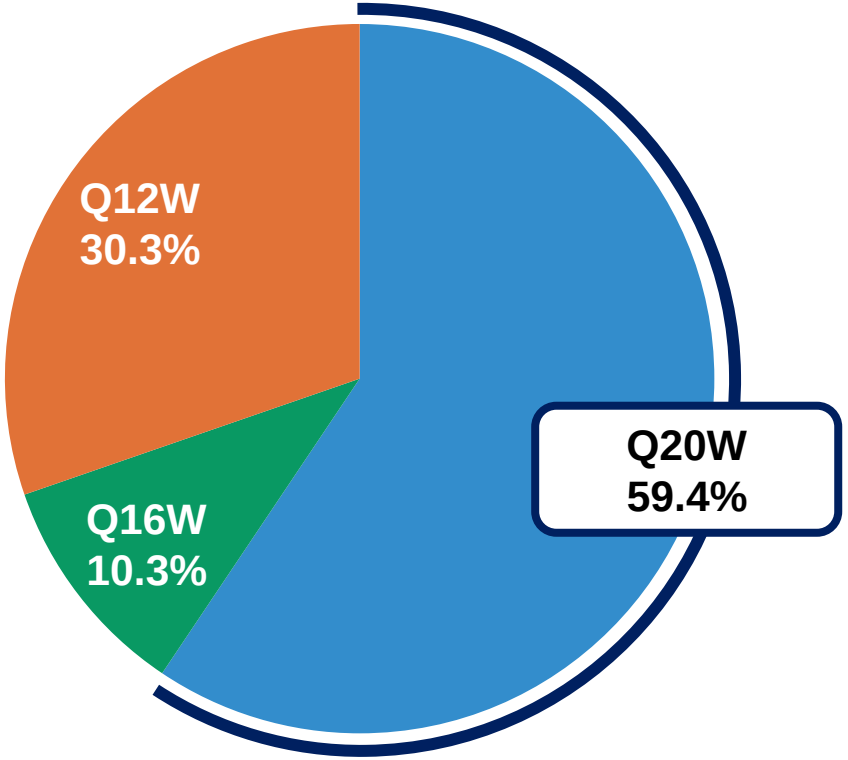
	Average of weeks 48 & 52
KSI-301 5mg	-91.5 (-102, -81)*
Aflibercept 2mg	-133.9 (-144.5, -123.4)*

Least square means BCVA change from baseline and 95% CI are based on MMRM model with treatment, visit, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment by visit interaction. Least square means CST change from baseline and 95% CI are based on MMRM model with treatment, visit, baseline OCT, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment by visit interaction. *Adjusted mean BCVA/CST change from baseline at year 1, averaged over weeks 48 and 52.

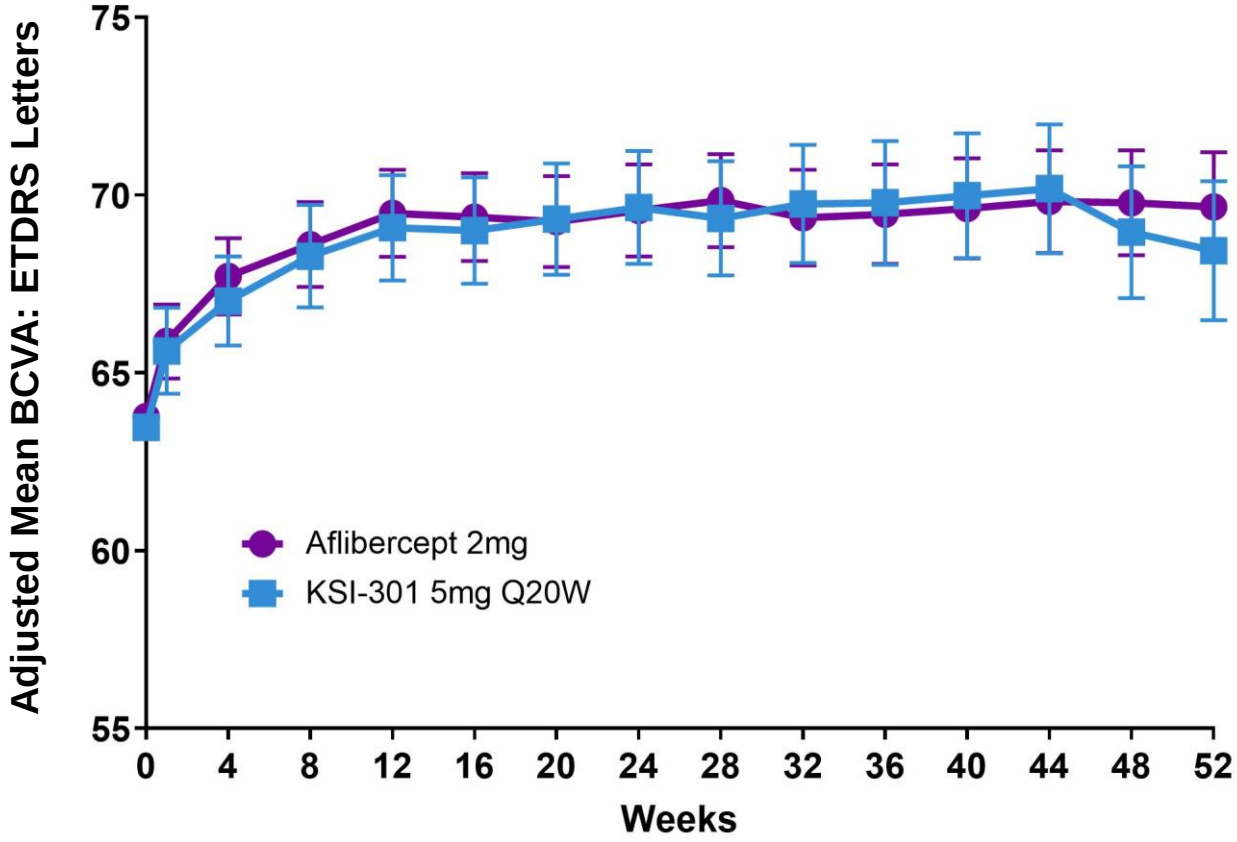
BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography; CST: central subfield thickness.

Durability with KSI-301: The majority of KSI-301 patients achieved a 20-week interval at Year 1 with visual acuity gains comparable to the overall aflibercept group

Proportion of patients in the KSI-301 arm on each treatment interval, among those completing Year 1



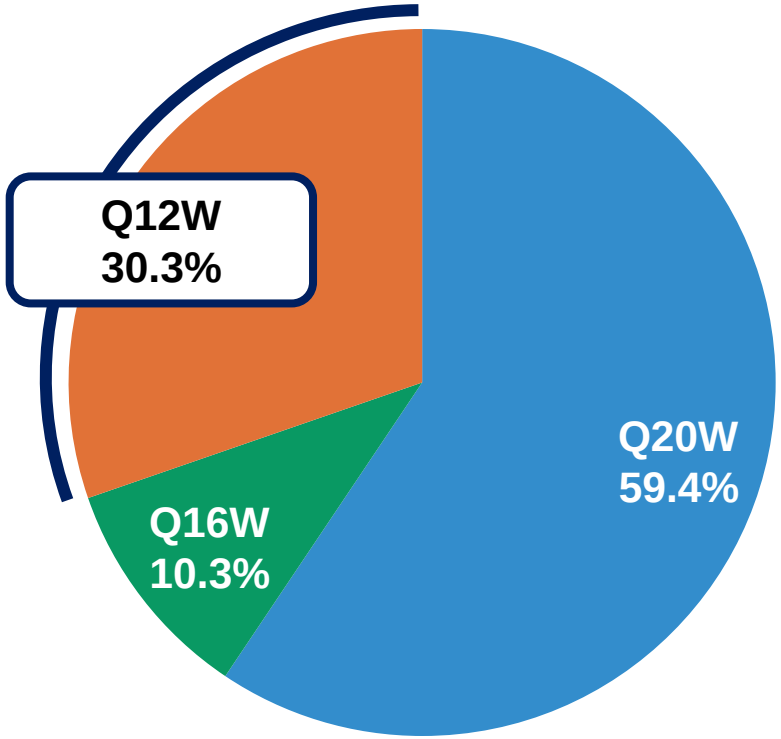
BCVA Over Time by Patient Subgroup, among those completing Year 1



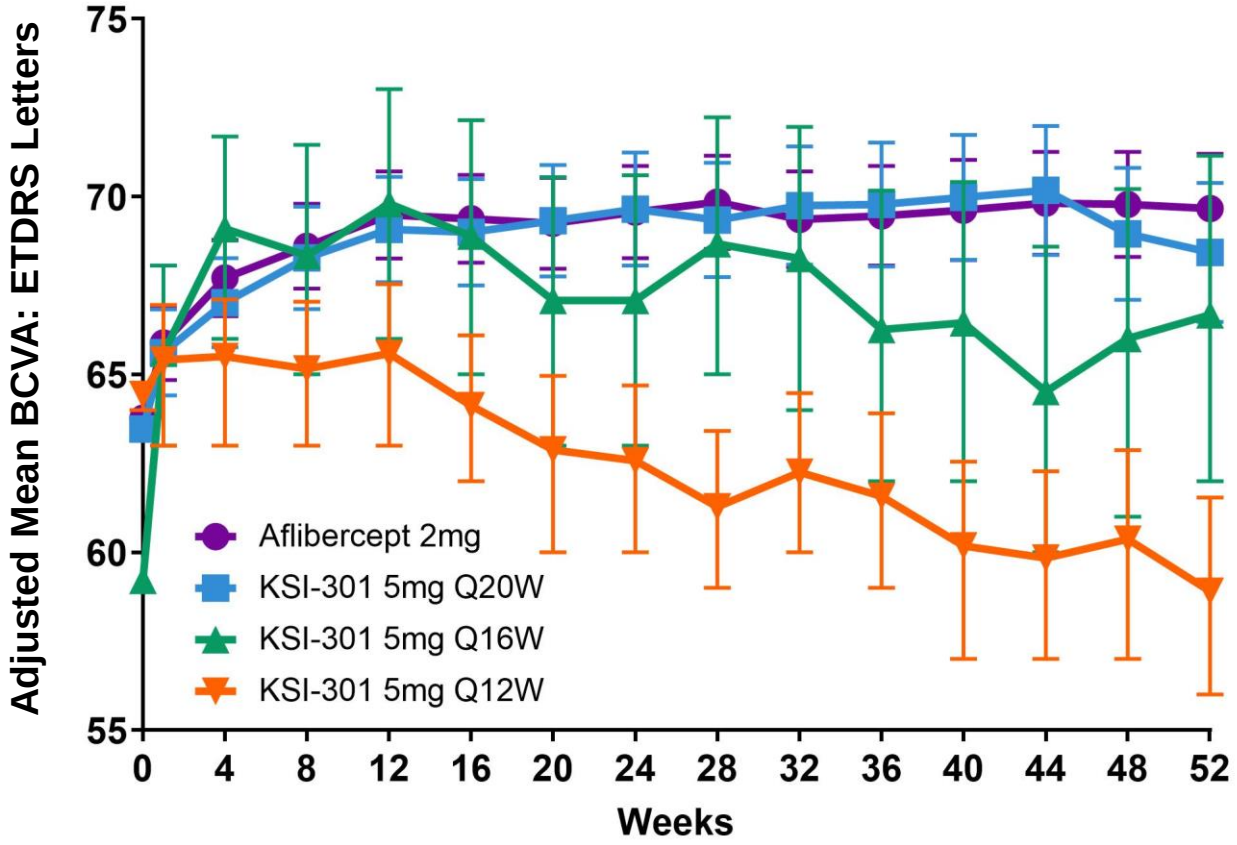
Least square means and 95% CI are based on MMRM model with treatment, visit, baseline BCVA, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment (KSI-301 Q20W, Q16W, Q12W, Aflibercept Q8W) by visit interaction.
Q12W: every 12 weeks; Q16W: every 16 weeks; Q20W: every 20 weeks. BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study.

At the same time, allowing treatment with KSI-301 no more often than every 12 weeks after the loading phase turned out to be insufficient for some patients

Proportion of patients in the KSI-301 arm on each treatment interval, among those completing Year 1



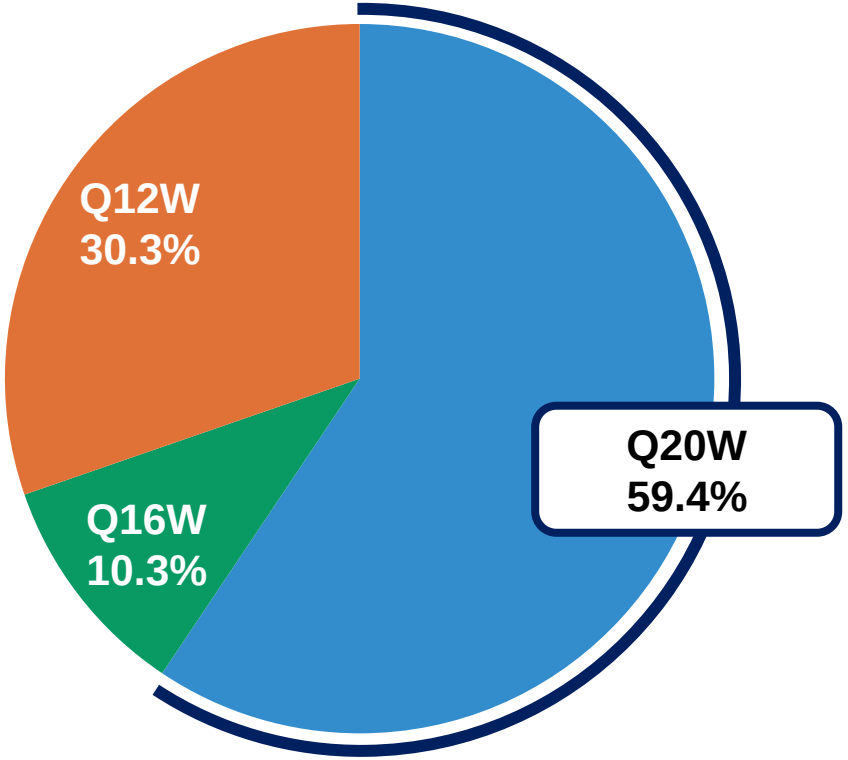
BCVA Over Time by Patient Subgroup, Among those completing Year 1



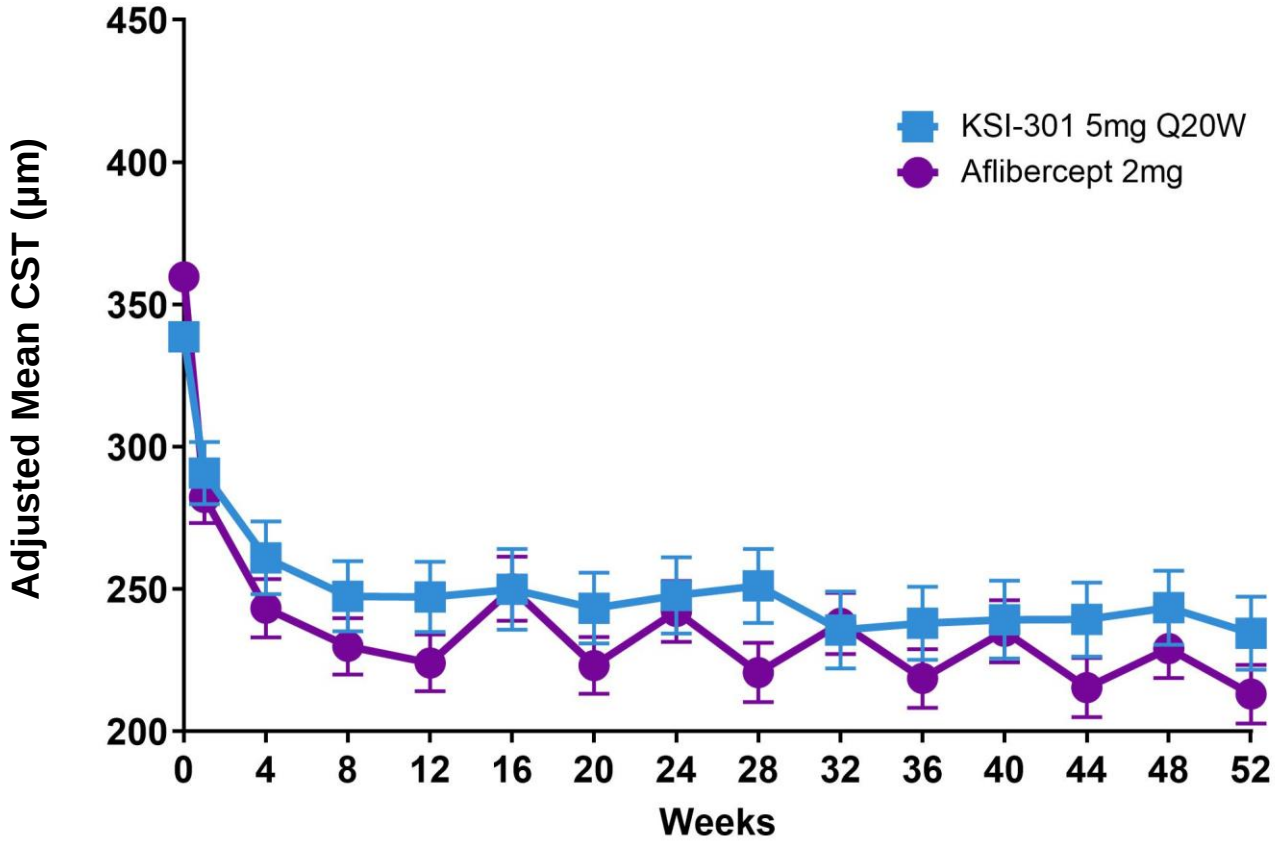
Least square means and 95% CI are based on MMRM model with treatment, visit, baseline BCVA, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment (KSI-301 Q20W, Q16W, Q12W, Aflibercept Q8W) by visit interaction.
Q12W: every 12 weeks; Q16W: every 16 weeks; Q20W: every 20 weeks; BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study.

An initial improvement in retinal anatomy was seen in all KSI-301 durability subgroups and was comparable to aflibercept in the KSI-301 patients who achieved Q20W dosing

Proportion of patients in the KSI-301 arm on each treatment interval, among those completing Year 1



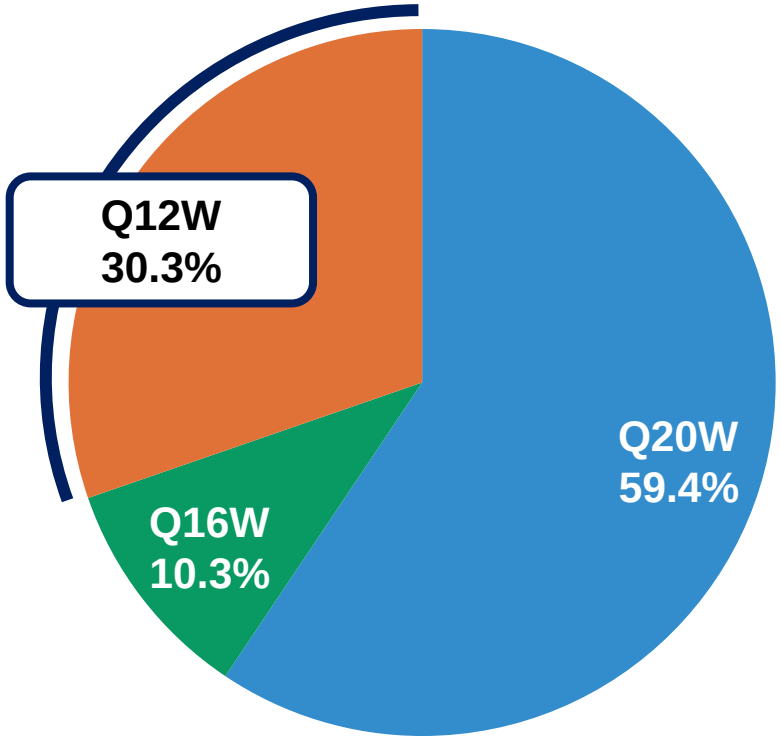
OCT / CST Over Time by Patient Subgroup, among those completing Year 1



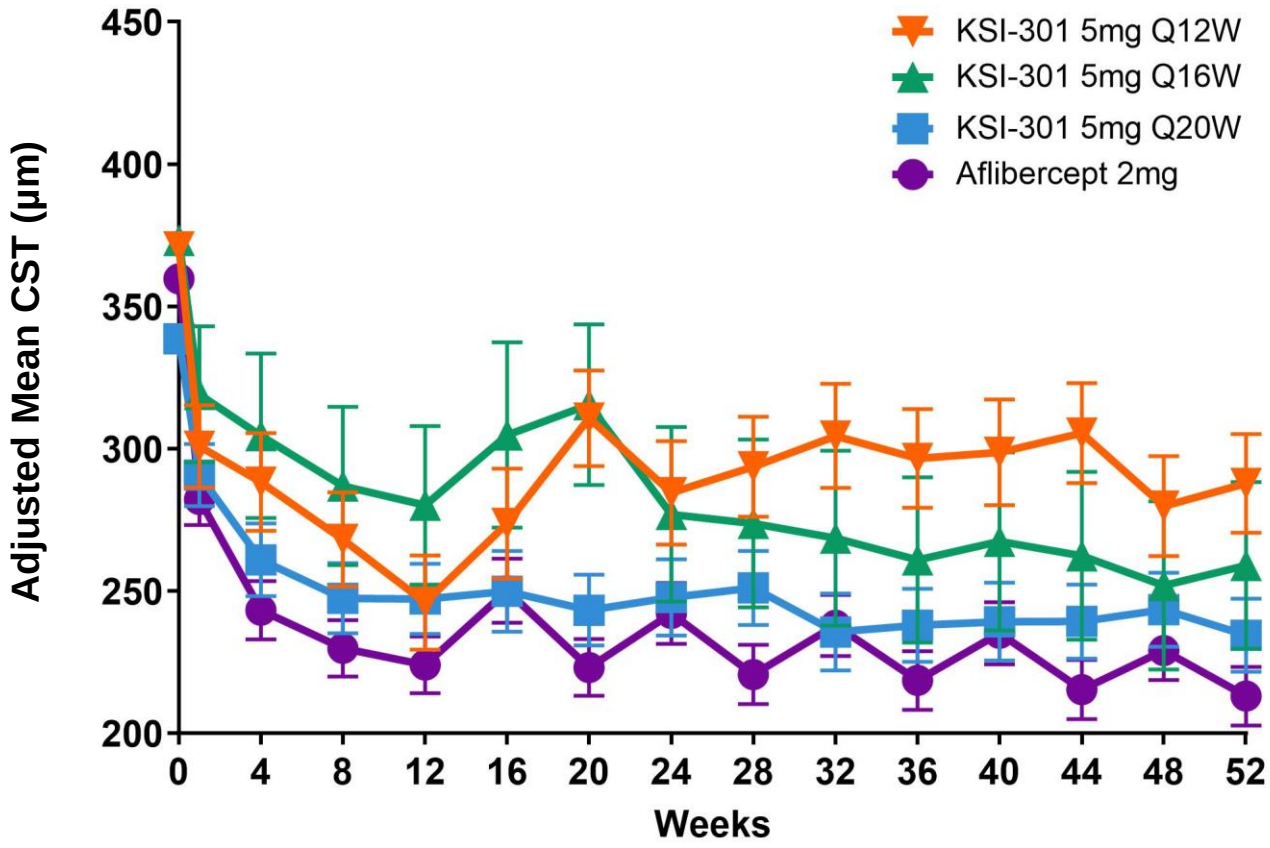
Least square means and 95% CI are based on MMRM model with treatment, visit, baseline CST, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment (KSI-301 Q20W, Q16W, Q12W, Aflibercept Q8W) by visit interaction.
Q12W: every 12 weeks; Q16W: every 16 weeks; Q20W: every 20 weeks; OCT: optical coherence tomography; CST: central subfield thickness.

After the loading phase, the initial clinical effect deteriorated in the patients who met criteria for adjustment to the Q12W dosing interval, and subsequent Q12W dosing was insufficient

Proportion of patients in the KSI-301 arm on each treatment interval, among those completing Year 1



OCT / CST Over Time by Patient Subgroup, among those completing Year 1



Least square means and 95% CI are based on MMRM model with treatment, visit, baseline CST, baseline BCVA categories, BCVA-low luminance VA baseline categories, geographical location categories, and treatment (KSI-301 Q20W, Q16W, Q12W, Aflibercept Q8W) by visit interaction.
Q12W: every 12 weeks; Q16W: every 16 weeks; Q20W: every 20 weeks; OCT: optical coherence tomography; CST: central subfield thickness.

Safety: KSI-301 overall was well-tolerated

Adverse Events (AEs) During Year 1	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
Ocular - Study Eye		
Total Number of ocular AEs	215	169
Subjects with any ocular AE	127 (45.8%)	102 (36.4%)
Subjects with any ocular serious AE (SAE)	6 (2.2%)	0
Subjects with any Injection Procedure Related AEs	42 (15.2%)	45 (16.1%)
Subjects with any Injection Procedure Related SAE	1 (0.4%)	0
Non-Ocular		
Total Number of Non-Ocular AEs	431	452
Subjects with any Non-Ocular AE	157 (56.7%)	162 (57.9%)
Subjects with at Least One Non-Ocular SAE	30 (10.8%)	33 (11.8%)
Any Deaths	4 (1.4%)	8 (2.9%)

Results presented for the Year 1 Safety Population. Events are investigator reported and relatedness of an event to study drug or injection procedure is investigator assessed. AEs or SAEs are those occurring on or after the initiation of study drug and until a minimum of 28 days after the last dose of study drug.
AE: adverse event; SAE: serious adverse event; Q8W: every 8 weeks, Q12W: every 12 weeks; Q20W: every 20 weeks.

Common ocular AEs (≥2% in any arm) were generally balanced between groups, with some differences in rates of AEs typical of undertreatment

Common Ocular Adverse Events (AEs) During Year 1 (>2% in any treatment arm)	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
Subjects with any AE in the Study Eye	127 (45.8%)	102 (36.4%)
Retinal hemorrhage	18 (6.5%)	4 (1.4%)
Cataract	16 (5.8%)	11 (3.9%)
Conjunctival hemorrhage	14 (5.1%)	24 (8.6%)
Vitreous floaters	14 (5.1%)	12 (4.3%)
Posterior capsule opacification	9 (3.2%)	4 (1.4%)
Vitreous detachment	9 (3.2%)	10 (3.6%)
Visual acuity reduced	8 (2.9%)	1 (0.4%)
Eye Pain	7 (2.5%)	8 (2.9%)
Intraocular pressure increased	6 (2.2%)	3 (1.1%)
Neovascular age-related macular degeneration	6 (2.2%)	5 (1.8%)
Punctate keratitis	2 (0.7%)	6 (2.1%)

Results presented for the Year 1 Safety Population. Events are investigator reported and relatedness of an event to study drug is investigator assessed. AEs and SAEs occurring on or after the initiation of study drug and until a minimum of + 28 days of the last dose of study drug.
AE: adverse event; SAE: serious adverse event; Q8W: every 8 weeks, Q12W: every 12 weeks; Q20W: every 20 weeks.

Rates of intraocular inflammation and procedure-related endophthalmitis with KSI-301 were low and within the range previously reported for aflibercept

Intraocular Inflammation During Year 1	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
Subjects Reporting at Least 1 Intraocular Inflammation AE	9 (3.2%)	0
Vitreal Cells	3 (1.1%)	0
Vitritis	3 (1.1%)	0
Eye inflammation	2 (0.7%)	0
Uveitis	1 (0.4%)	0

Endophthalmitis (Procedure-Related) During Year 1	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
Endophthalmitis (Procedure-Related)	2 (0.7%)	0

- None of the intraocular inflammation events was serious.
- No patient discontinued the study due to the event.
- In all cases, the clinical findings of inflammation resolved.
- No cases of intraocular inflammation with vascular occlusion were observed.

Results presented for the Year 1 Safety Population. Events are investigator reported.
AMD: age-related macular degeneration; AE: adverse events; Q8W: every 8 weeks; Q12W: every 12 weeks; Q20W: every 20 weeks.

Other serious ocular or non-ocular events were infrequent and within the range expected for this patient population

Ocular Serious Adverse Events (SAEs) During Year 1 – Study Eye	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
Retinal hemorrhage	2 (0.7%)	0
Cataract	1 (0.4%)	0
Neovascular age-related macular degeneration	1 (0.4%)	0
Rhegmatogenous retinal detachment	1 (0.4%)	0
Endophthalmitis	1 (0.4%)	0

Arteriothromboembolic Adverse Events During Year 1	KSI-301 5 mg Q12W-Q20W (N=277)	Aflibercept 2 mg Q8W (N=280)
Subjects with any APTC-classified ATE events	6 (2.2%)	4 (1.4%)
Acute myocardial infarction	2 (0.7%)	0
Ischemic stroke	2 (0.7%)	1 (0.4%)
Death	1 (0.4%)	0
Myocardial infarction	1 (0.4%)	0
Cerebral infarction	0	1 (0.4%)
Cerebrovascular accident	0	1 (0.4%)
Hemorrhagic stroke	0	1 (0.4%)

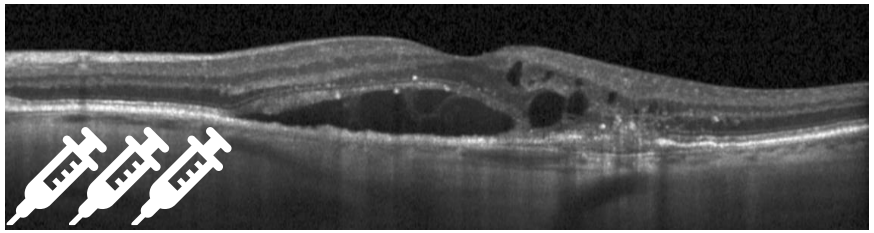
Results presented for the Year 1 Safety Population. Events are investigator reported. APTC was used to classify all ATE events;
APTC: anti-platelet trialists' collaboration; ATE: Arteriothromboembolic; Q8W: every 8 weeks; Q12W: every 12 weeks; Q20W: every 20 weeks

Questions about KSI-301 in Wet AMD arising from the study results

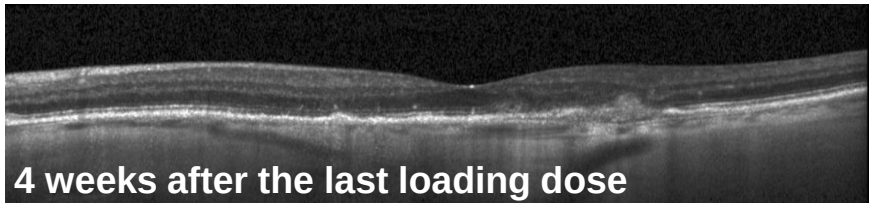
1. Does undertreatment explain the outcomes - would more frequent treatment have helped?
2. Is there a potency issue that explains the CST curves in the first 12 weeks?
3. Are the ~60% of patients treated with Q20W dosing just “easy” patients?
4. Is the 20-week treatment durability seen in the majority of patients real?
5. What are implications of these data for the ongoing KSI-301 phase 3 studies?

Q1: Does undertreatment explain the outcomes - would more frequent treatment have helped? Were patients who met criteria for Q12W dosing having initial treatment success?

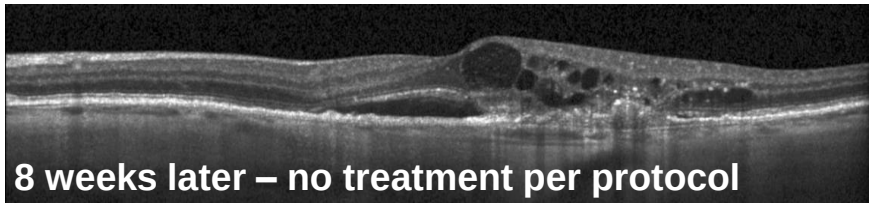
Day 1
69 letters



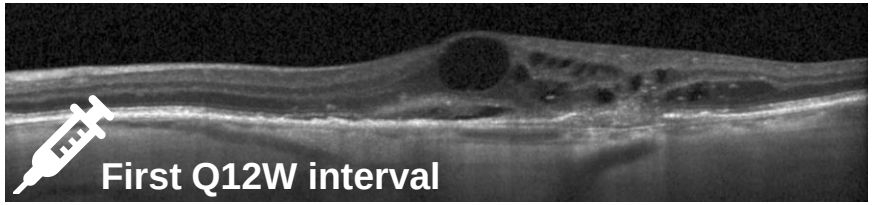
Week 12
+11 letters



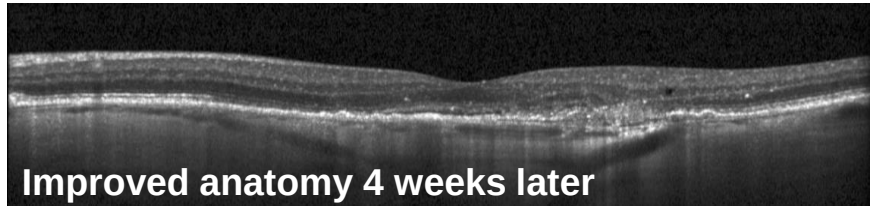
Week 16
+5 letters



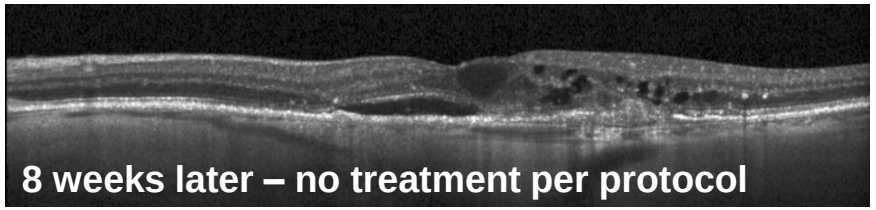
Week 20
+5 letters



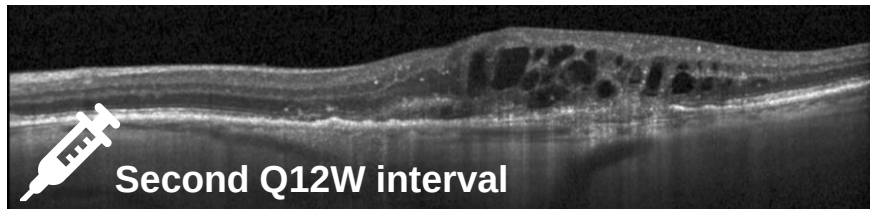
Week 24
+8 letters



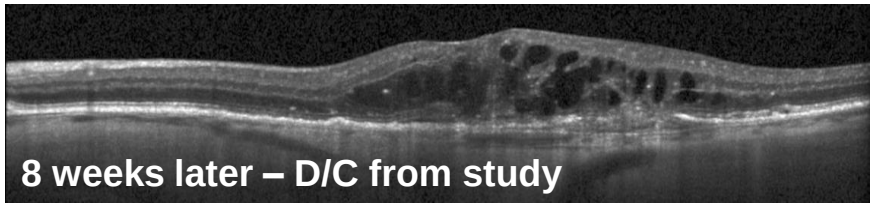
Week 28
+4 letters



Week 32
-9 letters



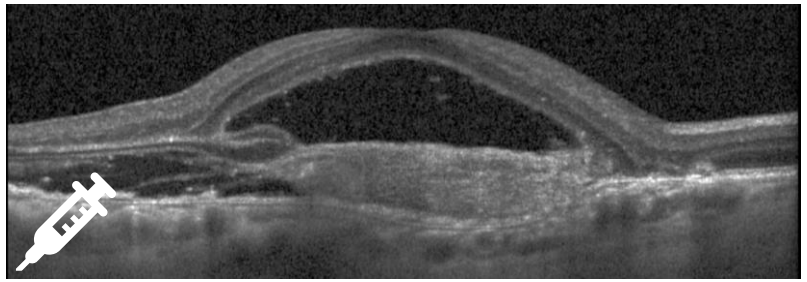
Week 40
-19 letters



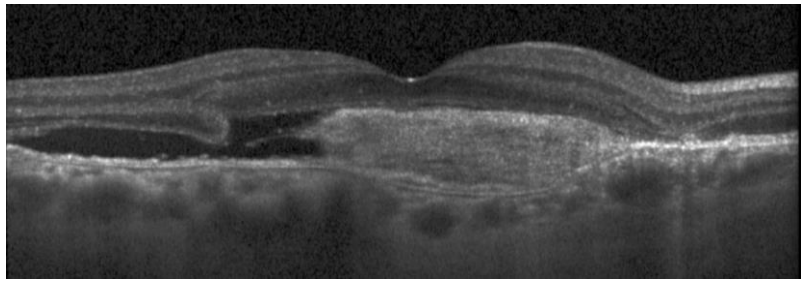
Case example: KSI-301 patient achieved 20/25 vision and improved anatomy after loading; subsequently deteriorated with repeated Q12W intervals

Q2: Is there a potency issue that explains the CST curves in the first 12 weeks?
Q3: Are the ~60% of patients treated with Q20W dosing the “easy” patients?

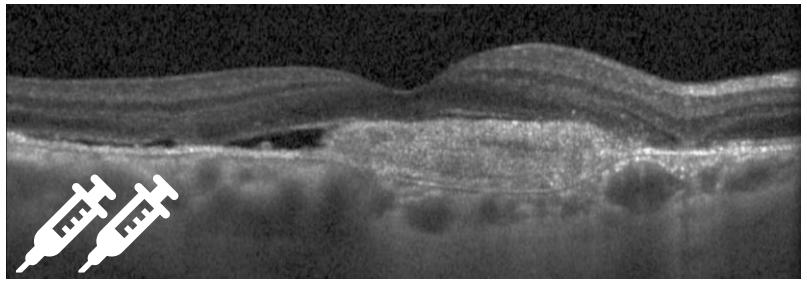
Day 1
50 letters
831 microns



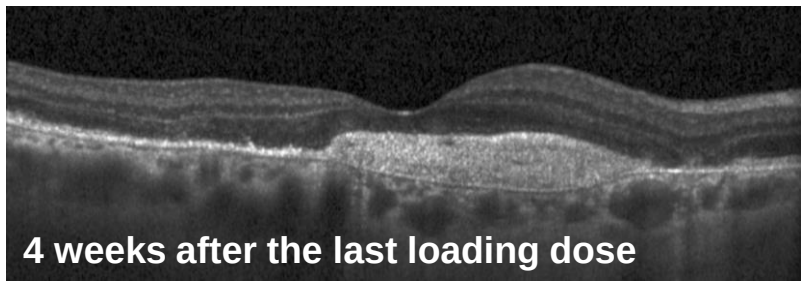
Week 1
-371 microns



Week 4
-644 microns

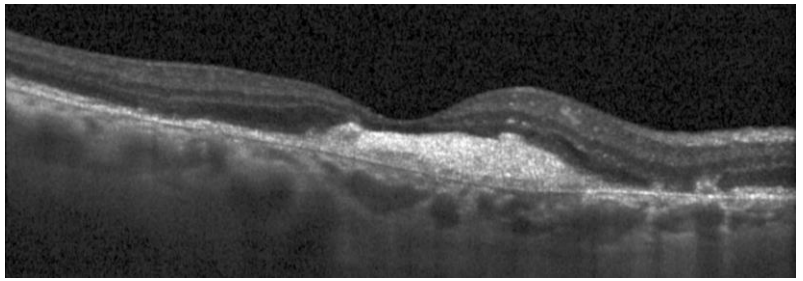


Week 12
-678 microns



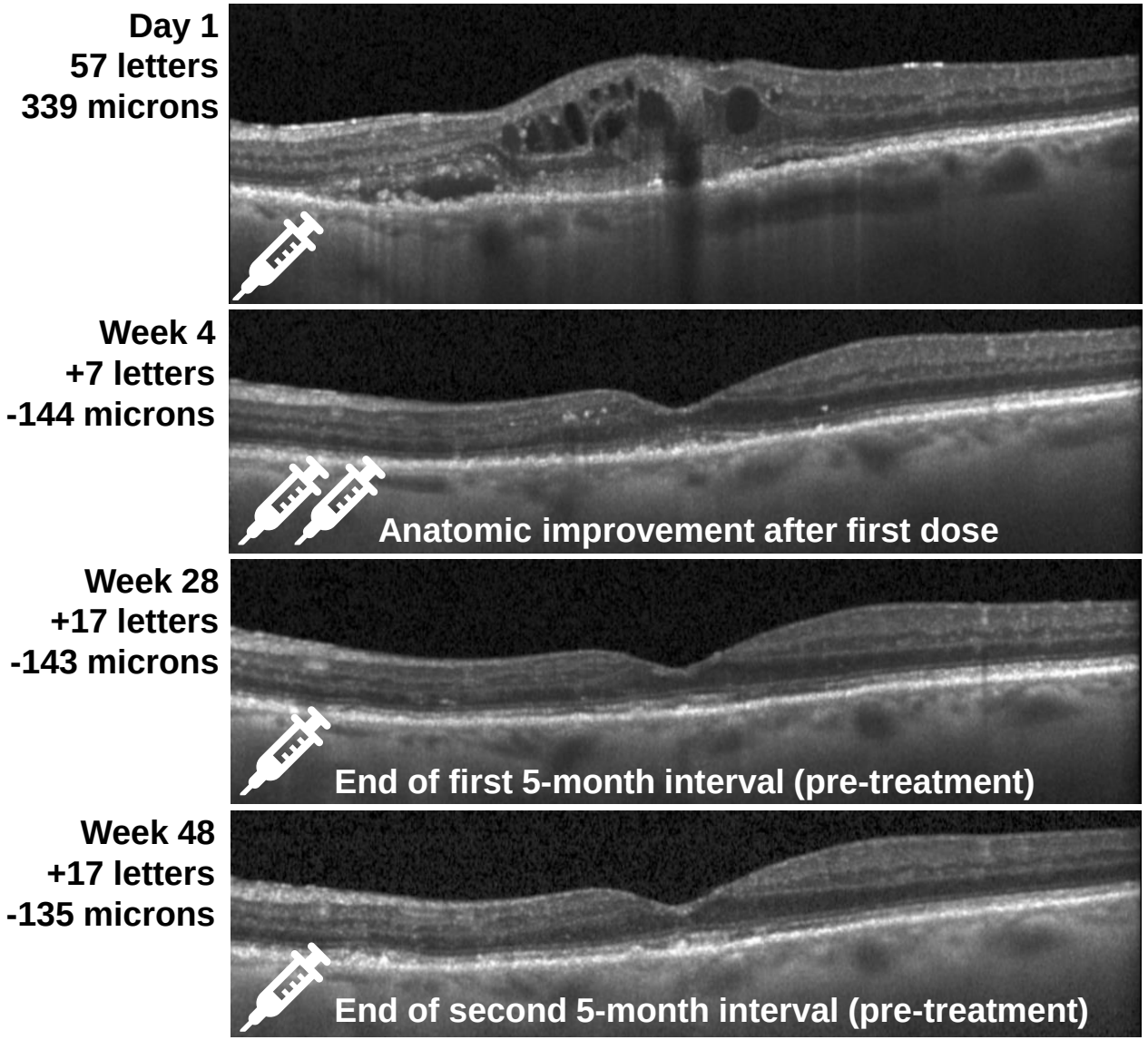
Case example: patient with significant disease treated with KSI-301 shows substantial reduction in CST after just one dose and complete retinal drying after the loading phase

Week 52
-660 microns



The patient continued to have a dry retina and received two Q20W doses, achieving a 13-letter BCVA gain at Week 52

Q4: Is the 20-week treatment durability seen in the majority of patients real? Are the retinas of Q20W patients actually dry?



Case example: dry retina after first dose and remains dry, successfully treated on successive 5-month (Q20W) dosing cycles with KSI-301

The ongoing phase 3 studies have lower risk of undertreatment in their designs, while still providing an opportunity to show meaningful improvements in treatment durability

Wet AMD	Retinal Vein Occlusion	Diabetic Macular Edema	Non-Proliferative Diabetic Retinopathy
Comparator	**Comparator**	**Comparator**	**Comparator**
Aflibercept **once every 2 months** after 3 monthly loading doses	Aflibercept **once every month**	Aflibercept **once every 2 months** after 5 monthly doses	Sham
DAYLIGHT Study[1]	**BEACON Study[2]**	**GLEAM and GLIMMER Studies[3]**	**GLOW Study[4]**
KSI-301 **once every month**	KSI-301 **once every 2 months or longer** after 2 monthly loading doses	KSI-301 **once every 2 to 6 months** after 3 monthly loading doses	KSI-301 **once every 6 months** after 3 initiating doses
Monthly Dosing[a]	4 Minimum doses in Year 1[a]	4 Minimum doses in Year 1[a]	4 Doses in Year 1[a]
Monthly dosing **Intensive treatment addresses questions on potency and BCVA outcomes in high-needs patients**	**Fixed interval dosing every 8 weeks**	**Proactive, individualized dosing as often as every 8 weeks** **Protocols amended to tighten disease activity criteria**	**Preventive therapy** **Infrequent dosing, with objective of reducing risk of diabetic retinopathy complications**

1. NCT04964089. 2. NCT04592419 3. NCT04611152 and NCT04603937. 4. NCT05066230 a. Based on study design; AMD: age-related macular degeneration

Questions about KSI-301 in wet AMD arising from the study results

1. **Does undertreatment explain the outcomes - would more frequent treatment have helped?**
   - There is evidence of patients in the Q12W dosing group achieving initial treatment success that was subsequently lost due to disease recurrence before the minimum 12-week interval. Undertreatment played an important role in the outcomes.
2. **Is there a potency issue that explains the CST curves in the first 12 weeks?**
   - There is evidence of patients with significant disease achieving high-potency responses with KSI-301. The upcoming study results from DAYLIGHT (short interval study in wet AMD) will help determine this in a robust way.
3. **Are the 60% of patients treated with Q20W dosing the “easy” patients?**
   - There is evidence of patients with significant disease achieving Q20W dosing successfully.
4. **Is the 20-week treatment durability seen in the majority of patients real?**
   - There is evidence of patients having a dry OCT at the 5-month interval visits. These patients were also seen in Phase 1b, where they were successfully treated every 6 months.
5. **What are implications of these data for the ongoing KSI-301 phase 3 studies?**
   - The ongoing phase 3 studies have lower risk of undertreatment in their designs, while still providing an opportunity to show meaningful improvements in treatment durability.

Conclusions

Primary Endpoint not met	• Data and case studies suggest this was at least in part due to undertreatment of some patients. Treatment with KSI-301 more often than Q12W was not allowed in this protocol
Robust durability with nearly 60% on Q20W	• Durability with KSI-301 at Year 1: 59.4% on Q20W dosing & 69.7% on ≥ Q16W dosing • Treatment durability was real. Patients on Q20W KSI-301 achieved meaningful and stable reductions in CST and improvements in vision comparable to the aflibercept Q8W group
KSI-301 is safe and well-tolerated	• Higher overall rate of AEs and discontinuation due to AEs in the KSI-301 arm, at least in part due to undertreatment in patients who may have needed treatment more often than Q12W
Learnings for KSI-301 Program	• **Robust treatment effects can be observed with KSI-301** • **Treatment effect can be maintained at long intervals for the majority of patients** • **Protocol design needed to better anticipate/accommodate high-need patients** • **Phase 3 DME studies have been amended to strike a more conservative balance between high-need patients and durability**
Future Analyses	• Identifying possible predictors of treatment response and treatment durability