What Will We Be Using to Treat Patients with Wet AMD in the Future?

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Disclosures

Financial:

Aerie (C, R), Allergan (C), Asclepix (C), Boehringer Ingelheim (C, R), Genentech (C), Kodiak (C, S) Novartis (C, R), Regeneron (C, R) , Santen (C, R), Mallinckrodt (C), Gilead (R), Eyepoint (C)

C: Consultant; R: Research Grant; S: Shareholder

Intravitreal VEGF Inhibitors remain first-line therapy for wet AMD in 2021

Aflibercept	Bevacizumab	Ranibizumab	Brolucizumab

Real-World Data: Most Patients with Wet AMD Receive ~5 Injections per Year

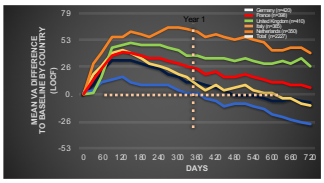
Undertreatment of Wet AMD

	Study Population	Injection Duration, Year	Mean Injection Rate
Medicare analysis[1]	459,237	1	4.3
LUMINOUS[2]	4437	1	4.3-5.7
Retrospective claims analysis[3]	11,688	1	4.5-6.8
Retrospective claims analysis[4]	53,621	1	4.6-6.9

1. Lad EM et al. *Am J Ophthalmol.* 2014;158:537-543.e2; 2. Holz FG et al. *Br J Ophthalmol.* 2013;97:1161-1167; 3. Kiss S et al. *Ophthalmic Surg Lasers Imaging Retina.* 2014;45:285-291; 4. Holekamp NM et al. *Am J Ophthalmol.* 2014;157:825-833.e1.

AURA Study

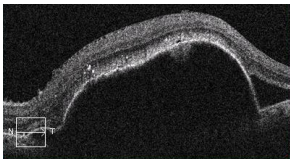
In real-life use of anti-VEGF therapy, poorer visual outcomes compared with clinical trial outcomes



*Only countries meeting or exceeding enrollment target (n=444) were included.
Reprinted with permission from Holz FG et al. *Br J Ophthalmol*. 2015;99:220-226.

Unmet Need in Wet AMD

- Durable medicines that can be clinically effective and decrease injection burden



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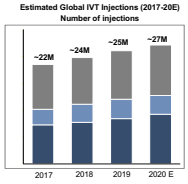
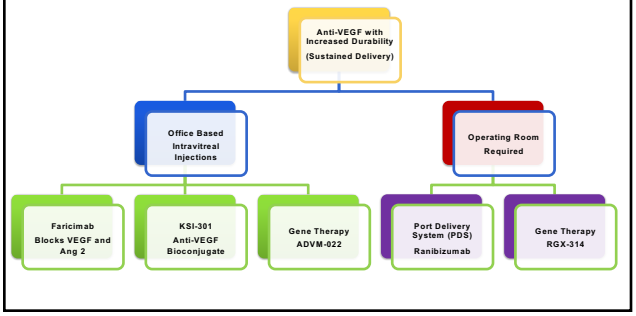
Nearly 27M intravitreal (IVT) anti-VEGF injections will be administered in 2020 to treat retinal diseases



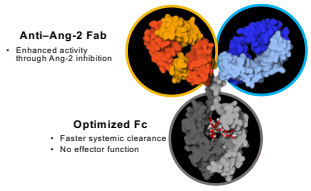
- Of the estimated 27 million IVT injections that will be performed in 2020
  - ~60% are for wet AMD
  - ~30% are for DME
  - remainder mostly RVO
- IVT injections in wet AMD patients are well established and penetrated
- IVT injections in DME patients are estimated to be half-way saturated with room for further growth
- Non-proliferative diabetic retinopathy is unmet need
  - Longer durability medicines may be helpful



Faricimab: First Bispecific Antibody Designed for Intravitreal Use

Engineered for efficacy, duration within the eye, and fast systemic clearance

1 molecule, 2 targets



Anti–Ang-2 Fab
- Enhanced activity through Ang-2 inhibition

Anti–VEGF-A Fab
- Proven efficacy through VEGF-A inhibition

Optimized Fc
- Faster systemic clearance
- No effector function

Regula JT et al. *EMBO Mol Med*. 2016;8:1265-1288; Figure reprinted from Sahni J et al. *Ophthalmology*. 2019;126:1155-1170.

TENAYA[1] and LUCERNE[2]

Wet AMD Phase 3 Clinical Trial Program
2 Identical, Randomized, Multicenter Trials

Anti-VEGF treatment-naive patients with nAMD, BCVA 20/32 to 20/320 (n ~ 640 per study)

R
1:1

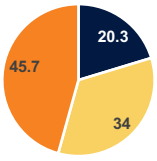
Treatment	*Arm A:* Faricimab Q16W flex[a]	*Arm B:* Aflibercept Q8W
Objectives	Extended dosing and efficacy	Anti-VEGF comparator

Patients will be randomized 1:1 into 2 arms.
[a]Q8W, Q12W, or Q16W regimen based on patient's individual disease activity.
Q16W: every 16 weeks.
1. https://clinicaltrials.gov/ct2/show/NCT03823287. Accessed September 30, 2019; 2. https://clinicaltrials.gov/ct2/show/NCT03823300. Accessed September 30, 2019.

TENAYA[1] and LUCERNE[2]

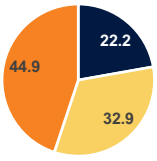
Wet AMD Phase 3 Clinical Trial Program of Faricimab
DURABILITY AT WEEK 48

TENAYA



· Q8W · Q12W · Q16W ·

LUCERNE



· Q8W · Q12W · Q16W ·

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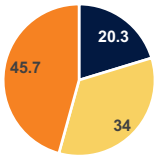
Wet AMD Phase 3 Clinical Trial Program
DURABILITY AT WEEK 48

TENAYA



· Q8W · Q12W · Q16W ·

- **Faricimab was non-inferior to aflibercept at week 48**
- **45% of eyes dosed Q16W with faricimab**
- **Safety:**
  - **2% intraocular inflammation with faricimab**
  - **1.2% intraocular inflammation with aflibercept**

Patients will be randomized 1:1 into 2 arms.
[a]Q8W, Q12W, or Q16W regimen based on patient's individual disease activity.
Q16W: every 16 weeks.
1. https://clinicaltrials.gov/ct2/show/NCT03823287. Accessed September 30, 2019; 2. https://clinicaltrials.gov/ct2/show/NCT03823300. Accessed September 30, 2019.

Extended Durability in Exudative Retinal Diseases Using the Novel Intravitreal Anti-VEGF Antibody Biopolymer Conjugate KSI-301

Phase 1b Study in Patients with wAMD, DME and RVO

Year 1 Results

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KSI-301 Phase 1b Study – Year 1 Results Key Questions

Do the data support the potential for KSI-301 to meaningfully advance the treatment paradigm for major retinal vascular diseases?

- Can KSI-301 provide the expected **efficacy gains in line with current anti-VEGF agents**?
- Can KSI-301 achieve **clinical durability of 6-months or longer** in the majority of patients, and **with fewer loading doses**?
- Does KSI-301 have the **excellent safety profile** expected for intravitreal anti-VEGF agents ranibizumab and aflibercept?

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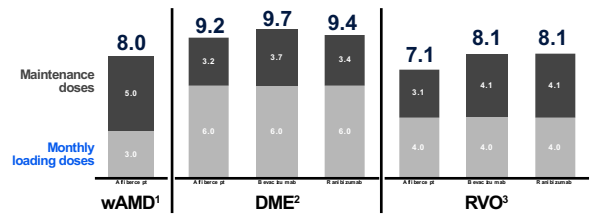
Current anti-VEGF agents depend on high-frequency treatment to be most efficacious

Mean number of injections required in Year 1



1. Heier JS. VIEW Studies. Ophthalmology. 2012 Dec;119(12):2537-48.
2. Wells JA. DRCR.net Protocol T. N Engl J Med. 2015 Mar 26;372(13):1193-203 (supplemental data).
3. Rykin P. LEAVO trial. JAMA Ophthalmol. 2019 Aug 29;137(11):1256-1264.

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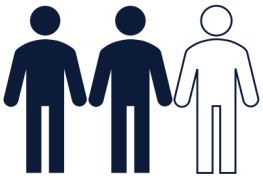
KSI-301 shows impressive and consistent durability across retinal vascular diseases in Year 1



2 in every 3 patients are on a ≥ 6-month treatment-free interval at Year 1 after only 3 loading doses

Interval at Year 1	wAMD n=50	DME n=32	RVO n=32
≥6 months	66%	69%	66%

Phase 1b interim data. 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Two RVO patients were not included as they discontinued at the Week 12 and 16 visits, respectively, without receiving a retreatment dose. Interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52.

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KSI-301

Clinical Data

130 patients dosed in Phase 1a/1b Program

168+ patient years of clinical experience

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KSI-301 Phase 1b Study Design

Randomized, open label study to evaluate multidose safety, efficacy & durability

wAMD (n=51) | **DME** (n=35) | **RVO** (n=35)

Randomized 1:3

KSI-301 2.5 mg (50 µL) | KSI-301 5 mg (100 µL)

	Loading Phase			Durability Assessment Phase	Extension Study
Weeks	0	4	8	12 to 72 (months 3 to 18)	76 to 148 (months 19 to 36)
	■	■	■	Monthly monitoring with protocol guided retreatment	Monthly monitoring with protocol guided retreatment

wAMD = wet age-related macular degeneration; DME = diabetic macular edema; RVO = retinal vein occlusion; Clinicaltrials.gov ID: NCT03790852

■ Fixed Treatment

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KSI-301 Phase 1b Retreatment Criteria

- **wAMD**
  - Increase in CST ≥75 µm with a decrease in BCVA of ≥ 5 letters compared to Week 12, *OR*
  - Decrease in BCVA of > 5 letters compared to Day 1, due to worsening wAMD activity, *OR*
  - Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening wAMD activity, *OR*
  - 6 months have elapsed since the last retreatment
- **DME and RVO**
  - Increase in CST ≥75 µm with a decrease in BCVA of ≥ 5 letters compared to Week 12 or the prior visit, *OR*
  - Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening DME/RVO disease activity

For all subjects, investigators can retreat at their discretion if significant disease activity is present that does not meet the above criteria

wAMD = wet age-related macular degeneration; DME = diabetic macular edema; RVO = retinal vein occlusion; CST = central subfield retinal thickness; BCVA = best corrected visual acuity. Clinicaltrials.gov ID: NCT03790852

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Baseline Characteristics

Variable	wAMD Cohort (n=51)	DME Cohort (n=35)	RVO Cohort (n=35)
Age, mean (SD), years	77.9 (10.5)	59.7 (11.7)	63.6 (12.6)
Gender, n (%), female	32 (62.7)	14 (40.0)	13 (37.1)
Race, n (%), White	48 (94.1)	28 (80.0)	31 (88.6)
BCVA, mean (SD), ETDRS letters	**63.3 (13.3)**	**66.8 (10.2)**	**54.9 (15.4)**
Snellen equivalent	~20/50	~20/50	20/80
Snellen 20/40 or better, n (%)	20 (39.2)	16 (45.7)	6 (17.1)
OCT CST, mean (SD)	450 (182)	453 (110)	675 (237)

Includes [illegible] BCVA = best corrected visual acuity; [illegible] CST= central subfield retinal thickness

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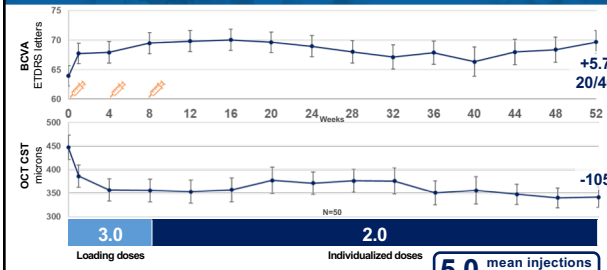
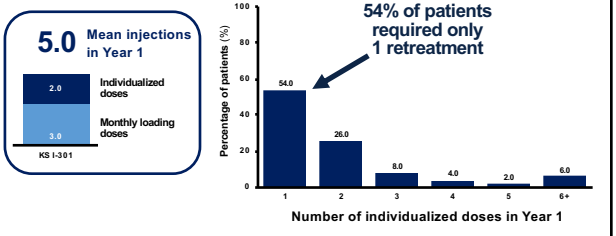
KSI-301 Phase 1b
wAMD
Year 1 Data

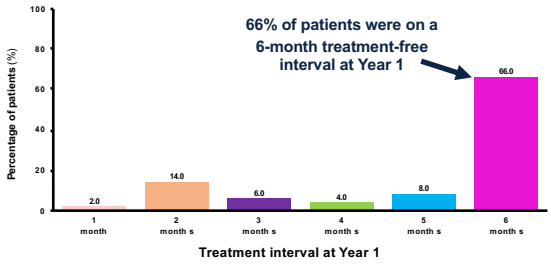
Efficacy of KSI-301 in Wet AMD
Change from baseline to Week 52 in mean BCVA & OCT



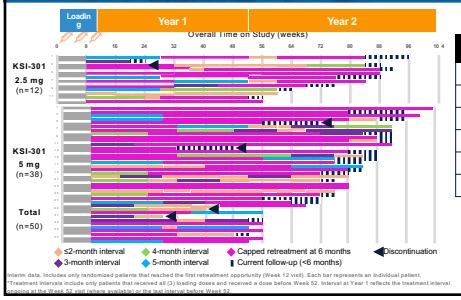
Durability of KSI-301 in Wet AMD
80% of patients received 2 or fewer retreatments in Year 1



Durability of KSI-301 in Wet AMD
Distribution of retreatment intervals at Year 1



KSI-301 in wAMD: *the majority of patients can achieve 6-month durability*



Interval at Year 1*	n=50
1 month	2%
2 months	14%
3 months or longer	84%
4 months or longer	78%
5 months or longer	74%
6 months	66%

80% have achieved a 6-month treatment-free interval at least once during follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit). Each bar represents an individual patient.
*Treatment intervals include only patients that received all (3) loading doses and received a dose before Week 52. Interval at Year 1 reflects the treatment interval missing at the Week 52 visit (where available) or the last interval before Week 52.

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KSI-301 Phase 1b DME Year 1 Data

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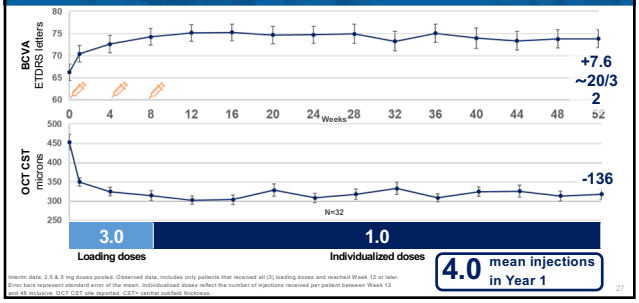
Efficacy of KSI-301 in DME

Change from baseline to Week 52 in mean BCVA & OCT



Interim data; 2.5 & 5 mg doses pooled. Observed data, includes only patients that received all (3) loading doses and reached Week 12 or later. Error bars represent standard error of the mean. Individualized doses reflect the number of injections received per patient between Week 12 and 48 inclusive. OCT CST site reported. CST= central subfield thickness.

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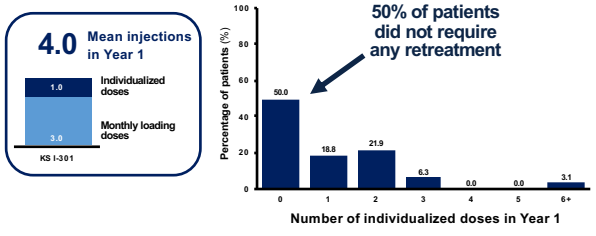
Durability of KSI-301 in DME

90% of patients received 2 or fewer retreatments in Year 1



Interim data; 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Individualized doses reflect the

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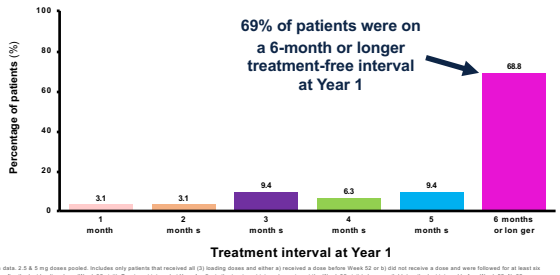
Durability of KSI-301 in DME
Distribution of retreatment intervals at Year 1



Interim data. 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Treatment interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52. N=32

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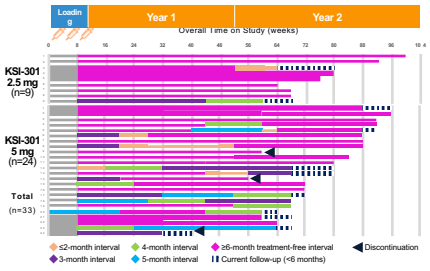
KSI-301 in DME: *3 loading doses can provide sustained disease control of 3 to 6+ months*



Interval at Year 1*	n=32
1 month	3%
2 months	3%
3 months or longer	94%
4 months or longer	84%
5 months or longer	78%
6 months or longer	69%

81% have achieved a 6-month or longer treatment-free interval at least once during follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit). Each bar represents an individual patient. *Treatment intervals include only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Interval at Year 1 reflects

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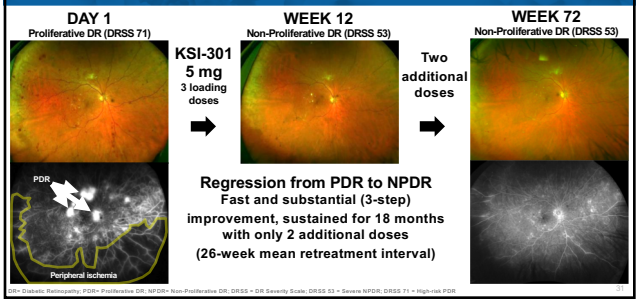
6-month disease control after only 3 loading doses is also seen in proliferative diabetic retinopathy



Regression from PDR to NPDR
Fast and substantial (3-step) improvement, sustained for 18 months with only 2 additional doses
(26-week mean retreatment interval)

DR= Diabetic Retinopathy; PDR= Proliferative DR; NPDR= Non-Proliferative DR; DRSS = DR Severity Scale; DRSS 53 = Severe NPDR; DRSS 71 = High-risk PDR

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KSI-301 Phase 1b
RVO
Year 1 Data

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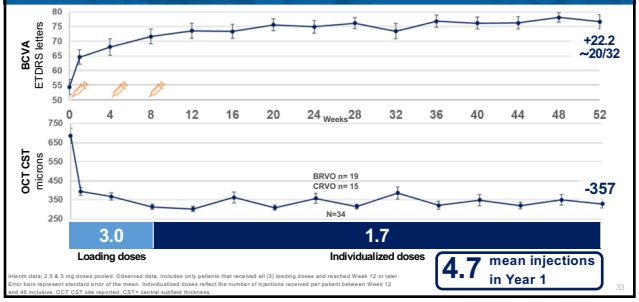
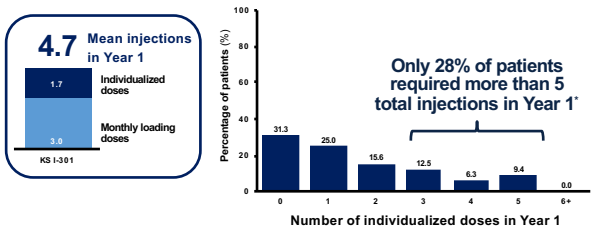
Efficacy of KSI-301 in RVO

Change from baseline to Week 52 in mean BCVA & OCT



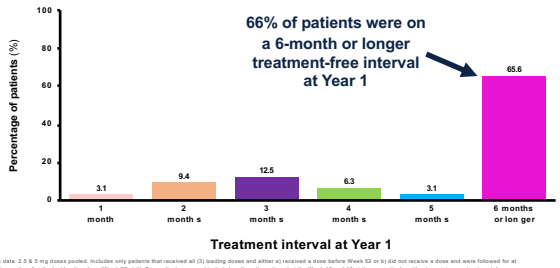
Durability of KSI-301 in RVO

72% of patients received 2 or fewer retreatments in Year 1



Durability of KSI-301 in RVO

Distribution of retreatment intervals at Year 1



KSI-301 in RVO: *3 loading doses can provide sustained disease control of 2 to 6+ months*

Interval at Year 1*	n=32
1 month	3%
2 months	9%
3 months or longer	87%
4 months or longer	75%
5 months or longer	69%
6 months or longer	66%

69% have achieved a 6-month or longer treatment-free interval at least once during follow-up

How can KSI-301 achieve strong efficacy *and* remarkable durability?

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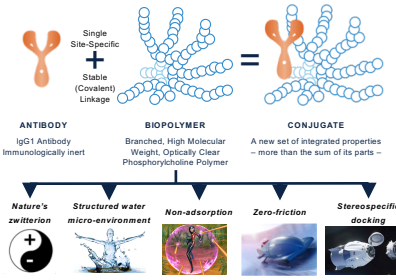
Antibody Biopolymer Conjugates (ABC)

Biologics precision-engineered for increased durability and efficacy



SAME WHERE IT MATTERS

- Clinically proven targets
- Antibody-based biologic
- Intravitreal: safest method of administration
- Optically clear, no residues
- Fast and potent clinical responses

DIFFERENT WHERE IT COUNTS

- Designed-in ocular durability
- Designed-in rapid systemic clearance
- Improved bioavailability
- Improved biocompatibility
- Deeper potency

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KSI-301: Next-Generation anti-VEGF

ABC Platform and higher dose for longer treatment duration

	Ranibizumab	Bevacizumab	Aflibercept	KSI-301
Molecule type	Antibody fragment	Antibody	Recombinant fusion protein	Antibody Biopolymer Conjugate (ABC)
Molecular structure				
Molecular weight	48 kDa	149 kDa	115 kDa	**950 kDa**
Clinical dose	0.3-0.5 mg	1.25 mg	2 mg	**5 mg** (by weight of antibody)
Equivalent molar dose	0.5	0.9	1	**3.5**
Equivalent ocular PK	0.7	1	1	**3**
Equivalent ocular concentration at 3 months	0.001	NA[1]	1	**1,000**

Equivalent values are shown as (approximate) fold difference relative to aflibercept. kDa= kilodalton

1. Lower affinity of bevacizumab precludes a valid comparison

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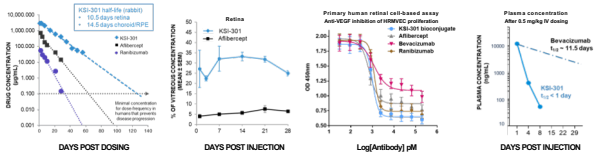
Integrated properties of ABC Platform are ideal for a long-acting intravitreal therapeutic

More than the sum of its parts

Remarkable Intraocular Half-life[1]	Excellent Retinal Bioavailability[2]	Deeper Inhibitory Potency[3]	Fast Systemic Clearance[4]



1. Data from rabbit model. Ranibizumab data: Gaudreault et al (2007) IOVS 48(2) 726 Gaudreault et al (2007) Retina 27(9) 1260 Bakri et al (2007) Ophthalmol 114(12) 2179 2) Aflibercept data: EVER Congress Portorož Slovenia (2009) Struble (Covance) Koehler-Stec (Regeneron). Aflibercept data adjusted arithmetically to reflect 2,000µg dose administered (based on rabbit in vivo dosing of 500 µg). 3) KSI-301 data on file, adjusted arithmetically to reflect 5,000 µg dose administered (based on rabbit in vivo dosing of 725 µg). Error bars reflects standard error of the mean
2. KSI-301 data: data on file; Aflibercept data: EVER Congress Portorož Slovenia (2009) Struble (Covance), Koehler-Stec (Regeneron); KSI-301 data (2017) Covance study, data on file. Error bars reflects standard error of the mean
3. KSI-301 data: data on file; Bevacizumab data: Young et al 2010 Cancer Research.
4. KSI-301 data: Monkey/human pharmacokinetic study, data on file; Bevacizumab data: Yasuda et al 2010 Cancer Science

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KSI-301 Phase 1b

Safety

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Safety of KSI-301: *Excellent safety profile*

130	710	168	121	96
Subjects dosed	Total doses	Patient-years	Completed the loading phase in Phase 1b	Phase 1b subjects at Week 12 or later that have received all three loading doses plus at least one additional retreatment
Across the Phase 1a/1b program				

- Most AEs were assessed as mild and are consistent with profile of intravitreal anti-VEGFs
- To date, 43 SAEs have been reported in 24 subjects – none drug related
- Three ocular SAEs in the study eye, not drug related, all resolved
  - Worsening DME secondary to systemic fluid overload
  - Worsening cataract in a diabetic patient
  - Subretinal hemorrhage in a wAMD patient
- Only two AEs of intraocular inflammation, both trace to 1+ vitreous cells, with complete resolution
  - Rate of 0.28% (2/710 injections)
  - No vasculitis or retinal artery occlusion in either patient

Includes all Phase 1a+1b patients randomized as of 26 Jan 2021, all doses administered across cohorts. Interim safety data as of 26 Jan 2021; AE: adverse event; SAE: serious adverse event
Inflammation scored based on the 0 – 4+ standardized vitreous grading scale (Foster 2002)

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How do the Phase 1b Study data inform the design of KSI-301 pivotal studies?

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KSI-301 Phase 1b data in treatment-naïve patients inform the design of Kodiak pivotal studies

Maintained

- Treatment-naïve patients
- 3 loading doses in wAMD and DME
- Monthly visits

Optimized

- Only high dose (5 mg) advanced
- Tighter disease activity criteria
- Proactive dosing
- Tighter dosing intervals
- 2 loading doses in RVO
- Decreased subjectivity (treatment based strictly on IRT)
- High statistical power for non-inferiority

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KSI-301 pivotal program: long-interval dosing to meaningfully change the treatment paradigm

Wet AMD	Diabetic Macular Edema	Retinal Vein Occlusion	Non-Proliferative Diabetic Retinopathy
Comparator: Aflibercept once every 2 months after 3 monthly loading doses	Comparator: Aflibercept once every 2 months after 5 monthly doses	Comparator: Aflibercept once every month	Comparator: Sham
DAZZLE Study[1]	GLEAM and GLIMMER Studies[2]	BEACON Study[3]	GLOW Study
KSI-301 once every 3, 4 or 5 months after 3 monthly loading doses	KSI-301 once every 2 to 6 months after 3 monthly loading doses	KSI-301 once every 2 months or longer after 2 monthly loading doses	KSI-301 once every 6 months after 3 initiating doses
5 Minimum doses in Year 1[4]; 2 Minimum doses in Year 2[4]	4 Minimum doses in Year 1[4]; 2 Minimum doses in Year 2[4]	4 Minimum doses in Year 1[4]	4 Doses in Year 1[4]; 2 Doses in Year 2[4]
Completed Recruitment	Now Recruiting	Now Recruiting	Starting in 1H2021

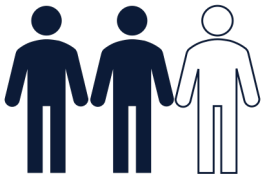
1. NCT04063085. 2. NCT04611152 and NCT04500937. 3. NCT04500419. 4. Based on study design.

45

What is the potential impact of KSI-301 in clinical practice and patients' lives?

46

KSI-301 has the potential to be the longest-acting intravitreal biologic



2 in every 3 patients are on a ≥ 6-month treatment-free interval at Year 1 after only 3 loading doses

Interval at Year 1	wAMD n=50	DME n=32	RVO n=32
≥6 months	66%	69%	66%

Phase 1b interim data. 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Two RVO patients were not included as they discontinued at the Week 12 and 16 visits, respectively, without receiving a retreatment dose. Treatment interval reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52.

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KSI-301 Phase 1b Study – Year 1 Results Key Questions

The data support the potential for KSI-301 to meaningfully advance the treatment paradigm for major retinal vascular diseases

- Can KSI-301 provide the expected **efficacy gains in line with current anti-VEGF agents**? **Yes**
- Can KSI-301 achieve **clinical durability of 6-months or longer** in the majority of patients, and **with fewer loading doses**? **Yes**
- Does KSI-301 have the **excellent safety profile** expected for intravitreal anti-VEGF agents ranibizumab and aflibercept? **Yes**

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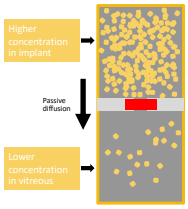
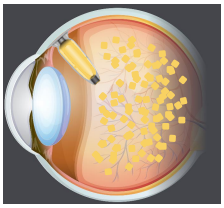
Sustained Drug Delivery

- Port delivery system (PDS)
  - ranibizumab
- Gene therapy
  - Subretinal delivery: RGX-314
  - Intravitreal delivery: ADVM-022

PDS Mechanism of Continuous Delivery: Passive Diffusion

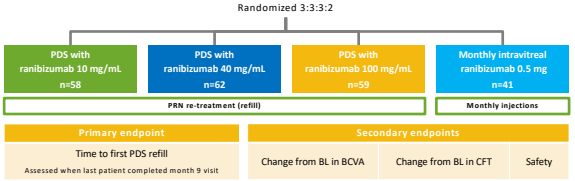


- Continuous delivery mediated by passive diffusion
- Rate of diffusion is concentration dependent and decreases over time
- Follows Fick's Law



Regillo C. Presented at: Bascom Palmer Eye Institute Angiogenesis, Exudation, and Degeneration 2019 Meeting; Miami, FL; February 9, 2019.

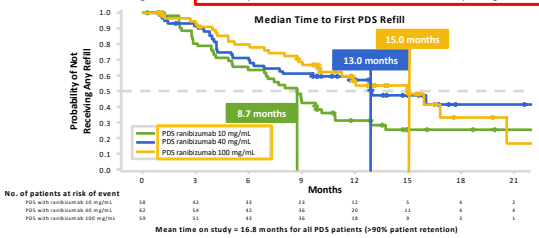
Ladder Phase 2 Study Design: Characterize the Treatment Effect, Durability, and Safety of the PDS



[a]≥2 anti-VEGF injections before screening to determine responsiveness; ranibizumab must be most recent anti-VEGF treatment (≤7 days before screening). [b]Modified intent-to-treat population for efficacy analyses: 232 patients were enrolled in the trial, with 63, 63, 63, and 43 patients randomized to PDS with ranibizumab 10 mg/mL, 40 mg/mL, and 100 mg/mL, and the intravitreal ranibizumab 0.5 monthly treatment arms, respectively. 7 patients were excluded due to study site noncompliance and 5 patients were randomized but withdrew before treatment.
CFT: central foveal thickness.
https://clinicaltrials.gov/ct2/show/NCT02510794. Accessed September 30, 2019; Campochiaro PA et al. *Ophthalmology*. 2019;126:1141-1154.

Primary Endpoint: Time to First PDS Refill

In the 100-mg/mL arm, 80% of patients went ≥6 months without requiring a refill



Mean time on study = 16.8 months for all PDS patients (>90% patient retention)

All PDS patients completed each visit through month 9; from month 9 on, data for patients who completed each visit (data collection ongoing). Patients censored if last visits were before cutoff date or if they discontinued the study, whichever occurred first. Time to first refill censored at the time of intravitreal injection, at the time refill criteria could not be assessed, and at the time of explant before the first refill.
Campochiaro PA et al. *Ophthalmology*. 2019;126:1141-1154.

PDS-Associated AEs: PDS Implantation Surgery and Refill Procedure Well Tolerated by Patients

Postoperative vitreous hemorrhage rate reduced significantly after modified surgical procedure implemented

	PDS Ranibizumab 10 mg/mL (n=62)		PDS Ranibizumab 40 mg/mL (n=63)		PDS Ranibizumab 100 mg/mL (n=59)		Pooled PDS Arms (n=184)	
	Time From Surgery		Time From Surgery		Time From Surgery		Time From Surgery	
MedDRA, Preferred Term, n (%)	≤1 Month	>1 Month	≤1 Month	>1 Month	≤1 Month	>1 Month	≤1 Month	>1 Month
Eye disorders								
Vitreous hemorrhage before May 2016 procedure update	6/10 (60.0%)	0	2/7 (28.6%)	0	3/5 (60.0%)	0	11/22 (50.0%)	0
Vitreous hemorrhage after May 2016 procedure update	2/52 (3.8%)	1/52 (1.9%)	3/56 (5.4%)	1/56 (1.8%)	2/54 (3.7%)	0	7/162 (4.3%)	2/162 (1.2%)
Cataract*	0	2 (3.2%)	0	4 (6.3%)	0	8 (13.6%)	0	14 (7.6%)
Conjunctival bleb	3 (4.8%)	0	2 (3.2%)	1 (1.6%)	0	0	5 (2.7%)	1 (0.5%)
Conjunctival erosion	0	1 (1.6%)	0	2 (3.2%)	1 (1.7%)	1 (1.7%)	1 (0.5%)	4 (2.2%)
Rhegmatogenous retinal detachment	1 (1.6%)	1 (1.6%)	0	1 (1.6%)	0	1 (1.7%)	1 (0.5%)	3 (1.6%)
Tractional retinal detachment	0	1 (1.6%)	0	0	0	0	0	1 (0.5%)
Infections and infestations								
Endophthalmitis	1 (1.6%)	0	0	1 (1.6%)	0	1 (1.7%)	1 (0.5%)	2 (1.1%)
Injury, poisoning, and procedural complications								
Hyphema	4 (6.5%)	2 (3.2%)	1 (1.6%)	0	3 (5.1%)	0	8 (4.3%)	2 (1.1%)
Conjunctival retraction	0	0	1 (1.6%)	1 (1.6%)	1 (1.7%)	0	2 (1.1%)	1 (0.5%)
Conjunctival filtering bleb leak	0	0	1 (1.6%)	0	0	0	1 (0.5%)	0

May 2016 procedure update implemented optimized surgical technique for PDS implant insertion.

* 2 (7.3%) for cataract in intravitreal ranibizumab 0.5-mg monthly group when >1 month onset and 0 when ≤1 month.
Observed data; all treated patients who received ≥1 dose of study drug according to the actual treatment. Patients from site 260647 were also included. Month 1 visit include data up to 37 days.
MedDRA = Medical Dictionary for Regulatory Activities.
Regillo CD et al. Presented at: AAO 2018; Chicago, IL; October 27-30, 2018.

Ladder Phase 2 Trial Summary

- In the PDS with ranibizumab 100-mg/mL treatment arm
  - 80% of patients went ≥6 months until the first refill
  - Median time to first implant refill was 15.0 months
  - BCVA and anatomic outcomes were comparable to those of monthly intravitreal ranibizumab
- PDS implant insertion surgery and refill procedure were well tolerated
  - Systemic safety comparable to monthly intravitreal injections
- The phase 3 program, Archway, using fixed 24-week interval dosing, began enrolling in September 2018

Campochiaro PA et al. *Ophthalmology*. 2019;126:1141-1154.

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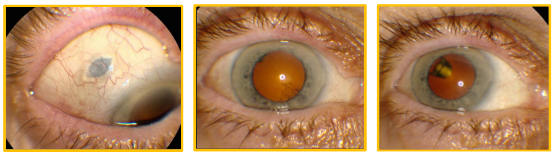
PDS = Port Delivery System with ranibizumab.
Images courtesy of Dr. Regillo.

PDS 1-Month Post-op Patient Images



Port Delivery System : Phase 3 ARCHWAY Study

- PDS was non-inferior to monthly ranibizumab
- 98.4% of PDS patients were able to go 6 months without needing additional treatment
- At primary endpoint,
  - PDS arm gained 0.2 letters from baseline
  - Ranibizumab monthly gained 0.5 letters

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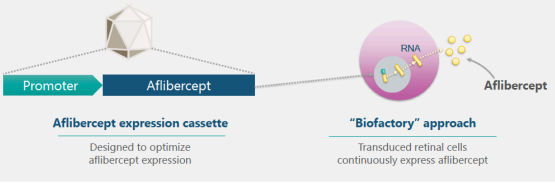
Gene Therapy

ADVM-022 Designed for Continuous Delivery of Aflibercept by Single IVT Injection

AAV.7m8

Capsid engineered by directed evolution to target retinal cells following IVT injection and deliver long-term VEGF inhibition



Aflibercept expression cassette

Designed to optimize aflibercept expression

"Biofactory" approach

Transduced retinal cells continuously express aflibercept

Adverum

OPTIC Study in Wet AMD

Status
- 4 cohorts fully enrolled
- Follow-up to 92 weeks

Primary Objective
- Assess the safety and tolerability of a single IVT injection of ADVM-022

Secondary Objective
- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy

	Prophylaxis Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops, 6wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops, 6wks

Supplemental Aflibercept (2 mg IVT) Criteria:

1. Loss of ≥10 letters in BCVA from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75 µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

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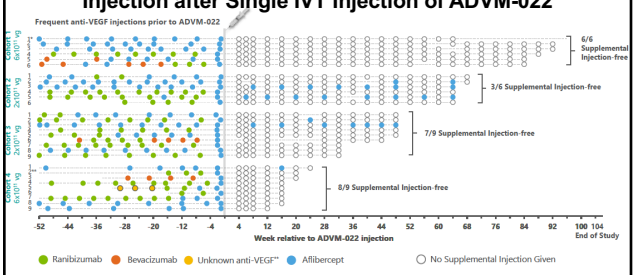
Majority of Patients Do Not Require Supplemental Injection after Single IVT Injection of ADVM-022



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ADVM-022 Safety

- No ADVM-022 elated non-ocular adverse events
- Intraocular inflammation
  - Responsive to steroids
  - Manageable with steroid eye drops
- No evidence of vasculitis, retinitis, or vascular occlusions

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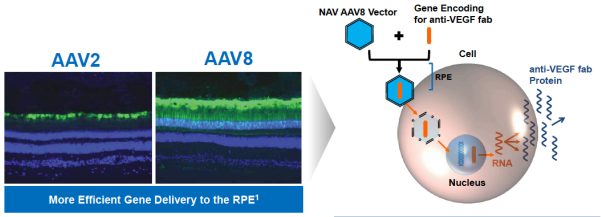
Gene Therapy

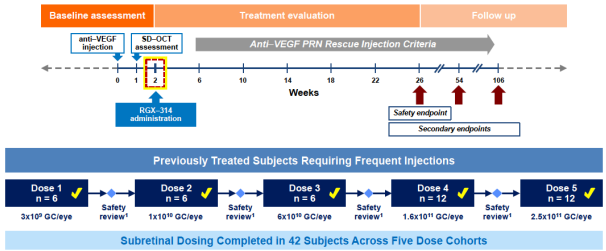
RGX-314 Uses a Novel AAV8 Vector to Deliver an anti-VEGF Fab



1. Vandenberghe et al. 2011 *Science Translational Medicine*

3

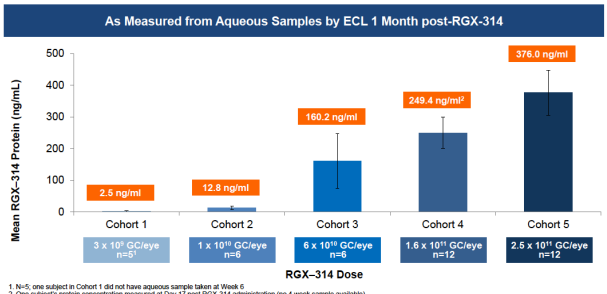
RGX-314 Phase I/IIa wAMD Study Has Fully Enrolled 5 Dose Cohorts



1. Dose escalation safety review to occur four weeks after final subject in each cohort has been dosed
SD-OCT = spectral domain optical coherence tomography

4

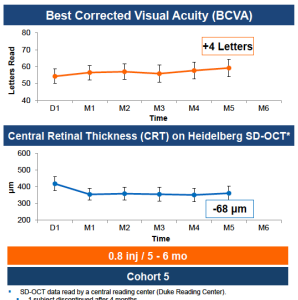
Dose Dependent Increase in RGX-314 Protein Observed Across Cohorts



1. N=5; one subject in Cohort 1 did not have aqueous sample taken at Week 6
2. One subject's protein concentration measured at Day 17 post RGX-314 administration (no 4 week sample available)

8

Cohort 5: Visual and Anatomic Outcomes



- **Stable to improved vision and OCT** on average
- **75% (9 of 12) injection free** at 5-6 months
- Highest clinical response observed

* SD-OCT data read by a central reading center (Duke Reading Center).
• 1 subject discontinued after 4 months

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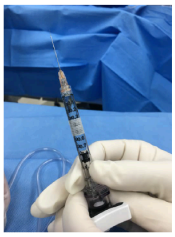
Key takeaways from the RGX-314 Phase I/IIa wAMD Clinical Trial

- RGX-314 Phase I/IIa wAMD study has fully enrolled 42 patients in 5 dose cohorts
- Patients enrolled were severe wAMD requiring frequent anti-VEGF injections
- Subretinal RGX-314 was well tolerated in 5 dose Cohorts
- Dose dependent increase in ocular protein observed across cohorts
- Cohort 3: subjects continue to demonstrate good vision and anatomic outcomes over 1.5 years
- Cohort 4: reduction in injection burden with stable to improved anatomic and visual outcomes
- Cohort 5: highest clinical response observed with 75% of subjects injection-free with stable to improved anatomic and visual outcomes*
- RGX-314 moving into Phase IIb trial for wet AMD, Phase II diabetic retinopathy trial, and in-office suprachoroidal delivery via SCS Microinjector™



* Data cut October 9 2019

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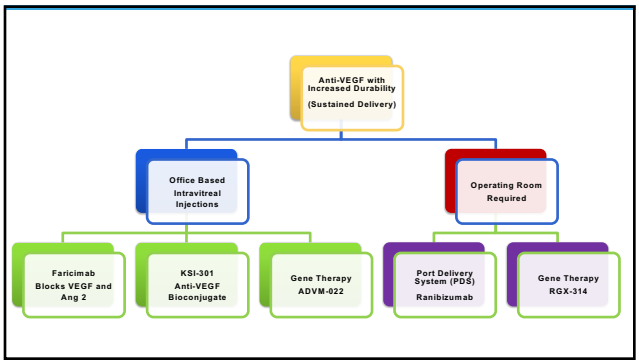
RGX-314 Program Next Steps

wAMD moving to Phase IIb Study by the end of the year

Diabetic Retinopathy IND by end of the year

Expanding to evaluate SCS delivery using Clearside's proprietary, in-office SCS Microinjector™


Anti-VEGF with Increased Durability (Sustained Delivery)
Office Based Intravitreal Injections
Operating Room Required
Faricimab Blocks VEGF and Ang 2
KSI-301 Anti-VEGF Bioconjugate
Gene Therapy ADVM-022
Port Delivery System (PDS) Ranibizumab
Gene Therapy RGX-314