Primary Analysis Results of the Phase 3 Archway Trial of the Port Delivery System With Ranibizumab (PDS) for Patients With Neovascular AMD

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OBJECTIVE Present topline results from the phase 3 Archway trial of the Port Delivery System with ranibizumab (PDS) for the treatment of patients (pts) with neovascular age-related macular degeneration (nAMD).

PURPOSE In pts with nAMD, real-world analyses show that visual outcomes are worse than in clinical trials, in part due to the high treatment burden of frequent anti-VEGF injections. The PDS is an investigational drug delivery system for the continuous intravitreal delivery of a customized formulation of ranibizumab (RBZ). The Archway phase 3 trial is evaluating the safety and efficacy of the PDS for nAMD.

METHODS Archway (NCT03677934) is an ongoing, phase 3, randomized, active treatment–controlled trial. Eligible pts had nAMD diagnosed within 9 months of screening and were responsive to anti-VEGF therapy. Pts were randomized 3:2 to treatment with PDS with RBZ 100 mg/mL with fixed 24-week (Q24W) refill-exchanges or intravitreal RBZ 0.5 mg injections every 4 weeks (Q4W). The trial evaluated the noninferiority (NI) and equivalence of PDS 100 mg/mL Q24W versus RBZ 0.5 mg Q4W; the primary endpoint was change in BCVA score from baseline (BL) averaged over weeks (W) 36 and 40 (NI margin, –4.5 letters; equivalence margin, ±4.5 letters). Primary analysis results with data through W40 are reported.

RESULTS A total of 248 and 167 pts were treated in the PDS 100 mg/mL Q24W and RBZ 0.5 mg Q4W (RBZ Q4W) arms, respectively; retention rate of 98.3% through W40. At BL, pts had a mean BCVA of 74.8 letters (20/32 Snellen) and a mean of 5.0 prior anti-VEGF injections. Change in BCVA score from BL averaged over W36 and W40 (95% CI) was +0.2 (−0.7, +1.1) and +0.5 (−0.6, +1.6) letters in the PDS and RBZ Q4W arms, respectively. With a difference (95% CI) of −0.3 (−1.7, +1.1) between arms, PDS was both noninferior and equivalent to RBZ Q4W. Change from BL in center point thickness at W36 was +5.4 µm (PDS) versus +2.6 µm (RBZ Q4W). 98.4% of PDS pts did not receive supplemental RBZ treatment during the first refill-exchange interval. The mean total number of RBZ treatments through W40 was 2.0 (PDS) versus 10.7 (RBZ Q4W). PDS implant insertion and refill exchange procedures were generally well tolerated. Systemic safety findings were comparable across arms.

CONCLUSION The PDS phase 3 Archway trial met its primary endpoint and demonstrated that PDS 100 mg/mL Q24W treatment resulted in vision outcomes at W36/W40 that were equivalent to RBZ 0.5 mg Q4W injections with ~5-times fewer treatments. The PDS was generally well tolerated with a favorable benefit-risk profile.

HUMAN RESEARCH Yes: Approved by institutional review board

Intravitreal AAVCAGsCD59 as Adjunct Anti-VEGF Treatment for Wet Age-Related Macular Degeneration

- Jeffrey S. Heier, MD

OBJECTIVE This study will evaluate if intravitreal AAVCAGsCD59 blocking membrane attack complex (MAC) of the complement cascade reduces anti-VEGF burden in eyes with new onset, treatment naïve wet AMD.

PURPOSE Levels of MAC, the final step of the complement cascade, are elevated in choroidal neovascularization (CNV). The transgene product of AAVCAGsCD59, soluble CD59 (sCD59), mimics natural CD59 and blocks MAC formation on cell membranes. The purpose is to evaluate if intravitreal AAVCAGsCD59 in eyes with new onset wet AMD reduces CNV activity and anti-VEGF burden.

METHODS This prospective, non-randomized trial evaluated 25 subjects at two sites with new onset, treatment naive wet AMD who received intravitreal anti-VEGF at Day 0 followed by intravitreal AAVCAGsCD59 at Day 7. Subjects 1-22 received 3.56x1011 vg AAVCAGsCD59 and subjects 23-25 received 1.017x1012 vg AAVCAGsCD59. Exams were monthly through Month 12 and intravitreal anti-VEGF was given based on an increase in central subfoveal thickness (CST) of >50 mm on OCT from Day 0, new subretinal hemorrhage, loss of 10 or more ETDRS letters from the previous month, or based on the expertise of the treating ophthalmologist.

RESULTS Overall, twenty-two subjects have a mean follow-up of 9.2 months (range, 5 to 12 months), received a mean of 1.95 anti VEGF injections, and 4 (18.2%) required no anti-VEGF rescue therapy. Thirteen subjects with 9 months or more follow-up received a mean of 2.2 anti-VEGF injections, and 2 of 13 (15.4%) have received no additional rescue treatments. Eyes rapidly responding to anti-VEGF with no intra or subretinal fluid on OCT at Days 7 and 30 (n=9; mean follow-up 9.3 months; range 6 to 12 months) demonstrate reduced anti-VEGF burden with a mean 1.1 injections/subject. Intraocular inflammation occurred in 3 eyes (13.6%) 2-3 months following AAVCAGSCD59 injection. No SAEs

associated with AAVCAGsCD59 have been reported.

CONCLUSION Preliminary results of intravitreal AAVCAGsCD59 7 days after intravitreal anti-VEGF for the treatment of new onset wet AMD demonstrates a reduction in the need for anti-VEGF therapy. Eyes rapidly responding to anti-VEGF treatment without fluid on OCT at Days 7 and 30 demonstrate a greater response to AAVCAGsCD59. Further evaluation of AAVCAGsCD59 in moderate and advanced AMD is warranted.

HUMAN RESEARCH Yes: Approved by institutional review board

RGX-314 for Neovascular AMD: Ongoing Phase I/IIa Results for Cohorts 1-5

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- Darin Curtiss
- Keunpyo Kim, PhD
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OBJECTIVE To evaluate the safety and tolerability of RGX-314 in patients previously treated with intravitreal anti-VEGF injection for neovascular AMD through six months.

PURPOSE In randomized controlled clinical trials, frequent IVT anti-VEGF injections has been shown to reduce the risk of blindness, However real world evidence shows patients lose visual acuity over time. RGX-314 is designed as a one-time therapy utilizing the AAV8 vector to deliver a transgene for a soluble anti-VEGF fab to produce continuous anti-VEGF therapy in subjects previously treated for nAMD.

METHODS Phase I/IIa trial is evaluating five doses of RGX-314 (3 x 109, 1 x 1010, 6 x 1010, 1.6 x 1011, and 2.5 x 1011 genome copies/eye) administered via subretinal delivery. Assessments of safety and efficacy are being conducted with the Primary Endpoints at week 26 and continued assessments to week 106. Measurements include: ocular and systemic adverse events, RGX-314 aqueous protein level, vision, central retinal thickness (CRT), and additional anti-VEGF injections needed post-RGX-314.

RESULTS As of October 9, 2019, RGX-314 has been well-tolerated with no drug-related serious adverse events (SAEs) reported for 42 subjects with nAMD (Cohort 1 - 5). Fifteen non-drug-related SAEs had been reported among nine subjects. Dose dependent protein production was observed across all five cohorts. Cohort 3 showed sustained RGX-314 protein production at one month, six months, and one year with stability in vision and anatomy despite few to no injections. Three subjects (50%) in Cohort 3 have not received any additional anti-VEGF injections for 18 months following RGX-314 administration, with

anatomic stability (CRT -21 µm) and improved vision (+11 ETDRS letters) from baseline at 18 months. At six months, Cohort 4 showed reduction in injection burden with anatomic stability (CRT -42 µm) and stable vision (+2 ETDRS letters). Cohort 5 showed anatomic stability (CRT -68 µm) and stable vision (+4 ETDRS letters) at five months, with 75% of subjects injection-free at 5-6 months.

CONCLUSION In the 42 subjects with nAMD, subretinal administration of RGX-314 has been well-tolerated and initial results show potential for a one-time administration of RGX-314 to provide sustained clinical outcomes in the treatment of nAMD.

HUMAN RESEARCH Yes: Approved by institutional review board

Treatment Burden and Vision Analysis of Anti-VEGF Therapies for the Treatment of Neovascular AMD

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- David A. Eichenbaum, MD
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- Saira Khanna, MD

OBJECTIVE To review Level 1 evidence on anti-vascular endothelial growth factor injection patterns for neovascular age-related macular degeneration in order to determine the 'optimal' dosing regimen.

PURPOSE Age-related macular degeneration is the leading cause of vision loss in the developed world. Anti-VEGF injection therapy has been revolutionary for treatment, and numerous clinical trials have examined varying dosing regimens. When analyzing anti-VEGF agents, more injections have yielded better vision. However, this comes at the cost of a high treatment burden on patients and providers.

METHODS We reviewed the Level 1 evidence for currently approved anti-VEGF agents and those likely to undergo review by regulatory authorities. The anti-VEGF agents and treatment dosing regimen were analyzed for each study, and we collected the baseline ETDRS letters, mean number of injections over a 12-month period, and change in ETDRS letters over 12 months.

RESULTS A total of 23 different injection regimens were analyzed from studies involving 6,860 eyes. Eight (31.6%, n=2165) were ranibizumab every 4 weeks or pro re nata (PRN). Six (28.6%, n=1962) were aflibercept dosed either every 4 or every 8 weeks. Four (15.4%, n=1059) were abicipar every 8 weeks or 12 weeks. Three (15.8%, n=1088) were brolucizumab dosed at every 12 or 8 weeks based on clinical activity. Two (8.7%) were bevacizumab every 4 weeks or PRN. The mean number of injections in these studies over 12

months was 9.36 ± 2.66 and the mean change in ETDRS letters was 7.86 ± 1.37. The correlation coefficient between the number of injections and mean change in ETDRS letters is 0.60.

CONCLUSION Despite the varying durability of the different anti-VEGF agents, there is a positive and clinically meaningful correlation between the number of injections in 12 months and the change in mean BCVA (ETDRS letters). Retina specialists should utilize this data in real-world practice, while considering the impact of treatment burden on neovascular AMD patients.

HUMAN RESEARCH Yes: Exempt from approval

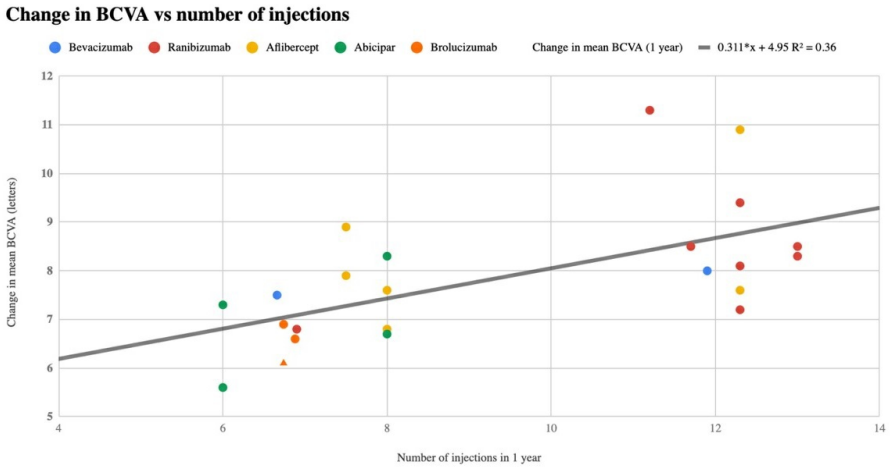


Figure 1: This figure explores the relationship between the number of injections and the number of ETDRS letter gained. Even though the agents have different durability, there is a positive and clinically meaningful correlation. Only FDA Registration and National Eye Institute trials were included in this analysis. Brolucizumab 3 mg dose is triangle data point above.

Study	Regimen	Drug	Sample size	Baseline BCVA (ETDRS Letter)	# Injections (1 year)	Change in ETDRS Letter (1 year)
CEDAR	q8	Abicipar	265	56	8	6.7
CEDAR	q12	Abicipar	262	56	6	5.6
SEQUOIA	q8	Abicipar	267	57.2	8	8.3
SEQUOIA	q12	Abicipar	265	56.4	6	7.3
VIEW 1	q4	Aflibercept	304	55.2	12.3	10.9
VIEW 1	q8	Aflibercept	303	55.7	7.5	7.9
VIEW 2	q4	Aflibercept	313	52.8	12.3	7.6
VIEW 2	q8	Aflibercept	313	51.6	7.5	8.9
HAWK	q8	Aflibercept	360	60.6	8	6.8
HARRIER	q8	Aflibercept	369	61.2	8	7.6
CATT	Monthly	Bevacizumab	286	60.2	11.9	8
CATT	PRN	Bevacizumab	300	60.4	6.66	7.5
HARRIER	q12/q8	Brolicizumab (6 mg)	370	61.2	6.74*	6.9
HAWK	q12/q8	Brolicizumab (3 mg)**	358	60.6	6.74*	6.1
HAWK	q12/q8	Brolicizumab (6 mg)	360	60.6	6.6*	6.6
ANCHOR	Monthly	Ranibizumab	140	53.7	11.2	11.3
MARINA	Monthly	Ranibizumab	240	47.1	12.3	7.2
VIEW 1	Monthly	Ranibizumab	306	54	12.3	8.1
VIEW 2	Monthly	Ranibizumab	303	53.8	12.3	9.4
CATT	PRN	Ranibizumab	286	61.5	6.9	6.8
CATT	Monthly	Ranibizumab	301	60.1	11.7	8.5
CEDAR	Monthly	Ranibizumab	290	56	13	8.5
SEQUOIA	Monthly	Ranibizumab	299	57.1	13	8.3

This table includes the study, the dosing regimen, anti-VEGF agent, sample size, number of injections and change in ETDRS letter at 1 year. q4 is every 4 weeks, q8 is every 8 weeks, q12 is every 12 weeks. PRN=pro re nata. *Extrapolated based on the study design given variable dosing in single study arm with weighted average based on minimum number of injections received 6 and maximum average injections received 7.5.

High-dose Aflibercept Therapy in nAMD and DME Eyes With Suboptimal Response to Standard Dose of Anti-VEGF Therapy: A Retrospective Analysis

- Jared S. Nielsen, MD, MBA

OBJECTIVE Can high dose aflibercept help eyes with neovascular age related macular degeneration (nAMD) and diabetic macular edema (DME) that are suboptimally responsive to standard dose injection therapy?

PURPOSE Some eyes with neovascular AMD or DME display suboptimal response despite therapy with standard doses of aflibercept. Treatment with high dose aflibercept (HDA) could provide additional benefit in these eyes. This study evaluated visual acuity, OCT findings, and injection burdens in eyes with a suboptimal response that were subsequently treated with HDA in a large retina practice.

METHODS This retrospective study evaluated eyes with nAMD or DME with a suboptimal response to aflibercept 2mg. Eyes were deemed suboptimal responders if they had clinically significant: a) disease activity despite aflibercept monthly therapy (AMT) (injection interval ≤35 days), or b) increased disease activity on interval extension (IAE)(> 36 days). Eyes received at least one aflibercept 2mg before being treated with high dose aflibercept (HDA; 3mg or 4mg) at the physician's discretion. Best visual acuity (BVA), central subfield thickness (CST), injection intervals, and safety events were evaluated at the first 4 HDA injections (HDA#1-4) and at the visits nearest to 6, 9, and 12 months.

RESULTS A total of 318 eyes of 288 patients were included in this analysis. Mean age was 74 years; 66% were female. Pre-HDA anti-VEGF treatment was extensive and summarized in Figure 1A. A total of 2566 HDA injections were administered during follow up. The number of eyes in each group were: nAMD (AMT, n=59; IAE, n=147); DME (AMT, n= 50; IAE, n=62). Visual acuity and OCT CST results are summarized for all groups in Figure 2. In all groups previously attained mean BVA was maintained where CST improved during HDA

therapy. These outcomes were achieved with reduced injection frequency relative to pre-HDA treatment (Figure 1B). The proportion of eyes receiving HDA 3 mg for nAMD was: 73% AMT and 58% IAE; for DME: was 49% AMT; 68% IAE. No new safety signals were identified, and intraocular pressure remained consistent with pre-HDA levels. General Linear Mixed Model analysis did not demonstrate any factors to predict BVA, CST, or injection intervals.

CONCLUSION In eyes with nAMD or DME where standard aflibercept results in suboptimal response, high dose aflibercept therapy may offer improved anatomic outcomes and decreased treatment burden while maintaining visual acuity with a safety profile similar to standard dose therapy.

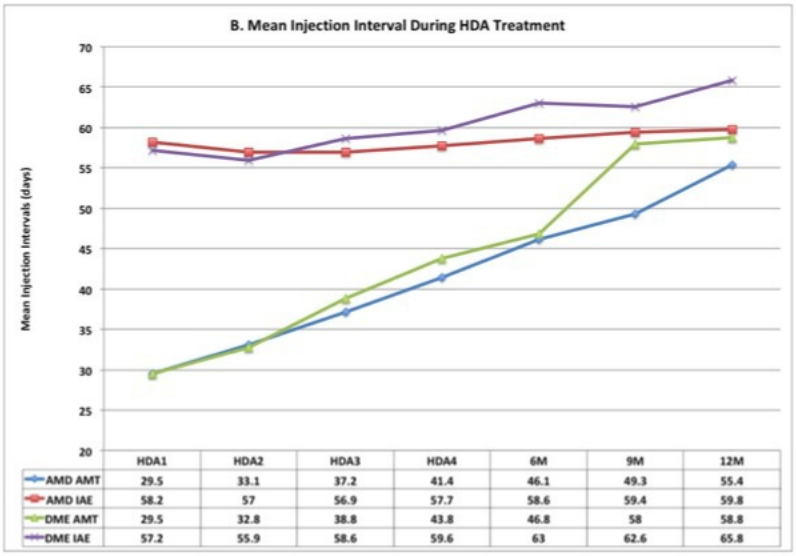
HUMAN RESEARCH Yes: Approval waived

Figure 1. Pre HDA treatment Summary and HDA Treatment Intervals

A. Summary of AntiVEGF Injection Treament prior to HDA- mean(±SD)

	Total IVI	IVB	IVR	SDA	Duration (days)	Interval (days)
AMD AMT	5.2 (±5.1)	1.4 (±3.0)	1.0 (±2.3)	2.8 (±3.2)	182.2 (±245.9)	31.1
AMD IAE	9.0 (±8.5)	2.04 (±3.3)	2.7 (±6.9)	4.3 (±3.6)	451.3 (±463.7)	47.8
DME AMT	10.6 (±14.3)	3.8 (±6.4)	3.9 (±9.4)	2.4 (±1.7)	346.5 (±476.5)	30.9
DME IAE	14.3 (±12.7)	6.0 (±8.6)	4.7 (±10.3)	3.7 (±2.2)	720.1 (±687.9)	50.1

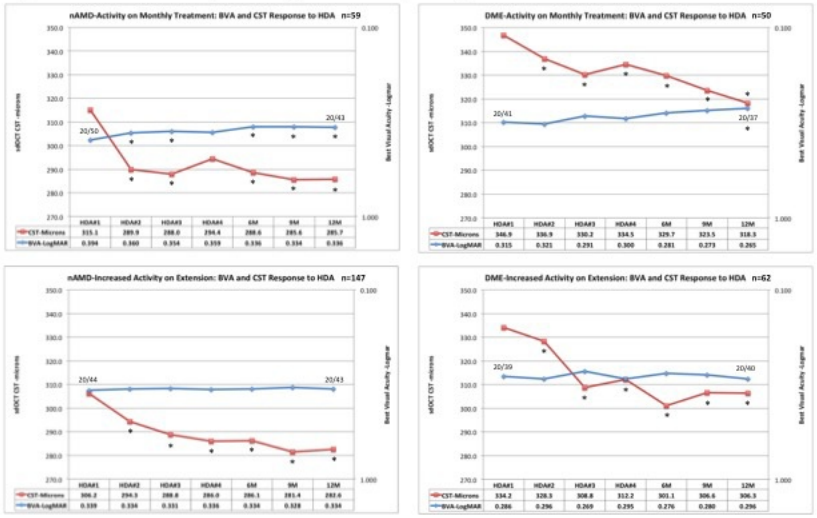
IVB= intravitreous bevacizumab, IVR= intravitreous ranibizumab, IVR= intravitreous ranibizumab, SDA= intravitreous standard dose aflibercept, IVI= intravitreous injection



	HDA1	HDA2	HDA3	HDA4	6M	9M	12M
AMD AMT	29.5	33.1	37.2	41.4	46.1	49.3	55.4
AMD IAE	58.2	57	56.9	57.7	58.6	59.4	59.8
DME AMT	29.5	32.8	38.8	43.8	46.8	58	58.8
DME IAE	57.2	55.9	58.6	59.6	63	62.6	65.8

Figure 1. A. Summary of pre high dose aflibercept (HDA) antiVEGF treatment in all groups.B. Mean injection intervals on high dose aflibercept (HDA) for all four groups through 12 months.

Figure 2. Mean BVA and CST Response to High Dose Aflibercept Therapy



Abbreviations:

nAMD: neovascular age-related macular degeneration
DME: diabetic macular edema
HDA: high dose aflibercept
BVA: best visual acuity
CST: central subfield thickness

Note: Mean BVA and CST at all observation points for all four groups, snellen equivalents noted on charts for baseline and 12 months observations, * denotes p<0.05 for paired t-test

Figure 2.Best Visual Acuity (logMar) and OCT Central subfield thickness response for all four groups through 12 months.

Abicipar Phase 2 MAPLE Trial: Evaluation of All Patients With Post-Injection Inflammation

- Tarek S. Hassan, MD

OBJECTIVE To evaluate the entire course of intraocular inflammation (IOI) in all 11 patients with neovascular age-related macular degeneration (nAMD) injected with abicipar pegol (abicipar) in the MAPLE trial.

PURPOSE MAPLE evaluated the safety of intravitreal injections of abicipar 2 mg produced using a modified manufacturing process, in patients with nAMD. 11 eyes developed IOI after injection and were exited from the trial. This study describes the presentations, treatments, courses and outcomes of all 11 patients with regard to vision, central retinal thickness, and any other adverse events.

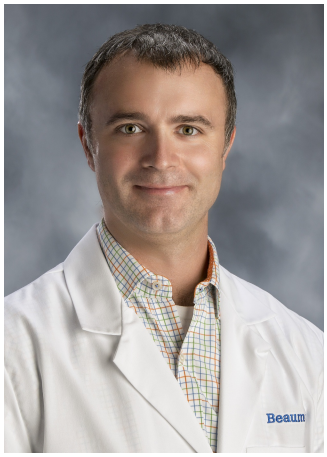
METHODS MAPLE was a Phase 2, multicenter, open-label, single-arm 28-week study. Enrolled patients (age ≥ 50, n=123) with nAMD were treatment-naïve (67.5% of subjects) or had prior anti-VEGF treatments (32.5% of subjects; excluding prior abicipar) and best-corrected visual acuity (BCVA) between 24 letters (20/320) and 78 letters (20/32) in the study eye. Patients received abicipar 2 mg at baseline, weeks 4, 8, 16 and 24. Safety was assessed at all visits. 11 patients were discontinued from the study due to IOI and we retrospectively evaluated their entire clinical courses including assessments of pre and post-treatment visual and anatomic changes, treatments, and other clinical characteristics.

RESULTS The overall incidence of treatment-related IOI of any severity was 8.9% (11/123). IOI was diagnosed after 1 injection in 3 study eyes, 2 injections in 2, and 4 injections in 6. Nine cases were assessed as mild (2.4% [3/123]) or moderate (4.9% [6/123]) in severity. Severe IOIs were reported in 1.6% (2/123) of study eyes with 1 case of iritis and 1 case of uveitis. All cases were treated with topical corticosteroids, 4 cases with moderate and/or severe IOI also received oral or intraocular steroids. After study completion, all IOI cases completely resolved with intraocular pressure returned to normal range, and overall vision in the majority of patients recovered to slightly better than baseline. There were no reported cases of endophthalmitis or retinal vasculitis in this study.

CONCLUSION This first-time report describes the courses of all 11 patients that developed IOI following abicipar injection for nAMD during the MAPLE trial. BCVA improved at the final visit in most eyes and inflammation completely resolved in all eyes. Abicipar produced through a modified manufacturing process demonstrated much improved safety compared to the abicipar used in the combined Phase 3 studies.

HUMAN RESEARCH Yes: Approved by institutional review board

Association Between CRT Fluctuation and BCVA With Abicipar Pegol Administered Every 12 Weeks for Neovascular AMD: CEDAR and SEQUOIA 52-Week Data



- Jeremy D. Wolfe, MD, MS
- Katelyn R Keyloun, PharmD, MS
- Xiaomeng Niu, PhD
- Joanna Campbell
- Nancy M. Holekamp, MD

OBJECTIVE To investigate retinal thickness fluctuation patterns in relation to visual acuity outcomes with abicipar pegol (abicipar) Q12 through Week 52 in a post-hoc analysis of CEDAR and SEQUOIA data.

PURPOSE CEDAR and SEQUOIA are phase III studies assessing abicipar Q12 and Q8 versus ranibizumab Q4 for neovascular age-related macular degeneration (nAMD). This post-hoc analysis of pooled CEDAR/SEQUOIA data reports the association between central retinal thickness (CRT) intra-injection fluctuation and best-corrected visual acuity (BCVA) gain at Week 52 with abicipar Q12.

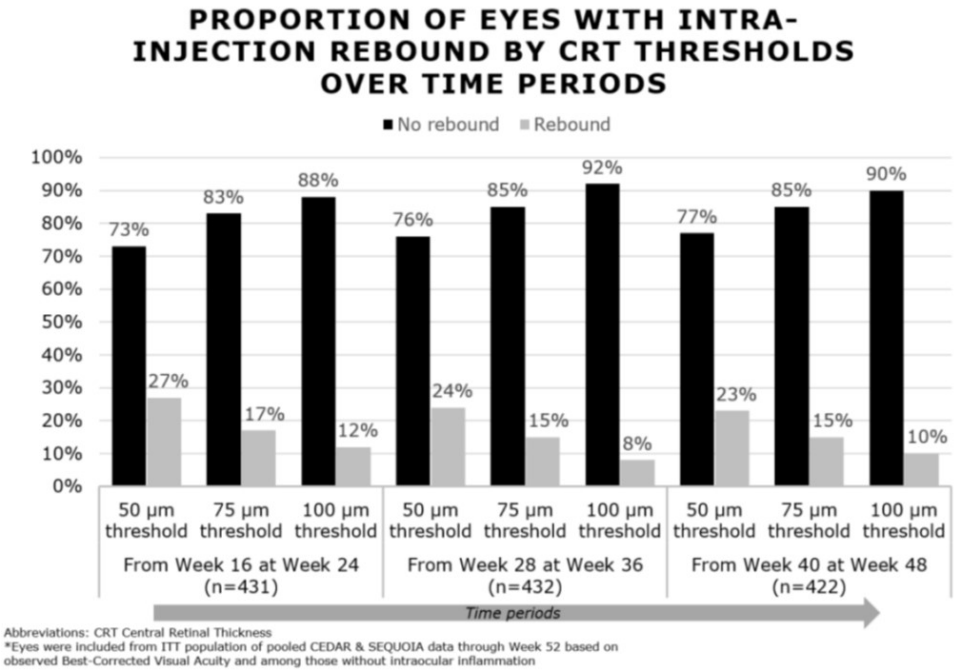
METHODS Observed CRT in eyes in the abicipar Q12 arm, without intraocular inflammation, were assessed after Week 12, 24, and 36 injections. CRT change or rebound was assessed between week 16 and 24, week 28 and 36, and week 40 and 48 (between 4 and 12 weeks after each injection, to reflect average CRT trough and peak). Eyes were stratified by change in CRT at 50 µm, 75 µm and 100 µm thresholds. Eyes fluctuating above the higher thresholds (i.e. ≥100 µm) were also included among those at the lower thresholds (i.e. ≥50 µm). Baseline characteristics and mean change from baseline in BCVA at Week 52 were reported for those who did and did not meet thresholds and assessed by pairwise t-tests.

RESULTS Analyses included weeks 16-24 (n=431), 28-36 (n=432), and 40-48 (n=422). A

minority of eyes from the abicipar Q12 population had intra-injection rebound over the 50, 75, or 100 µm thresholds (Table 1): 83-85% eyes experience rebound by <75 µm across injections and 88-92% eyes experience rebound by <100µm. There were no consistent, statistically significant differences in baseline characteristics by thresholds. Statistically significant differences in BCVA gain at Week 52 were consistently seen between eyes that did and did not rebound by 75 µm (2.1-3.6 vs 8.0-8.1 letters, p< 0.05) and 100 µm (1.4-2.3 vs 7.7-7.9 letters, p< 0.05). Differences in BCVA gain at Week 52 between eyes that did and did not rebound by 50 µm was not statistically significant after week 12 and 24. Eyes with intra-injection rebound between 50 and 74 µm (n=43, 38, 37, for each injection cycle) had a BCVA gain that was comparable to that in eyes with intra-injection rebound <50µm.

CONCLUSION Few abicipar Q12 patients had intra-injection OCT rebound that was associated with a decrease in BCVA. A negative association between BCVA gain at week 52 and intra-injection rebound was seen with rebounds ≥75 µm, where 83%-85% of patients experienced intra-injection rebound <75 µm. Thus, Q12 dosing maintained BCVA with minimal OCT fluctuation and reduced treatment burden for the majority of eyes.

HUMAN RESEARCH Yes: Approved by institutional review board



CEDAR & SEQUOIA: Proportion of Eyes With Intra-injection Rebound by CRT Thresholds Over Time Periods

Abicipar for nAMD Provides Faster Retinal Fluid Resolution, and Achieved Similar Dryness Through Week 104 With Fewer Injections

- Nancy M. Holekamp, MD

OBJECTIVE Evaluate time to first absence of fluid and retinal fluid status through Week 104 with abicipar pegol (abicipar) Q12/Q8 vs. ranibizumab Q4 in patients with nAMD in CEDAR and SEQUOIA Phase 3 studies.

PURPOSE This pre-planned analysis of the time to first absence of retinal fluid in CEDAR & SEQUOIA Phase 3 studies demonstrated that abicipar Q8 and Q12 dosing led to faster retinal drying and improved visual acuity outcomes with fewer injections compared to ranibizumab Q4 (rQ4). Post-hoc analysis demonstrated that abicipar Q8 and Q12 achieved similar dryness to rQ4 through Week 104 with fewer injections.

METHODS Pre-planned analysis included patients with nAMD treated with intravitreal abicipar 2 mg Q12 or Q8 after 3 initial monthly injections or 0.5mg rQ4 with known retinal fluid status. For all patients with subretinal (SRF), intraretinal (IRF), or any fluid (SRF/IRF/cystoid space) at baseline, time to first clearance of initial fluid during 52 weeks was analyzed in the intent-to-treat population (Kaplan–Meier method, log-rank test). The cumulative percent of patients who achieved absence of fluid was calculated for each group. For patients who completed the study to Week 104 without escaping to standard of care, the percent of patients with absence of fluid are reported for Weeks 12, 52 and 104.

RESULTS Majority of patients achieved fluid clearance during the first 12 weeks of treatment with higher percent of patients in the abicipar groups. The difference in time to first absence of subretinal, intraretinal, or any fluid was shorter for both abicipar Q12 (N=630) and Q8 (N=628) groups compared to rQ4 (N=630); statistical significance was achieved for SRF and any fluid ($P<0.001$ for SRF and $P<0.01$ for any fluid, Log-rank test).

The percentage of patients with cumulative incidences of fluid absence for SRF, IRF, and any fluid at Week 4, 8, and 12 are shown in Table 1 in the intent-to-treat population. The percentage of patients who completed the studies (completer set) with absence of SRF, IRF and any fluid was similar in the 3 treatment groups at Week 12 (3 injections for each arm), Week 52 (8 [Q8], 6 [Q12], and 13 [rQ4] injections) and Week 104 (14 [Q8], 10 [Q12], and 25 [rQ4] injections; Table 2), demonstrating that abicipar achieved fluid control up to Week 104 with fewer injections.

CONCLUSION Abicipar Q8 and Q12 showed faster initial clearance of subretinal, intraretinal, and any fluid compared to rQ4 group. The percent of patients with dry retinas at Week 104 were similar for each arm with fewer injections for abicipar Q8 (14 injections) and Q12 (10 injections) vs ranibizumab Q4 (25 injections).

HUMAN RESEARCH Yes: Approved by institutional review board

	Subretinal fluid			Intraretinal Fluid			Any fluid		
Time	Q8	Q12	rQ4	Q8	Q12	rQ4	Q8	Q12	rQ4
4 Weeks	8.0 (n=274)	7.8 (n=300)	5.7 (n=229)	9.5 (n=219)	8.1 (n=201)	7.9 (n=182)	6.2 (n=246)	6.0 (n=249)	5.4 (n=201)
8 Weeks	51.4 (n=373)	54.6 (n=379)	42.4 (n=310)	57.0 (n=273)	51.5 (n=252)	46.6 (n=222)	40.6 (n=358)	41.0 (n=335)	33.1 (n=280)
12 Weeks	70.0 (n=413)	69.2 (n=406)	59.9 (n=316)	71.2 (n=288)	64.8 (n=270)	56.9 (n=252)	59.3 (n=397)	55.3 (n=367)	46.2 (n=325)

CEDAR & SEQUOIA: Percentage of Patients with Absence of Retinal Fluid in First 12 weeks in the Intent-to-treat Population, Study Eye

	Subretinal fluid			Intraretinal Fluid			Any fluid		
Time	Q8	Q12	rQ4	Q8	Q12	rQ4	Q8	Q12	rQ4
Baseline	9.0 (n=40)	7.7 (n=34)	9.6 (n=50)	34.8 (n=154)	33.3 (n=147)	31.2 (n=162)	1.4 (n=6)	1.8 (n=8)	2.1 (n=11)
12 Weeks	65.4 (n=280)	49.5 (n=216)	56.1 (n=287)	67.1 (n=287)	54.6 (n=238)	56.8 (n=291)	59.3 (n=253)	35.6 (n=155)	45.7 (n=234)
52 Weeks	63.9 (n=273)	66.5 (n=288)	65.6 (n=330)	64.2 (n=274)	62.8 (n=272)	62.4 (n=314)	52.9 (n=226)	52.5 (n=227)	52.8 (n=265)
104 Weeks	58.0 (n=247)	60.8 (n=257)	59.4 (n=295)	51.9 (n=221)	49.6 (n=210)	54.7 (n=272)	45.3 (n=192)	42.1 (n=178)	42.5 (n=211)

CEDAR & SEQUOIA: Percentage of Patients with Absence of Retinal Fluid that Completed the Study to Week 104 (Completer Set)

Suprachoroidal CLS-AX (axitinib injectable suspension), as a Potential Long-Acting Therapy for Neovascular Age-Related Macular Degeneration (nAMD)

- David M. Brown, MD
- Thomas A. Ciulla, MD, MBA
- Viral Kansara

OBJECTIVE To assess ocular pharmacokinetic (PK) and pharmacodynamics (PD) of suprachoroidally injected CLS-AX in multiple species.

PURPOSE As a potent, selective tyrosine kinase inhibitor, axitinib inhibits VEGF receptors 1, 2, and 3. Pan-VEGF inhibition may be more effective versus current anti-VEGF-A monotherapy, which upregulate other angiogenic factors, including VEGF-C. In animal models, it inhibits corneal, retinal, and choroidal angiogenesis. Consequently, the potential of CLS-AX as long-acting therapy for nAMD was assessed.

METHODS Ocular distribution and PK of CLS-AX were assessed in Dutch-Belted pigmented rabbits. A single bilateral suprachoroidal injection (100µL) of CLS-AX was administered to each eye as 0.03 mg/eye (group 1) or 0.1 mg/eye (group 2). Efficacy of CLS-AX was evaluated in laser-induced choroidal neovascularization (CNV) models in rats and pigs. Brown Norway rats (n=10) were dosed once weekly for two weeks (0.2 mg/ 5µLs/ eye), Weanling pigs (n=8) were treated with 4 mg of CLS-AX in the right eye (OD) and with saline in the left eye (OS). Retinal lesions were evaluated on fundus photography, fluorescein angiography (FA) and on retinal flat mount tissue (n=16 eyes) by measuring the isolectin IB4 signal.

RESULTS CLS-AX was generally well tolerated in rats, rabbits and pigs with no overt signs of toxicity. No axitinib was detected in either plasma or aqueous humor. Sustained, high exposure of axitinib was observed throughout the 10-week study, highest in the sclera/choroid/RPE > retina > vitreous; consequently, preliminary estimation of human

ocular levels suggests that suprachoroidal CLS-AX may provide axitinib levels in choroid-retina that are >1000X higher than the in-vitro IC50 value, through 6 months. In rats, CLS-AX decreased the incidence of clinically important lesions (scores of 3 or 4) where 8/20 eyes (40%) showed a general improvement (scores of 0 to 2) by Day 21 compared to the control group. In pigs, CLS-AX significantly reduced fluorescein leakage at weeks 1 and 2 ($p < 0.009$ for both) compared to the control. IB4 quantification indicated significantly reduced growth of new blood vessels ($p=0.03$) at the site of the retinal laser lesion as compared to saline treatment.

CONCLUSION CLS-AX was well tolerated with durability in the suprachoroidal space. Results from the laser CNV studies corroborate others, showing inhibition of neovascularization in animal models. Given this PD effect, the ability to directly target affected tissues, and intrinsic highly potent pan-VEGF inhibition through receptor blockade, suprachoroidal CLS-AX has potential as long-acting therapy for wAMD.

HUMAN RESEARCH No: Study does not involve human research

Sustained Biweekly Aflibercept Improves Vision and Reduces Persistent Fluid in Refractory Neovascular AMD: Results From the Prospective TRISTAR Study

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- Carl C. Awh, MD
- David A Reichstein, MD
- Brandon G. Busbee, MD
- Franco M. Recchia, MD
- Kenneth P. Moffat, MD
- Peter L. Sonkin, MD
- Everton L. Arrindell, MD

OBJECTIVE To assess the safety and efficacy of biweekly aflibercept (AFL) in patients with neovascular age-related macular degeneration (NVAMD) and persistent subretinal fluid despite monthly dosing of AFL.

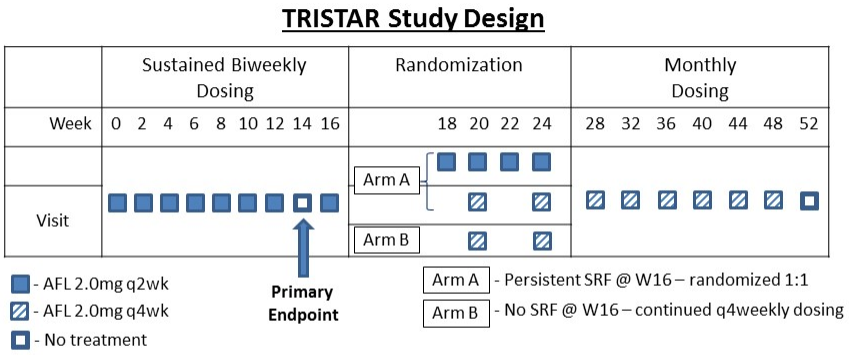
PURPOSE Symptomatic intra-/subretinal fluid persists in a subset of eyes despite chronic monthly anti-VEGF dosing. TRISTAR (NCT03468296) is the first prospective trial evaluating the utility of biweekly AFL therapy in this refractory population.

METHODS TRISTAR is 12-month prospective open-label study. Included patients had persistent subretinal (SRF) ± intraretinal fluid on SD-OCT despite a minimum of 1 year (median: 4.4y) of anti-VEGF therapy with at least 5 consecutive monthly (28-35d) AFL injections. A total of 22 eyes received 6 consecutive biweekly injections of AFL 2.0mg through week 12, followed by a 4 week treatment pause. Patients with any SRF at week 16 were randomized to 4 additional biweekly AFL 2.0mg doses or q4weekly dosing. After week 24, all patients received q4week treatments. Primary endpoints were change in ETDRS BCVA and central subfield thickness (CST) from baseline at week 14, two weeks after the 6th biweekly AFL.

RESULTS Overall, no additional safety signals were seen with biweekly AFL dosing. One patient developed endophthalmitis at week 12 requiring vitrectomy with a return to baseline BCVA by week 44. There were no additional drug/procedure-related adverse events. Excluding the patient with endophthalmitis, BCVA improved significantly from baseline to week 14 (+2.52 letters, $p<0.001$). Mean CST was also significantly improved at week 14 (-31.9um, $p<0.001$) with 8/22 eyes achieving complete SRF resolution. Only 2/8 eyes remained free of SRF at week 16 (4 weeks following the previous injection) with a corresponding significant increase in CST (+26.7um, $p=0.002$) compared to week 14. BCVA was not significantly different between week 14 and 16 (-0.33 letters, $p=0.952$) and remained significantly improved over baseline through week 24 for all patients irrespective of randomization group. By week 52, significant gain in BCVA and CST had been lost with a return to baseline levels in all treatment groups.

CONCLUSION In patients with refractory NVAMD-related SRF, sustained biweekly AFL resulted in significant functional and anatomic improvement during the biweekly dosing period. These gains, however, were lost upon return to monthly dosing. These findings suggest that efforts to reduce refractory SRF in NVAMD with sustained biweekly dosing may provide added benefit compared with standard of care treatment.

HUMAN RESEARCH Yes: Approved by institutional review board



TRISTAR Study treatment schemata

Characteristics of Fellow Eye Conversion to Neovascular Age-Related Macular Degeneration in Patients With Unilateral Neovascular Disease

- Matthew Starr, MD
- David Xu, MD
- Luv Girish Patel, MD
- Michael Ammar, M.D.
- Allen C. Ho, MD
- Namrata Saroj, OD

OBJECTIVE Identify the conversion rate from nonexudative to exudative macular degeneration in fellow eyes of patients with unilateral neovascular macular degeneration.

PURPOSE The fellow eye of patients with unilateral neovascular age-related macular degeneration (nAMD) treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections may undergo conversion to nAMD. Assessing the incidence of conversion in a real-world setting can yield clinically relevant insights

METHODS We retrospectively analyzed longitudinal, aggregated electronic health records from multiple retinal centers across the United States (Vestrum Health Retina Database). Patients were included with unilateral nAMD treated with anti-VEGF therapy between January 1, 2013 and August 31, 2019. All patients had at least 3 years of follow up after initiating treatment in the first eye. The frequency of fellow eye conversion within a 3-year window after onset of nAMD in the first eye was calculated. Visual acuity (VA) and central retinal thickness (CRT) at time of development of nAMD was recorded for both eyes when data was available.

RESULTS A total of 42,674 patients with unilateral nAMD who had received their first anti-VEGF treatment between January 1, 2013 and August 31, 2016 were included. Fellow eyes of 18,899 (44%) patients converted to nAMD during the study period. Among these, 6,098 (14%), 4,378 (10%) and 3,572 (8%) patients converted in years 1, 2 and 3 respectively after diagnosis of the first eye. The median time to conversion in the second eye was 655 days.

Mean VA at time of diagnosis of nAMD in the first eye (n=10,491) was 51.8 ETDRS letters (~ 20/100) and 57.2 ETDRS letters (~20/80) in the fellow eye (p<0.0001). At 12 months, mean VA was 52.6 ETDRS letters (~20/100) in the first eye and 57.5 ETDRS letters (~20/80) in the second eye (p<0.0001). The breakdown of VA is provided in Table 1. CRT at time of diagnosis (n=2,806) in the first eye was 326 microns versus 312 microns in the fellow eye (p <0.0001).

CONCLUSION Patients with unilateral nAMD have significant rates of conversion of the fellow eye. The fellow eye should be monitored at regular intervals to detect signs of neovascularization. Fellow eyes presented with significantly better vision at diagnosis than the initial eye and maintained better VA at 12 months.

HUMAN RESEARCH Yes: Exempt from approval

Combination of Dexamethasone Implant and Anti-VEGF Therapy in Neovascular Age-Related Macular Degeneration

- Raja Narayanan, MD, MBA
- Kushi Mallikarjun

OBJECTIVE To evaluate the efficacy of combination of Dexamethasone implant and anti-vascular endothelial growth factor (VEGF) therapy in eyes resistant to anti-VEGF therapy monotherapy in Age-Related Macular Degeneration (nAMD) in an Asian population.

PURPOSE Non-responders to anti-VEGF therapy have been reported to be be from 14-45% in nAMD. We report a cohort of Asian population resistant to anti-VEGF monotherapy who were treated with a combination of Dexamethasone implant and anti-VEGF injection.

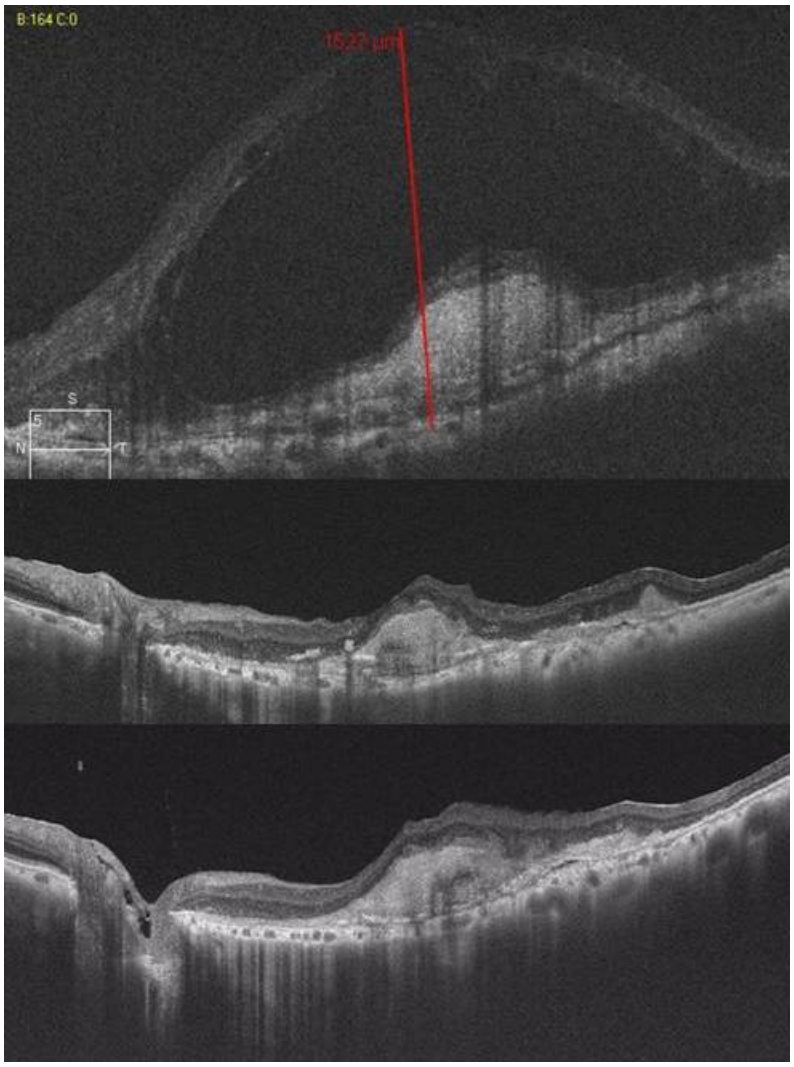
METHODS In this retrospective study, patients resistant to anti-VEGF injections were additionally injected with a Dexamethasone implant along with an anti-VEGF agent. Resistant cases were defined as less than 10% reduction in macular thickness on OCT. Best-corrected visual acuity (BCVA expressed in decimal value), slit lamp examination, intraocular pressure, fundus evaluation and optical coherence tomography (OCT) data were analyzed. Patients with presence of any macular fluid were re-injected with anti-VEGF therapy. The injection-free interval after the Dexamethasone implant was also analyzed. Student t-test and Fisher exact test were used to analyze continuous and categorical data respectively.

RESULTS Twenty-two patients were included in the study. The mean age of patients was 68.7 years, and there were 12 females. The mean BCVA immediately prior to Dexamethasone implant was 0.33 (20/60), compared to 0.35 (20/60) one month after the Dexamethasone implant ($p=0.853$). The mean number of anti-VEGF injections before Dexamethasone implant was 3.9.The mean injection-free interval in these patients after Dexamethasone implant was 89 days, which was significantly more than a pre-injection mean of 30 days ($p<0.001$). The mean OCT thickness prior to Dexamethasone implant was

571.86 microns, which was significantly different from the post-injection OCT thickness of 345.11 microns (p=0.011). Any macular fluid on OCT (either subretinal fluid, intraretinal fluid or pigment epithelial detachment) after Dexamethasone implant was significantly less than pre-Dexamethasone implant (p=0.02). The mean IOP before Dexamethasone implant was 14.63 mm Hg, and after the injection was 14.26 mm Hg (p=0.67).

CONCLUSION Dexamethasone implant combined with anti-VEGF treatment can be a useful option in eyes resistant to anti-VEGF monotherapy. While visual acuity is maintained, the treatment-free interval can be prolonged significantly in these eyes, and OCT thickness and macular fluid can be significantly decreased.

HUMAN RESEARCH Yes: Approved by institutional review board



Patient had received 12 anti-VEGF injections, 1 PDT over 2 years. Top panel: Severe macular edema in spite of 3 monthly injectionsMiddle panel: 1 month after Dexamethasone implant with bevacizumab injectionBottom panel: 4 months after Dexamethasone implant with bevacizumab injection

Two-Year Real-World Treat and Extend Patterns and Fluid Outcomes Among Neovascular Age-Related Macular Degeneration Patients Treated With Anti-VEGFs

- Michael A. Singer, MD
- Szilard Kiss, MD
- Katelyn R Keyloun, PharmD, MS
- Bijal Shah-Manek
- Andrew LaPrise
- Joanna Campbell
- Arghavan Almony, MD

OBJECTIVE To evaluate variability in treat and extend patterns and anatomic outcomes in the real-world among patients with neovascular age-related macular degeneration (nAMD) receiving anti-vascular endothelial growth factors (aVEGF).

PURPOSE aVEGF treatment regimens such as treat and extend (T&E) have been leveraged to reduce patient and clinic burden, however data on real world use and patterns, including number of injections, retreatment intervals, and switching has been limited. This analysis sought to identify and describe variability in potential treat and extend regimens and the impact on anatomic outcomes.

METHODS This was a retrospective analysis of the USRetina database, assessing patient-eyes receiving ≥1 aVEGF injection (bevacizumab [BEV], ranibizumab [RAN], aflibercept [AFL]) for nAMD between 10/1/16 and 12/1/17. Patient-eyes had no record of prior aVEGF treatment 12 months pre-index or concomitant retinal disease. Treatment sequences were constructed starting with the fourth injection, to remove the effect of loading doses. Sequences were re-started if a patient-eye switched aVEGF agents. Number of injections, maximum retreatment intervals, interval reduction/contraction (by ≥14 days), agent switch, and presence/absence of any fluid were assessed through 24 months from the index aVEGF injection.

RESULTS 1,410 eyes with ≥1 sequence were included over two years of treatment, with index aVEGF: BEV (44%); AFL (30%) and RAN (26%). The average number of injections per sequence was 4.4 (SD 1.9); and RAN had the highest mean injections 4.8 (SD 1.9). Average re-treatment interval was approximately 8 weeks (56.4 days; SD 26.1 days) and was comparable across agents, with eyes on BEV having the longest re-treatment interval (59.8 days). The median maximum re-treatment interval across agents was 63 days, and comparable across agents (59-63 days). First interval contraction occurred after mean of 4.3 (SD 1.4) injections and was similar across agents, (median 4.0 injections). Fluid presence was 53% for eyes treated with RAN, 59% for AFL, and 63% for BEV at the end the second year.

CONCLUSION In clinical practice, potential treat and extend regimens are largely delivered similarly across agents and anatomic outcomes still lag after 2 years of treatment. There remains a need for individualized treatment approaches, including extended duration aVEGFs that can better meet clinical constraints, and which may help to tailor therapy and improve clinical outcomes.

HUMAN RESEARCH No: Study does not involve human research

Clinical Evaluation and PK/PD Modeling of the DARPin Therapeutic Abicipar for the Treatment of Neovascular Age.Related Macular Degeneration

- Peter K. Kaiser, MD
- Ken Luu, PhD
- Jennifer Seal, PhD
- Mayssa Attar

OBJECTIVE Report 2 Year CEDAR/SEQUOIA and model simulations of visual outcomes for abicipar pegol (abicipar), a novel DARPin therapeutic, to treat neovascular age-related macular degeneration (nAMD).

PURPOSE CEDAR and SEQUOIA phase 3 studies were designed to investigate if abicipar pegol (abicipar) Q8 and Q12 dosing regimens could demonstrate efficacy compared with monthly ranibizumab and decrease patient burden by reducing the number of injections.

METHODS In CEDAR/SEQUOIA, multicenter, randomized, double-masked studies treatment-naïve patients with nAMD received abicipar Q8 or Q12 – after 3 initial doses administered over 12 weeks or 0.5 mg ranibizumab every 4 weeks. Year 2 pooled analysis assessing the percentage of patients with stable vision and mean changes from baseline in best corrected visual acuity (BCVA) and central retinal thickness (CRT) and safety data is reported. Population based pharmacokinetic/pharmacodynamic (PK/PD) modeling predicted stable vision for Q8/Q12/Q16 abicipar, BCVA for ranibizumab Q4 vs Q8/Q12 abicipar, and the proportion of patients with BCVA change of at least 5 letters for abicipar Q8/Q12/Q16/Q20 dosing.

RESULTS At Week 104, the percentage of patients with stable vision (abicipar Q8, 93% [n=426]; Q12, 90% [n=422]; rQ4 (94% [n=498]), mean changes in BCVA (abicipar Q8, 7.8 letters; abicipar Q12, 6.1 letters; ranibizumab Q4, 8.5 letters), and CRT (abicipar Q8, −147 µm; abicipar Q12, −146 µm; ranibizumab Q4, −142 µm) were comparable across arms. Abicipar groups maintained visual gains and improved anatomical changes while requiring

fewer injections (abicipar Q8, n=14; abicipar Q12, n=10; ranibizumab Q4, n=25). PK/PD modeling demonstrated good agreement with observed data in simulated mean change from baseline in BCVA for Q8, Q12 and rQ4 and stable vision (abicipar Q8, 91.4%; abicipar Q12, 91.3%; ranibizumab Q4, 90.8%) and also predicted the proportion of patients with a BCVA change of at least 5 letters (abicipar Q8, 62%; Q12, 55.1%; Q16, 47.6%; Q20, 36.5%). The overall incidence rates of treatment-emergent adverse events were similar between groups at the end of the second year.

CONCLUSION Abicipar is a novel anti-VEGF DARPin therapeutic that maintains vision gain and reduces treatment burden through less frequent dosing using an optimized combination of molar dose, a long vitreous half-life, and high binding affinity.

HUMAN RESEARCH Yes: Approved by institutional review board

Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Choroidal Neovascularization in AMD (ForeseeHomeDevice)

- Allen C. Ho, MD
- George E. Sanborn, MD
- Jennifer Jacobs, MD
- Gidi Benyamini
- Grace Chang, MS, MD, PhD
- Michael J. Elman, MD
- David A. Eichenbaum, MD

OBJECTIVE To evaluate real-world performance of a self-operated home monitoring system for early detection of choroidal neovascularization in AMD.

PURPOSE Evaluation of real-world (RW) performance of a monitoring strategy that includes an FDA-cleared self-operated home monitoring system on top of standard care, for early detection of choroidal neovascularization in AMD (ForeseeHome device, Notal Vision Inc), compared to performance in the NEI sponsored HOME study and AAO's IRIS registry.

METHODS A retrospective review of dry AMD patients participating in the ForeseeHome (FSH) device monitoring program was performed by an Independent Diagnostic Testing Facility (Notal Vision Diagnostics Center) from November 2009 to September 2018. All subjects were being monitored with the FSH device. Subjects with documented development of choroidal neovascularization (CNV) in one or both eyes were identified. Data related to the CNV event were collected, including modality of CNV diagnosis (device alert vs detection by other standard care means), and Snellen visual acuity (VA) at baseline and at CNV event. These data were compared with data from the HOME study and the IRIS registry.

RESULTS In these FSH-monitored patients, a total of 306 CNV events were recorded; 211 (69%) were detected after FSH alert. For all eyes with known VA, baseline VA (median) was 20/25-2, and at event 20/32-2. For eyes with events detected with FSH, baseline VA was

20/32+2 and at event 20/40+2. VA change was similar (p = 0.35) when events were detected by other means (i.e. through symptoms/during routine office visits), with a VA median loss of 4 letters. % of all eyes with baseline VA>=20/40 retaining >=20/40 vision at event was 80% (n=111), 82% for eyes detected with FSH, and 74% detected by other means. These data are comparable to the HOME study, where 64.1% of CNV events were detected after FSH alert, with baseline VA 20/32+2, event VA 20/40+2, a median VA loss of 3 letters and 91% (n=39) of eyes maintaining VA >=20/40. These data are substantially better than real-word IRIS registry data in which the reported VA at CNV event is 20/80 with only 33% of eyes maintaining VA>=20/40.

CONCLUSION RW performance of the strategy including the FSH Monitoring System is comparable to its performance in the HOME study. Coupled with standard of care, its usage demonstrated a substantial benefit to patients by helping preserve an additional 3 lines of vision at the onset of CNV, as compared to standard-of-care alone in real-world IRIS data, leading to excellent VA prognosis with current therapy.

HUMAN RESEARCH Yes: Exempt from approval

Table 1:

- VA at baseline for all eyes and by alerting modality
- VA at event for all eyes and by alerting modality
- Change in VA from baseline to event for all eyes and by alerting modality

All eyes with known VA				
	Baseline VA	Event VA	Event VA if BL VA available	VA change
# eyes	121	196	121	
Median VA (letters)	81	76	75	-4
Median VA (Snellen)	20/25-2	20/32-2	20/40+2	

Eyes with CNV event detected by FSH with known VA				
	Baseline VA	Event VA	Event VA if BL VA available	VA change
# eyes	95	151	95	
Median VA (letters)	80	75	75	-4
Median VA (Snellen)	20/32+2	20/40+2	20/40+2	

Eyes with CNV event detected by other means with known VA				
	Baseline VA	Event VA	Event VA if BL VA available	VA change
# eyes	26	42	26	
Median VA (letters)	83	78	76	-5
Median VA (Snellen)	20/25	20/32	20/32-2	

Table 2:

- % of eyes that retained VA >=20/40 at wet AMD conversion when monitored with FSH, compared with IRIS data
- VA of eyes at conversion

	FSH-Monitored RW Eyes	IRIS RW Eyes
Eyes with VA assessments available at both FSH Rx and at time of wet AMD diagnosis	121	162,000
Eyes that retained VA ≥ 20/40 at wet AMD conversion, %	80%	33%
Median VA at conversion	20/40+2	20/83

Ten-Year Follow-Up of Patients With Exudative Age-Related Macular Degeneration Treated With Intravitreal Anti-VEGF Injections

- Sophie Jane Bakri, MD
- Matthew Starr, MD
- Felix Kung, BA
- Camilo Mejia, BA
- Yvonne Bui, BS

OBJECTIVE To describe the long-term visual acuity outcomes of patients with age-related macular degeneration treated with intravitreal anti-vascular endothelial growth factor injections over a 10-year period.

PURPOSE To describe the visual acuity outcomes of patients with age-related macular degeneration treated with intravitreal anti-vascular endothelial growth factor injections over a 10-year period.

METHODS This was a retrospective, cohort study of eyes with exudative age-related macular degeneration that received ≥2 intravitreal anti-VEGF injections and had at least 10 years of follow-up after the initiation of treatment. Snellen visual acuity was recorded at baseline and then yearly until the last year of follow-up. Optical coherence tomography data were collected at the time of treatment initiation and at the last examination visit. A subanalysis was performed on patients who continued to receive anti-VEGF therapy using a modified treat and extend protocol versus those who discontinued treatment for longer than 1 year.

RESULTS One hundred thirty eyes of 115 patients met the inclusion criteria. The mean follow-up after treatment initiation was 11.1 ± 0.7 years. Eyes received an average of 45.1 ± 32.3 intravitreal injections in total and a mean of 5 to 7 injections per year. The baseline mean logMAR visual acuity was 0.61 ± 0.5 (Snellen acuity 20/81), and the final mean logMAR visual acuity was 0.88 ± 0.7 (20/152, P value = <0.0001). There were 40 eyes that received at least one injection every year. These eyes did not have a significant change in

visual acuity between the baseline and final examinations 0.47 ± 0.4 (20/59 vs. 0.58 ± 0.5 [20/76, P = 0.28]), whereas the eyes that did not receive at least one injection every year saw a significant decline in visual acuity 0.67 ± 0.5 (20/94 vs. 1.01 ± 0.7 [20/205, P < 0.0001]).

CONCLUSION Eyes with exudative age-related macular degeneration that received intravitreal anti-VEGF injections every year had stable visual acuity over a 10-year period. Continuous intravitreal anti-vascular endothelial growth factor therapy may stabilize visual acuity for 10 years and potentially longer.

HUMAN RESEARCH Yes: Approved by institutional review board

Clinical Effects of Blocking Ang-2 and VEGF with Faricimab in the Phase 2 STAIRWAY Trial

- Carl Joshua Danzig, MD
- Hugh S. Lin, MD
- Pascal Guibord, MSc
- David Silverman, MSc, MBChB
- Carlos Quezada-Ruiz, MD
- Ivaylo Stoilov, MD
- Zdenka Haskova, MD, PhD

OBJECTIVE To examine the effects of faricimab dosed at extended intervals compared with monthly ranibizumab on the macular anatomy of patients with neovascular AMD (nAMD) in the STAIRWAY trial.

PURPOSE Faricimab, the first bispecific antibody designed for intraocular use, can simultaneously bind and neutralize angiopoietin-2 and vascular endothelial growth factor-A (VEGF-A). The phase 2 STAIRWAY (NCT03038880) trial assessed extended durability of faricimab for the treatment of neovascular age-related macular degeneration (nAMD).

METHODS STAIRWAY was a 52-week, multicenter, randomized, active comparator–controlled, parallel-group, phase 2 trial. Treatment-naïve nAMD patients were randomized 2:2:1 to faricimab 6.0 mg every 16 weeks (Q16W) flex or Q12W fixed (both with 4 Q4W initiation injections) or ranibizumab 0.5 mg Q4W. Following disease activity assessment at week 24 of the trial, 12 weeks after the last faricimab initiation injection, the faricimab Q16W–assigned patients without disease activity continued Q16W dosing; patients with disease activity continued on Q12W dosing. No rescue treatment was allowed. Anatomic changes were measured by spectral domain optical coherence tomography (SD-OCT) and fluorescein angiography.

RESULTS Improvements in best-corrected visual acuity, reductions in central subfield thickness, choroidal neovascularization (CNV) lesion size, and area of leakage with faricimab Q16W flex and Q12W were comparable with ranibizumab Q4W. No new or unexpected safety signals were identified. At week 52, change from baseline in total lesion area was −4.2, −5.4, and −4.5 mm2 for the faricimab Q16W flex, faricimab Q12W, and

ranibizumab Q4W arms, respectively; change from baseline in CNV component area was −4.3, −5.6, and −4.8 mm2, respectively. Change from baseline in leakage area was −4.6, −5.6, and −5.3 mm2, respectively. Vision and macular anatomy were maintained with approximately half as many injections of faricimab Q16W flex or Q12W fixed versus ranibizumab Q4W dosing.

CONCLUSION Faricimab dosed at extended Q16W/Q12W intervals provided sustained anatomic and visual outcomes comparable with ranibizumab Q4W.

HUMAN RESEARCH Yes: Approved by institutional review board

Canadian Treat-and-Extend Trial With Ranibizumab in nAMD Patients: CANTREAT 36-Month Extension Results

- Peter J. Kertes, MD, FRCS(C)
- Tom Sheidow, MD, FRCS(C)
- R. Geoff Williams, MD, FRCS(C)
- Mark D.J. Greve, MD, FRCS(C)
- I. John Galic, MD, FRCS(C)
- Jason Baker, MSc, MBA

OBJECTIVE To assess treat.and.extend (T&E) ranibizumab dosing compared to once.monthly (OM) dosing in neovascular age.related macular degeneration (nAMD) patients with a 12.month T&E extension over 36 months.

PURPOSE Few large prospective studies have assessed the efficacy of a T&E ranibizumab regimen compared with OM dosing for treatment of nAMD. The main study assessed non-inferiority of T&E compared to OM, and the extension portion assessed the long-term effectiveness in those initially randomized to T&E remaining on T&E vs. those initially randomized to OM and switched to T&E at Month 24.

METHODS This was a 24.month randomized (1:1 T&E:OM), open.label, Canadian, post.authorization non.inferiority study. A subset of consecutive patients completing the 24.month main study (T&E or OM) were offered a 12.month ranibizumab extension with a T&E regimen for a total of 36.months of follow-up. Subject disposition, Best Corrected Visual Acuity (BCVA; in ETDRS letters), and injection frequency were assessed at 36.months. Data are presented for extension patients only by treatment group randomization in the main study + extension (T&E vs. OM-T&E).

RESULTS The study was approved by ethics boards and an Institutional Review Board. A total of 139 patients (73 T&E: 66 OM-T&E) from the main study entered the extension phase and 121 patients (68 [93.2%] T&E: 53 [80.3%] OM.T&E) completed the 12-month extension. Demographics and Baseline BCVA were comparable between groups. Mean (SD) changes from Baseline in BCVA at 36-months were 6.3 (11.61) letters for T&E group and

3.9 (13.91) letters for OM.T&E. After 36 months, 35.6%, 21.9%, and 13.7% of T&E patients gained ≥5, ≥10, and ≥15 letters from baseline, respectively, compared to 24.2%, 13.6%, and 6.1% of OM-T&E patients. Fewer patients experienced loss of ≥10 or ≥15 letters in the T&E (4.1%, 2.7%) than the OM.T&E group (9.1%, 7.6%) at 36 months. During the extension period, a mean (SD) of 7.3 (2.73) and 7.1 (2.80) injections were administered to patients in T&E and OM.T&E arms.

CONCLUSION After 36 months of treatment, the mean BCVA improvements achieved at 24.months were maintained for both the patients exclusively treated with the T&E regimen and those patients that switched to T&E after 24 months of the OM regimen.

HUMAN RESEARCH Yes: Approved by institutional review board

Peripheral Exudative Haemorrhagic Chorioretinopathy - A New Addition to the Spectrum of Pachychoroid Disease?

- Daraius N Shroff, MS FMRF FRCS
- Minal Sharma
- Jay Chhablani, MD
- Charu Gupta, MBBS, MS
- Cyrus M. Shroff, MD

OBJECTIVE To study the choroidal thickness trend in eyes with Peripheral Exudative Haemorrhagic Chorioretinopathy (PEHCR) using a 16 mm Swept source OCT scan and to compare this to age matched controls.

PURPOSE PEHCR is a peripheral exudative hemorrhagic disease of the elderly. It is considered to be a subtype of peripheral age-related macular degeneration which was thought to be associated with decreased choroidal thickness. The purpose of this study was to evaluate choroidal thickness in eyes with PEHCR and compare these with age-matched control eyes.

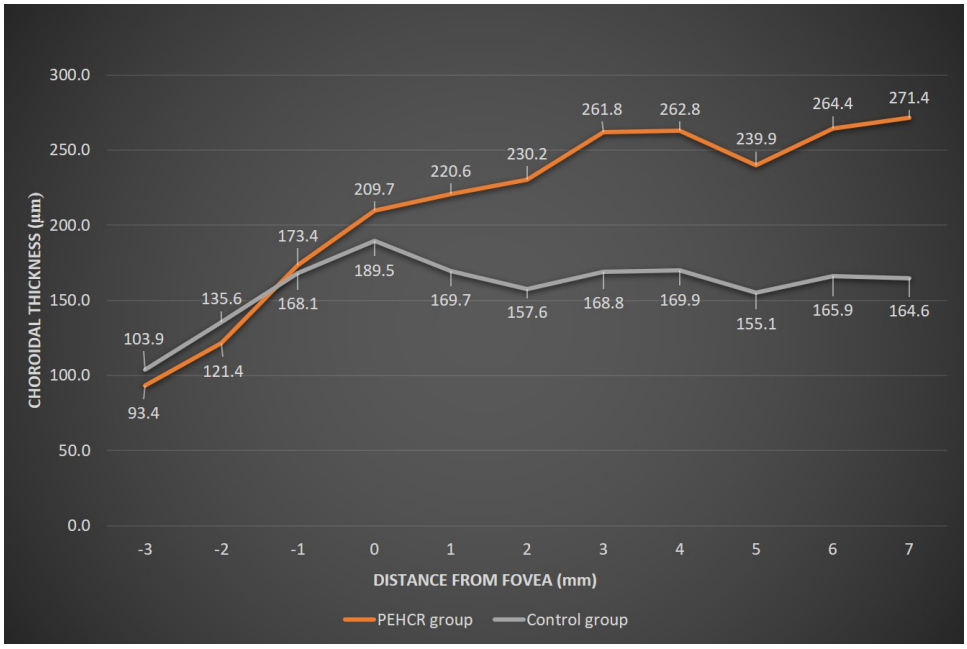
METHODS Retrospective, comparative case series. Fourteen eyes each in PEHCR and control group were included. All eyes underwent complete ophthalmic evaluation including swept-source optical coherence tomography (SS-OCT) with a high-definition line scan (HD Spotlight 16 mm) through the fovea. Choroidal thickness (CT) was measured from posterior edge of retinal pigment epithelium-Bruch's membrane to choroid-scleral junction. A total of 11 measurements were obtained from each eye one subfoveally, seven temporally and three nasal to fovea. The mean thickness at each of these points was plotted for both groups to analyse the trend in choroidal thickness for each of the groups.

RESULTS Twenty eight eyes were included (14 eyes each in PEHCR group and age-matched healthy-control group). Mean age was 77.2 years (range 68- 85 years) in PEHCR group and 78 years (range 68-85 years) in control group. Mean subfoveal CT was 209.7 µm in PEHCR group and 189.5 µm in control group. Mean CT 3000 µm nasal to fovea, 3000 µm temporal to fovea and 7000 µm temporal to fovea was 93.4 µm, 261.8 µm and 271.4 µm in PEHCR group; and 103.9 µm, 168.8 µm and 164.6 µm in control group. Mean CT was lowest in

nasal periphery and highest in temporal periphery in PEHCR group, with a progressive increase in CT from nasal to temporal periphery. In the control group, mean CT was lowest in nasally and highest in subfoveal region.

CONCLUSION We found a trend of increasing CT from nasal to temporal quadrant in PEHCR eyes with thickest part of the choroid present temporally, in contrast to control eyes where thickest part of the choroid was subfoveal. Our study supports inclusion of PEHCR in the pachychoroid disease spectrum. This could influence future management protocols. Larger studies would be required to confirm our findings.

HUMAN RESEARCH Yes: Approved by institutional review board



Graph showing the trend of choroidal thickness variation in PEHCR group and control group. Negative and positive values along the horizontal axis refer to points nasal and temporal to fovea respectively.

One-Year and Beyond: Results of Phase 1b Study of KSI-301, an Anti-VEGF Antibody Biopolymer Conjugate With Extended Durability, in wAMD, DME, and RVO

- Mark R. Barakat, MD
- Daniel Janer, MD
- Bryce Miller
- Jason S Ehrlich, MD PhD
- Victor Perlroth, MD, MBA
- J. Pablo Velazquez-Martin, MD

OBJECTIVE To evaluate the efficacy, safety and durability of repeated intravitreal injections of the novel anti-VEGF antibody biopolymer conjugate KSI-301 in patients with wet AMD, DME/DR and RVO.

PURPOSE KSI-301 is an anti-VEGF antibody biopolymer conjugate designed for meaningfully improved intraocular durability. An ongoing Phase 1b study has demonstrated promising initial safety, efficacy, and durability of multiple doses of KSI-301 in patients with wAMD, DME/DR, and RVO. In this paper, data with patient follow-up beyond one year and following multiple re-treatments over time will be reported.

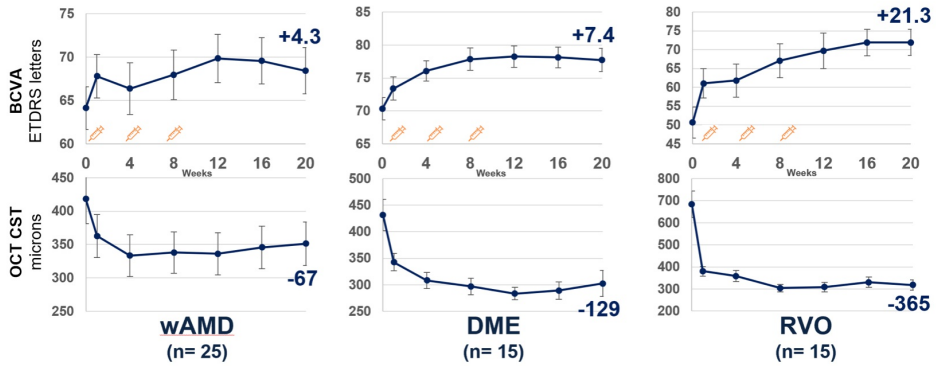
METHODS The Phase 1b study of KSI-301 is designed to provide a scientific and clinical proof of concept for the safety, efficacy and durability of KSI-301 and the ABC Platform in treatment-naïve subjects with wAMD, DME/DR and RVO. The study is open-label and patients are randomized to one of two KSI-301 dose levels, 2.5 mg or 5 mg. In the study, patients are being treated with three monthly doses of either 2.5 mg or 5 mg KSI-301 and followed thereafter, with additional treatments according to disease-specific, protocol-specified retreatment criteria. The criteria are based on changes in vision and/or retinal anatomy. Approximately 115 subjects (35 in each disease cohort) have been enrolled.

RESULTS The phase 1b study is on-going. As of November 8, 2019, ocular safety of KSI-

301 has been encouraging with no reports of intraocular inflammation and no drug-related adverse events after 338 doses. We have observed strong and typical anti-VEGF efficacy measured as improvements in BCVA and OCT across the 3 major, phenotypically variable retinal diseases of wAMD, DME, and RVO. Durability following 3 initiating doses of KSI-301 is promising: thus far, 92% of wet AMD eyes have been extended to 3 months or longer after the last loading dose without receiving retreatment. Many patients have not received their first retreatment until five or even six months after the last loading dose. Similarly, in DME 72% of DME eyes have been extended to four months or longer, and half of RVO eyes have been extended to 3 months or longer. New data following longer follow-up, with many patients followed for more than a year, will be presented for the first time at the meeting.

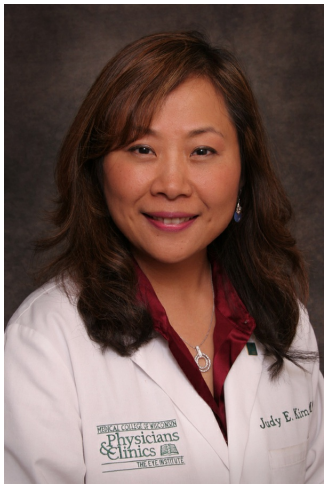
CONCLUSION Novel ABC Medicines leveraging the unique properties of phosphorylcholine biopolymers have been designed as extended duration intravitreal therapies. In a Phase 1b study, KSI-301 has demonstrated strong efficacy, excellent safety, and remarkable biological durability. A pivotal study in wAMD of KSI-301 given every 3-5 months versus Eylea every 2 months is now underway. Further studies are planned.

HUMAN RESEARCH Yes: Approved by institutional review board



Efficacy of KSI-301 in wAMD (n=25), DME (n=15) and RVO (n=15): change from baseline to week 20 in mean BCVA (top graphs) & OCT (bottom graphs). Includes only randomized patients that reached Week 20 visit by the data cutoff date of 8 Nov 2019; 2.5 & 5 mg doses pooled. Error bars represent standard error of the mean.

Performance of a Novel Deep Learning Algorithm for Automatic Retinal Fluid Quantification in Home OCT Images



- Judy E. Kim, MD
- David R Lally, MD
- Michael J. Elman, MD
- Oren Tomkins-Netzer, MD
- yael alon
- Elad Bergman, PhD
- Anat Loewenstein, MD

OBJECTIVE To evaluate the performance of a deep learning algorithm in identifying and quantifying retinal fluid in output of a patient self-operated home OCT device

PURPOSE Home OCT with automatic AI analysis has the potential to reduce monitoring burden from frequent office visits and to identify disease activity and changes in fluid volume between office visits. We evaluated the correlation between human and machine segmentation by the Notal OCT Analyzer (NOA) in quantifying intraretinal fluid (IRF) and subretinal fluid (SRF) in Notal Home OCT (NOCT) images.

METHODS Data was collected from 5 clinics where AMD patients self-imaged the central 10° of their maculae with the NOCT V2.5. From each cube scan (88 B-scans), average of 10 B-scans were selected for manual segmentation. Each B-scan was labeled pixel-wise into 4 compartments: Vitreous/outer layers (V/O), Retina (R), SRF, IRF. Eyes were randomly split into learning and validation sets (ratio 8/1). Quantifier was developed using semantic segmentation with convolutional neural network. Fluid quantification was evaluated by correlating each B-scan's fluid area segmented by human vs. machine. Pixel-wise fluid was compared with recall/precision. Presence of fluid in B-scans were compared for accuracy.

RESULTS 355 eyes from 239 subjects with a mean age of 78 years (range, 54-92 years) were enrolled. 3428 B-scans were manually segmented (75% with fluid). The learning set for the quantifier algorithm development included 2936 B-scans of 311 eyes. The validation set for the performance evaluation included 492 B-scans of 44 eyes. Based on the automatic segmentation, each pixel was classified to one of the 4 groups (V/O, R, SRF, IRF) and the area of SRF and IRF were compared to the human-defined segmented area. The Pearson correlation of fluid area was 0.98 ($p<0.00001$) for SRF and 0.90 for IRF ($p<0.00001$). The SRF Fluid pixel-wise recall was 0.72 and precision was 0.86; The IRF recall was 0.80 and the precision was 0.77. The sensitivity for detecting the presence of SRF in a B-scans was 0.99 and the specificity was 0.98. The sensitivity for detecting IRF was 0.99 and the specificity was 0.97.

CONCLUSION This version of NOA utilizing deep learning for automatic fluid quantification and segmentation on NOCT V2.5 images performed comparably to human readers. This home-based OCT, which can analyze fluid status, its dynamics, and visualize the locations of fluid, has the potential to accurately monitor AMD disease activity in a patient self-operated home-use environment.

HUMAN RESEARCH Yes: Approved by institutional review board

Loss to Follow-up in Patients With Neovascular Age-Related Macular Degeneration Treated With Anti-VEGF Therapy in the United States

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- Danielle Fujino, MPH
- Scott P Kelly, PhD
- Flora Lum, MD

OBJECTIVE To determine the incidence of loss to follow up in patients with neovascular age related macular degeneration treated with anti-VEGF therapy in the United States through the IRIS Registry.

PURPOSE When patients are lost to follow up, the ideal care is not delivered and patients likely suffer irreversible vision loss. The purpose of this study is to determine the incidence of loss to follow up in patients with neovascular age related macular degeneration (AMD) treated with anti-vascular endothelial growth factor (VEGF) injections in the United States and identify associated risk factors.

METHODS This is a retrospective cohort analysis involving 292,080 patients with neovascular AMD identified from the national IRIS Registry®. The patients were newly diagnosed between January 1, 2013- December 31, 2015 and treated with anti-VEGF therapy between January 1, 2013- December 31, 2018. Loss to Follow up (LTFU) was defined as interval greater than 12 months from last intravitreal injection. Multivariable logistic regression analysis involving baseline demographic and clinical conditions were utilized to determine odds ratios (OR) and 95% confidence intervals (CI).

RESULTS For neovascular AMD, 20.14% of patients were LTFU and 78.62% of patients had a follow up within 12 months. 1.24% of patient who were LTFU did have later follow up. Odds of LTFU were greater among patients 76-80 years of age (OR, 1.252; 95% CI, 1.302-

1.302; p<0.0001), 81-85 years of age (OR, 1.252; 95% CI, 1.203-1.302; p<0.0001), 86-90 years of age (OR, 1.436; 95% CI, 1.381-1.483; p<0.0001) and >90 years of age (OR, 1.681; 95% CI, 1.613-1.751; p<0.0001) compared with patients 70 years of age and younger. Odds of LTFU were lower for women (OR, 0.897; 95% CI, 0.879-0.915; p<0.0001) compared to men. Odds of LTFU among Hispanic patients (OR, 1.167; 95% CI, 1.105-1.234; p<0.0001) and patients of unreported race (OR, 3.025; 95% CI, 2.943-3.109; p<0.0001) were greater than with white patients. Odds of LTFU with patients with baseline visual acuity of 20/50-20/200 (OR, 1.214; 95% CI, 1.187-1.242; p<0.0001) were greater than patients with baseline visual acuity of 20/40 or better. Odds of LTFU with bilateral involvement (OR, 0.145; 95% CI, 0.142-0.149; p<0.0001) were less than unilateral involvement.

CONCLUSION There is a high rate of LTFU after anti-VEGF injections among patients with neovascular AMD. Risk factors identified included increasing age, male sex, Hispanic ethnicity, unreported race and unilateral involvement. Improving treatment adherence and follow up is critical to improve visual outcomes in neovascular AMD.

HUMAN RESEARCH Yes: Approved by institutional review board

Agitation of the Syringe as a Cause of Inflammation After Intravitreal Injection of Aflibercept: A Randomized, Double-blind, Controlled Clinical Trial

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- Natasha Cruz, MD
- Clarice Morais, PhD
- Murilo Polizelli
- Felipe Muralha, MD FICO
- Geoffrey G. Emerson, MD, PhD
- Octaviano Magalhães, MD
- Mauricio Maia, MD, PhD
- Michel Eid Farah, MD, PhD

OBJECTIVE To assess whether agitation of the syringe is a possible cause of inflammation after intravitreal injection of aflibercept.

PURPOSE Noninfectious endophthalmitis may be misdiagnosed as infectious endophthalmitis, leading to serious clinical implications. Although uncommon, most retina specialists have faced this problem in their clinical practice. So far, its causative factors remain unknown. Therefore, this study assessed the role of agitation in the development of inflammation after intravitreal injection of aflibercept.

METHODS A randomized, double-blind, controlled clinical trial included subjects with an indication of intravitreal antiangiogenic therapy prior to vitrectomy for proliferative diabetic retinopathy. Aflibercept was injected 48 hours before surgery. Control group received the injection without agitation while the intervention group was injected with a previously agitated syringe by flicking (brand: SR). The primary endpoint was the presence of anterior chamber (AC) cells, assessed at baseline and 48 hours later. Aqueous samples were collected at both time points and underwent cytometric bead array (CBA) for quantification of MIG, MCP-1, IP-10, RANTES, IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNF.

RESULTS Eleven individuals were included in the control group and 10 in the agitation group. Seven individuals were male in the former and six in the latter. None of the included eyes presented baseline signs of AC cells, hyperemia or pain complaint. Two subjects out of

11 (19%) in the control group and 8 out of 10 (80%) in the agitation group presented AC cells 48 hours after an intravitreal injection of aflibercept (P=0.009, Fisher's exact test). Three out the 8 eyes with AC cells in the intervention group also presented conjunctival hyperemia. Agitation by flicking has an 18-fold higher likelihood of AC cells than unagitated controls (OR=18.00; 95%CI: 2.04 – 159.09; p=0.009). The findings of the inflammatory cytokines assessed by CBA will be presented at the meeting. Although inflammation tends to decrease after antiangiogenic therapy, it is expected to find an increase, or a lower decrease, in one or more markers that could explain this remarkable difference between the groups.

CONCLUSION This clinical trial discloses a potential role of agitation in the development of inflammation after an intravitreal injection of aflibercept. Additional studies with different syringes and drugs should also be carried out in order to have a broader and more consistent perspective of this matter.

HUMAN RESEARCH Yes: Approved by institutional review board

	Control	**Agitation**	**Total**
	n (%)	*n (%)*	
Post-injection anterior chamber cells at 48h			
Yes	2 (**18.18**)	8 (**80**.00)	10 (47.62)
No	9 (81.82)	2 (20.00)	11 (52.38)
Total	11 (100.00)	10 (100.00)	21 (100.00)

Effects of Ketoconazole on Clinical Recovery, Choroidal Thickness and Hormonal Profile in Patients With Central Serous Chorioretinopathy

- Yodpong Chantarasorn, MD
- Itsara Lertjirachai, MD

OBJECTIVE To evaluate the effects of ketoconazole on clinical outcomes in central serous chorioretinopathy (CSCR), and to analyze a relationship between patients' choroidal thickness and steroid hormones.

PURPOSE Hypercortisolism has long been correlated with choroidal hypermeability in CSCR. This may explain the inconsistency of therapeutic responses of the mineralocorticoid receptor (MR) antagonist since hyperaldosteronism has rarely been detected in such cases. Hence, an early treatment using ketoconazole, the first line cortisol inhibitor that also blocks the MR ligand, appears to be rational.

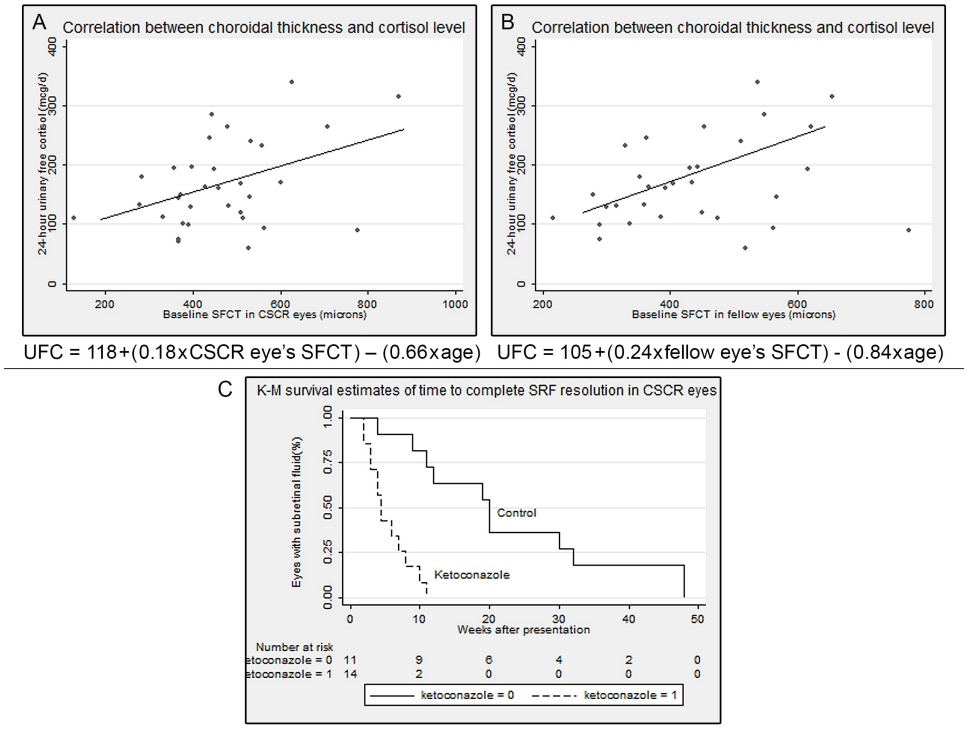
METHODS This retrospective 2-center cohort study analyzed 36 eyes with CSCR that were categorized into the control (n=16) and the treatment group (n=20) that received oral ketoconazole at a daily dose of 600 mg, which was tapered by 200 mg at 3 weeks, and stopped once the macula was dry. The maximal treatment duration was 6 weeks. Rescue laser therapy was applied to cases whose subretinal fluid persisted at 12 weeks. We performed a survival analysis to determine the time to resolution, and the Cox regression to identify any factors affecting therapeutic response. Best-corrected visual acuity (BCVA), central subfield thickness (CST) and subfoveal choroidal thickness (SFCT) were analyzed at 6 months.

RESULTS All baseline features including onset duration (treatment group, 23±3; control group, 18±9 weeks) were not different between two groups. Baseline urinary free cortisol (UFC) was elevated at 185±19 and 181±28 µg/day (range, 50-150) in the treatment and control group respectively, whereas mean serum aldosterone and testosterone levels in both groups were normal. After adjusting for age and gender, baseline UFC levels showed a

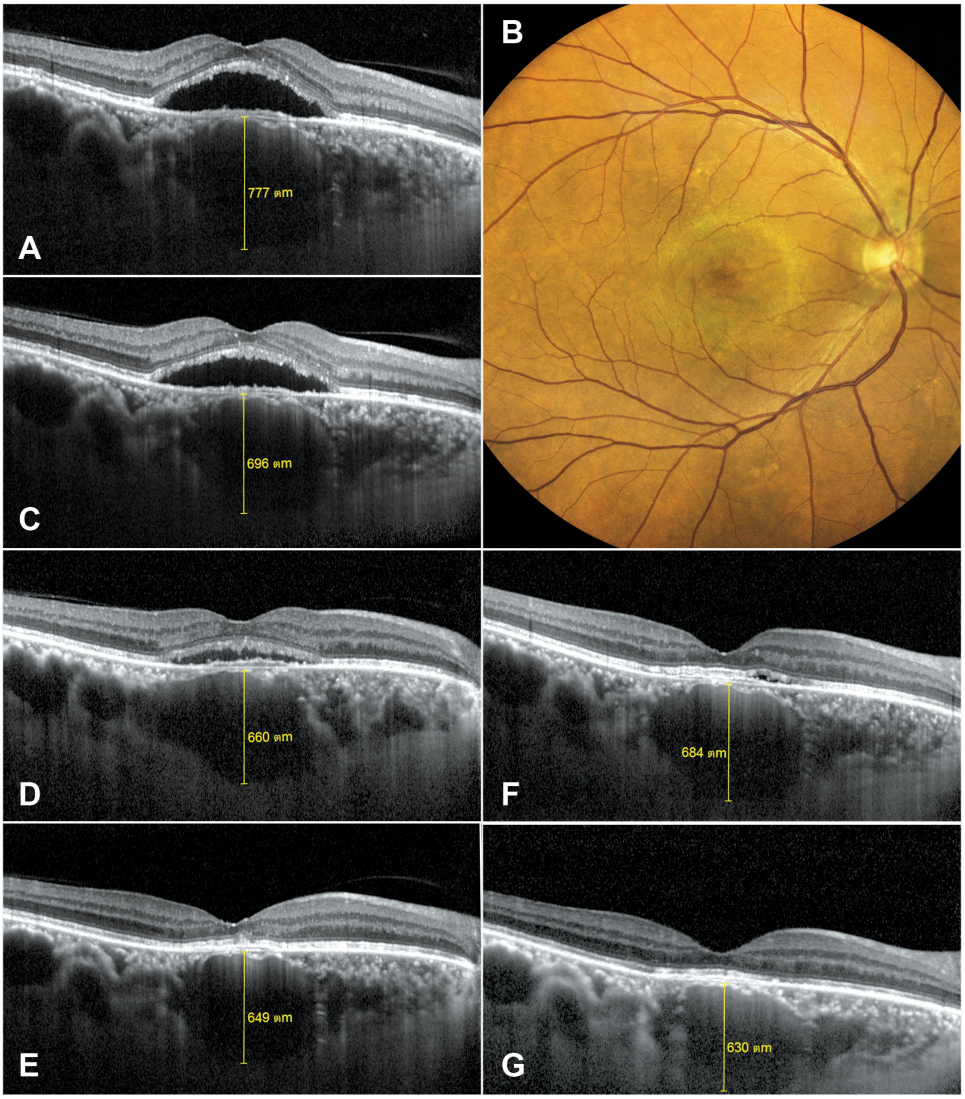
positive linear correlation with SFCT in both eyes (CSCR eyes, p=0.04; fellow eyes, p=0.01). The formulas are shown in Figure 2. In the Cox regression analysis, ketoconazole significantly speeded up the resolution of CSCR (the median time to resolution of 4.5 and 20 weeks; adjusted hazards ratio (AHR), 2.86) (Figure 2C), and resulted in better logMAR BCVA in the treatment group at 6 months (adjusted differences, 0.12±0.04; p=0.01). Slow responders are likely found in older age group (AHR, 0.89). Sleep apnea was detected in 73% of cases whose body mass index above 25.

CONCLUSION As elevated glucocorticoids are likely responsible for the pathogenesis of CSCR, a temporary decrease in choroidal hypermeability by using oral ketoconazole may further reduce the incidence of persistent CSCR by allowing subretinal fluid to be absorbed more quickly. Patients receiving ketoconazole also showed better visual results than those receiving conventional treatment at 6 months follow-up.

HUMAN RESEARCH Yes: Approved by institutional review board



The scatter plots of all study eyes show a positive linear correlation between 24-hour urinary free cortisol (UFC) levels and subfoveal choroidal thickness (SFCT) in eyes with central serous chorioretinopathy (CSCR) (Figure 1A) and fellow eyes (Figure 1B). In addition, Kaplan-Meier estimates showed that the median time to complete subretinal fluid absorption was 4.5 weeks in the ketoconazole treated eyes, and 20 weeks in the control group (p=0.01, log-rank test) (Figure 1C).



A 54-year-old obese man had been diagnosed with CSCR in the right eye for 6 months. The presenting UFC was 190 µg/day (Figure 2A-2B). After a 6-week course of ketoconazole, the choroidal thickness gradually decreased, and submacular fluid resolved at 10 weeks post-treatment (UFC=90 µg/day) (Figure 2C-2E). 6 months later, CSCR recurred; the sleep laboratory revealed 34 episodes of apnea per hour. The macula was dry after 6 weeks of airway ventilation therapy (Figure 2F-2G).

Comparative Efficacy of Different Anti-VEGF Treatment Regimens in Patients With nAMD: A Network Meta-Analysis

- Diana V Do, MD
- Ivaylo Stoilov, MD
- Caroline Solon
- Ferhina S Ali, MD, MPH
- Jennifer Uyei
- S. Pinar Bilir, MS
- Andreas Karabis
- Rajpal Singh
- Yilin Jiang, MSc
- Vincent S Garmo, MHS

OBJECTIVE To examine the comparative efficacy of anti-vascular endothelial growth factor (VEGF) regimens for neovascular age-related macular degeneration (nAMD) using a network meta-analysis (NMA).

PURPOSE Numerous clinical trials have compared the efficacy of different anti-VEGF agents, dosing, and/or injection frequencies, but no single trial can compare all of the treatment regimens available. We used an NMA approach (which focuses exclusively on those studies that have a comparator in common) to evaluate how outcomes compare between different anti-VEGF regimens for nAMD across clinical trials.

METHODS A systematic literature review identified randomized controlled trials (RCTs) of anti-VEGF therapy for nAMD (Table). Interventions were defined by drug, dose, and regimen (fixed Q4W, Q8W, Q12W, pro re nata [PRN], or treat-and-extend [T&E]). Over 20 anatomic, vision, and safety outcomes were assessed to determine if they were evaluated/reported with sufficient consistency across studies to allow inclusion in the NMA (feasibility analysis). Then the literature and expert opinion were consulted to assess whether or not differences in specific baseline characteristics between studies would impact the outcomes included and, if so, that impact was factored into the NMA.

RESULTS Feasibility analysis determined that the outcomes that could be compared using

NMA were 3 best-corrected visual acuity (BCVA) outcomes (measured in Early Treatment Diabetic Retinopathy Study letters): mean change from baseline at month (M)12 and M24 and patients (%) gaining ≥15 letters at M12. Many outcomes could not be compared, particularly anatomical outcomes related to fluid measurements, due to data heterogeneity or lack of data. All studies reported similar baseline characteristics, with few exceptions; no effect modification. For the most commonly reported outcome (BCVA change at M12) 21 RCTs were included (Table). Baseline VA varied from 52−65 letters across all trials. Ranibizumab (RAN) Q4W and PRN (the most commonly compared treatment regimens across studies) were used as reference cases. The NMA found no statistically significant differences in any of the evaluable outcomes in any pairwise comparison with RAN Q4W or PRN (comparisons with RAN PRN are shown in Figure).

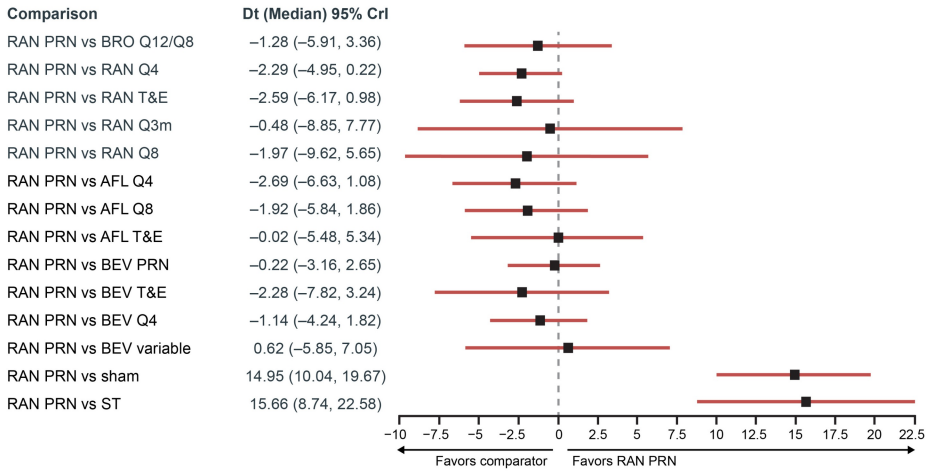
CONCLUSION This NMA suggests that the different regimens evaluated have not resulted in superior vision benefits compared with RAN PRN or Q4W. If confirmed, these results suggest that greater visual acuity improvements may require a different approach to treatment, such as a different drug delivery paradigm or the development of drugs with different or multiple mechanisms of action.

HUMAN RESEARCH Yes: Approved by institutional review board

Study	Treatment	Treatment/ Strategy	Mean (SE) Diff in BCVA
ABC	BEV 1.25 mg	BEV PRN	6.4 (2.0)
	ST*	ST	-9.5 (1.9)
BRAMD	BEV 1.25 mg	BEV Q4	5.1 (1.1)
	RAN 0.5 mg	RAN Q4	6.4 (0.9)
CANTREAT Study	RAN 0.5 mg	RAN Q4	6.0 (0.7)
	RAN 0.5 mg	RAN T&E	8.4 (0.7)
CATT 1	RAN 0.50 mg	RAN Q4	8.5 (0.8)
	BEV 1.25 mg	BEV Q4	8.0 (1.0)
	RAN 0.50 mg	RAN PRN	6.8 (0.8)
	BEV 1.25 mg	BEV PRN	5.9 (1.0)
El-Mollayess	BEV 1.25 mg†	BEV Q4	11.0 (1.3)
	BEV 1.25 mg‡	BEV Variable	9.2 (2.0)
GEFAL	BEV 1.25 mg	BEV PRN	5.4 (1.1)
	RAN 0.5 mg	RAN PRN	3.6 (1.1)
HARBOR	RAN 0.5 mg	RAN Q4	10.1 (0.8)
	RAN 0.5 mg	RAN PRN	8.2 (0.8)
HARRIER	BRO 6.0 mg§	BRO Q12/Q8	6.9 (0.6)
	AFL 2.0 mg (loading/Q8)	AFL Q8	7.6 (0.6)
HAWK	BRO 6.0 mg	BRO Q12/Q8	6.6 (0.7)
	AFL 2.0 mg	AFL Q8	6.8 (0.7)
IVAN	RAN 0.50 mg	RAN Q4	6.4 (0.7)
	BEV 1.25 mg	BEV Q4	4.7 (0.7)
LUCAS	BEV 1.25 mg	BEV T&E	7.9 (1.0)
	RAN 1.25 mg	RAN T&E	8.2 (0.9)
MANTA	RAN 0.5 mg	RAN PRN	4.9 (1.2)
	BEV 1.25	BEV PRN	4.1 (1.2)
MARINA	RAN (Pooled, 0.3 mg/0.5 mg)	RAN Q4	6.9 (0.6)
	Sham	Sham	-10.4 (1.0)
OSPREY	BRO 6.0 mg	BRO Q12/Q8	4.9 (2.7)
	AFL 2.0 mg	AFL Q8	7.3 (2.0)
PIER	RAN (Pooled, 0.3 mg/0.5 mg)	RAN Q3m	-0.9 (1.3)
	Sham	Sham	-16.3 (2.8)
RABIMO	RAN 0.5 mg	RAN Q8	8.5 (2.3)
	RAN 0.5	RAN PRN	6.5 (2.7)
RIVAL	RAN 0.5 mg	RAN T&E	6.9 (0.9)
	AFL 2.0 mg	AFL T&E	4.4 (0.9)
TREND	RAN 0.5 mg	RAN T&E	6.6 (0.8)
	RAN 0.5 mg	RAN Q4	7.9 (0.7)
TREX-AMD Trial	RAN 0.5 mg	RAN Q4	9.2 (1.3)
	RAN 0.5 mg	RAN T&E	8.2 (2.0)
VIEW 1	RAN 0.5 mg	RAN Q4	8.1 (0.9)
	AFL 2 mg	AFL Q4	10.9 (0.8)
	AFL 2 mg	AFL Q8	7.9 (0.9)
VIEW 2	RAN 0.5 mg	RAN Q4	9.4 (0.8)
	AFL 2 mg	AFL Q4	7.6 (0.7)
	AFL 2 mg	AFL Q8	8.9 (0.8)

*photodynamic treatment with verteporfin, or intravitreal pegaptanib or sham treatment; †Loading/Q6W and switch to Q4W if evidence of fluid on OCT; ‡Loading/Q6W, if evidence of fluid at 6W second injection with continued 6-W follow up, if continued evidence then 4W. After 3 consecutive injections option for physician to stop and observe; §Loading/Q12 with Q8 option depending on clinical signs.
AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab

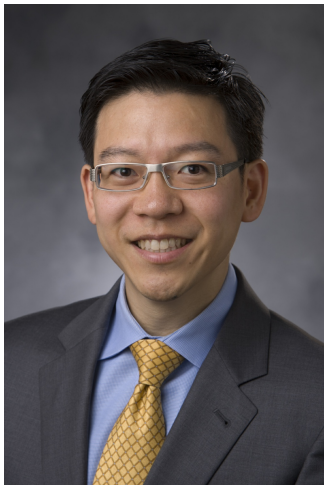
Table. Randomized Controlled Trials Included in Network Meta-Analysis (N=21)



AFL, aflibercept; BEV, bevacizumab; BRO, brolucizumab; CrI, credible interval; Dt, treatment difference; PRN, pro re nata; Q3m, every 3 months; Q4, every 4 weeks; Q8, every 8 weeks; Q12, every 12 weeks; RAN, ranibizumab; ST, standard therapy (photodynamic treatment with verteporfin or intravitreal pegaptanib or sham treatment); T&E, treat-and-extend.

Figure: Forest plot comparing mean change from baseline in BCVA at month 12 between RAN PRN and other treatment regimens.

Predicting Long-term Response to Ranibizumab After Three Injections in Patients With Age-Related Macular Degeneration



- Paul Hahn, MD, PhD
- Min Tsuboi, Pharm.D.
- Steven Blotner, MS
- Ivaylo Stoilov, MD

OBJECTIVE To assess whether month (M) 3 outcomes in neovascular age-related macular degeneration (nAMD) can predict long-term outcomes to guide optimal therapeutic management.

PURPOSE It has been suggested that M3 response to anti-VEGF treatment in diabetic macular edema patients (pts) may predict long-term outcomes and that "early" switching of drug in poor responders may be indicated. As novel-mechanism treatments are approaching for nAMD, we conducted a similar analysis to see if M3 responses after 3 ranibizumab [RBZ] injections were predictive of long-term nAMD outcomes.

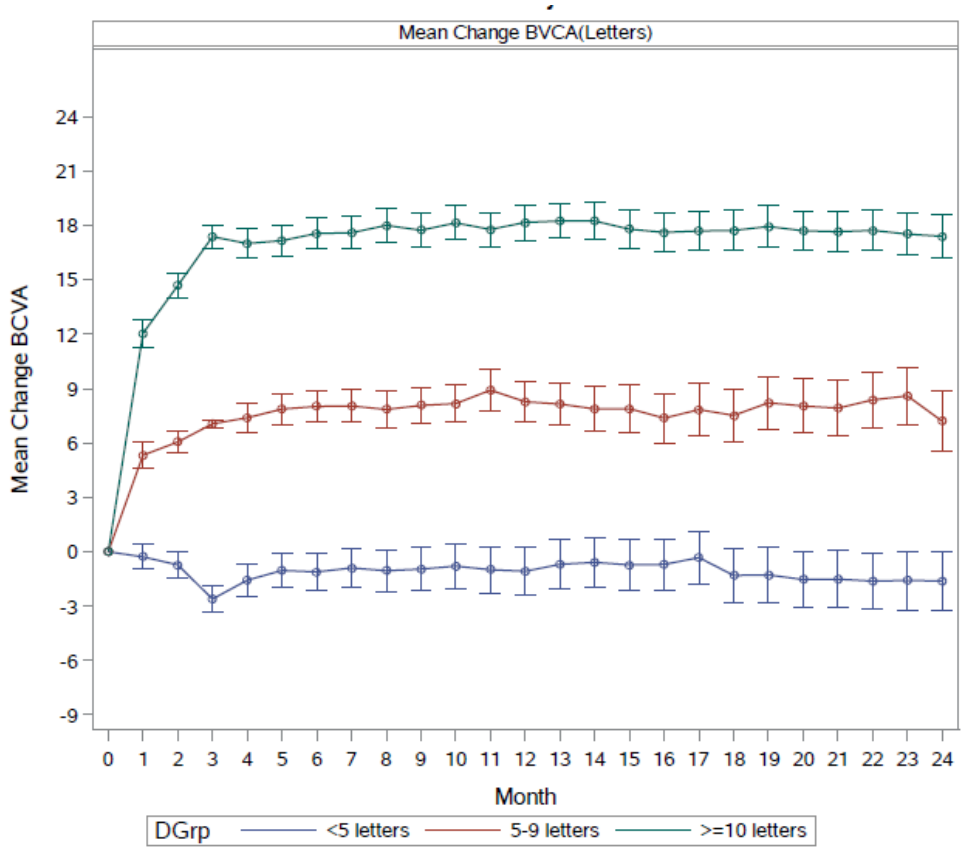
METHODS 1057 nAMD pts treated with RBZ (0.5 mg/2 mg; monthly/as needed [PRN]) in the phase III HARBOR trial (NCT00891735) were pooled and categorized into the following response 'lanes' by best-corrected visual acuity (BCVA) response at M3: improvement by <5 letters, 5-9 letters, and ≥10 letters. Baseline (BL) demographic and ocular characteristics were assessed for the M3 response groups and evaluated for between-lane differences. Mean change in BCVA at M3 and M24, mean BCVA over time by BCVA response at M3, and changes in central foveal thickness (CFT) were evaluated for all RBZ treatment groups pooled. Sensitivity analyses were conducted in the RBZ 0.5 mg monthly and RBZ 0.5 mg PRN groups.

RESULTS At M3, BCVA improved by <5 letters in 376 pts, 5-9 letters in 213 pts, and ≥10

letters in 468 pts. BL characteristics in 2 lanes (<5 letters, 5-9 letters) were similar, while pts with ≥10 letter gain at M3 were younger, with smaller lesion size, worse BCVA, and thicker retinas. Plotting of mean change in BCVA at a population level suggested that M3 vision change was predictive of long-term response, with pts 'swimming in their lanes' through M24 (Fig). However, at the individual patient level, notable movement between lanes was observed (Table). At M24, 38% of pts <5 letters at M3 had changed lanes, with 21% improving to ≥10 letters; 80% of 5-9 letter pts had moved either up or down lanes. Of pts with ≥10 letter gain at M3, 80% remained in lane but 11% declined to <5 letters at M24. In total, 38% pts switched lanes by M24. Irrespective of M3 vision response, CFT decreased dramatically in all pts by M3 and was maintained through M24. Sensitivity analyses produced similar results.

CONCLUSION Population-level data suggest that M3 vision outcomes may predict long-term nAMD outcomes, but patient-level data indicate that M3 vision outcomes are not predictive. Nearly 40% of pts changed BCVA 'lanes' after M3, with most showing improvement. Further biomarkers are needed to predict long-term nAMD outcomes and optimal timing for switching to novel-mechanism treatments when available.

HUMAN RESEARCH Yes: Approved by institutional review board



At population level, patients 'swim in lane' after 3 RBZ injections (M3 response). Data from HARBOR trial. All treatment groups pooled (RBZ 0.5 mg monthly, 0.5 mg PRN, 2 mg monthly, 2 mg PRN). Mean change and 95% confidence intervals.

All treatments Pooled	Change in BCVA at M24			
Change in BCVA at M3	<5 Letters	5-9 Letters	>=10 Letters	Total
<5 Letters	**62%** (n=202)	17% (n=54)	21% (n=69)	n=325
5-9 Letters	35% (n=66)	**20%** (n=37)	45% (n=83)	n=186
>=10 Letters	11% (n=45)	9% (n=38)	**80%** (n=337)	n=420
Total	n=313	n=129	n=489	n=931

BCVA response shows notable movement between response groups from M3 to M24 (numbers in red text). All patients with BCVA score at both M3 and M24 included in analysis. Data from HARBOR trial. All treatment groups pooled (RBZ 0.5 mg monthly, 0.5 mg PRN, 2 mg monthly, 2 mg PRN).

Number of Injections and Time to Dry Analysis of Brolucizumab Versus Aflibercept in Patients With Neovascular AMD: 96-Week Data From HAWK and HARRIER

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- Yit Yang, Dr
- Frank Holz, MD, FEBO
- Eric Souied, Dr
- Pravin U. Dugel, MD
- Jahangir Alam
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OBJECTIVE To compare the number of injections required to achieve sustained dryness over 96 weeks with brolucizumab vs aflibercept in patients with neovascular AMD from the HAWK and HARRIER trials.

PURPOSE Frequent anti-VEGF injections are standard in the treatment of neovascular AMD (nAMD). HAWK & HARRIER, two phase III prospective trials, investigated the efficacy and safety of brolucizumab (Bro) vs aflibercept (Afl) in patients with nAMD. This novel post-hoc analysis reports the number of injections required to achieve sustained retinal dryness over 96 weeks for Bro vs Afl.

METHODS Patients were randomized to Bro 3mg (HAWK only), 6mg, or Afl 2mg. After three loading doses, Bro patients received 12-weekly (q12w) dosing with an option to adjust to 8-weekly (q8w) if disease activity was present; Afl was dosed q8w. Sustained dryness was defined as ≥3 consecutive fluid-free (absence of both intra-retinal fluid and sub-retinal fluid) visits. Time to first sustained dryness and cumulative incidence were evaluated by the Kaplan-Meier method. The number of injections is presented as a weighted mean to account for the variability in the number of days to achieve ≥3 consecutive fluid-

free visits or early discontinuations.

RESULTS Sustained dryness was achieved faster with Bro vs Afl (50th/75th percentiles: Bro 3mg, Week 8/36; Bro 6mg, Week 8/32; vs Afl, Week 12/56 in HAWK; Bro 6mg, Week 4/20; vs Afl, Week 8/52 in HARRIER). At Week 96, a higher proportion of Bro patients achieved sustained dryness vs Afl (cumulative incidence rate [%]: Bro 3mg, 87.9; Bro 6mg, 86.1; vs Afl, 82.0 in HAWK; Bro 6mg, 91.2; vs Afl, 78.8 in HARRIER). Fewer Bro injections were required to achieve the 50th percentile (HAWK [Bro 3mg, 1.97; Bro 6mg, 1.96; Afl, 2.36]; HARRIER [Bro 6mg, 1.00; Afl, 1.96]) and 75th percentile (HAWK [Bro 3mg, 3.29; Bro 6mg, 3.11; Afl, 5.08]; HARRIER [Bro 6mg, 2.42; Afl, 3.78]) for sustained dryness from baseline.

CONCLUSION This analysis shows, compared with Afl, fewer Bro injections were required to achieve sustained dryness over 96 weeks. Sustained dryness was also achieved faster and more frequently in Bro-treated patients. These outcomes suggest that Bro treatment results in better disease control than Afl, thereby potentially reducing the treatment burden in nAMD in the long term.

HUMAN RESEARCH Yes: Approved by institutional review board

Pharmacokinetic Profile of the Port Delivery System With Ranibizumab: From PRN Refills in Phase 2 Ladder to Fixed 24-Week Refills In Phase 3 Archway

- Dilsher S. Dhoot, MD
- Shamika Gune, MD
- Mauricio Maia, PhD
- Katherine Maass

OBJECTIVE To characterize the pharmacokinetic (PK) profile of ranibizumab delivered via the PDS studied in the phase 2 Ladder trial and how it supports the phase 3 Archway trial 24-week refill interval.

PURPOSE The Port Delivery System with ranibizumab (PDS) includes a pars plana implant for continuous delivery of ranibizumab into the vitreous. Ranibizumab release from the implant follows first-order kinetics and is mediated by passive diffusion. This analysis characterizes the PK of ranibizumab in PDS 100 mg/mL patients after the initial fill and subsequent implant refills in the phase 2 Ladder trial.

METHODS In the phase 2, randomized, active treatment-controlled Ladder trial (NCT02510794) in patients with neovascular AMD (N=220), serum PK samples were collected on day 1 at least 60 minutes following implant insertion, at 1, 7, and 14 days after implant insertion, at each monthly study visit, and at 1 and 7 days after each refill. Serum samples were also collected from patients in the monthly intravitreal ranibizumab 0.5 mg arm at randomization, months 1, 3, 6, and 9, and at the final study visit to assess Ctrough levels. Serum ranibizumab concentrations were measured using a validated enzyme-linked immunosorbent assay with a lower limit of quantification of 15 pg/mL.

RESULTS Following implant insertion and before the first refill, the geometric mean (coefficient of variation) of the serum ranibizumab concentrations were 243 (146%), 160

(155%), 101 (137%), 50.8 (108%) pg/mL at months 6, 9, 12, and 16, respectively, in the PDS 100 mg/mL PK-evaluable population (ie, patients who never received ranibizumab injections in study or fellow eye after implant insertion or intravitreal bevacizumab treatment). At 6 months following the first refill but before the second refill, the geometric mean (coefficient of variation) serum ranibizumab concentration was 227 (32.7 %) in the PDS 100 mg/mL arm, consistent with the 6 months following implant insertion. Independent of the timing and number of refills, the median serum ranibizumab concentration at Month 6 was 296 pg/mL in the PDS 100 mg/mL arm compared with 82.9 pg/mL in the monthly intravitreal ranibizumab arm.

CONCLUSION The PDS implant continues to release ranibizumab for an extended period of time and has a consistent concentration-time profile following implantation and multiple refills. These findings suggest that fixed 24-week implant refills in Archway (NCT03677934) maintain drug concentrations in the therapeutic range.

HUMAN RESEARCH Yes: Approved by institutional review board

Fluctuations in Central Foveal Thickness and Vision Outcomes With Anti-VEGF Therapy for Neovascular Age-Related Macular Degeneration

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- Steven Blotner, MS
- Mila Malhotra
- Mitchell R D'Rozario, PhD
- Shamika Gune, MD

OBJECTIVE To describe the relationship between fluctuations in central foveal thickness (CFT) and vision outcomes in the HARBOR trial of ranibizumab for neovascular age-related macular degeneration (nAMD).

PURPOSE While the goal of treatment for nAMD has been to stabilize disease activity, the relationship between anatomic stability and vision outcomes is currently unclear. This post hoc analysis of HARBOR (NCT00891735) compared fluctuations in CFT between patients who received monthly or as-needed (PRN) ranibizumab for nAMD, and investigated its association with visual responses to treatment.

METHODS In HARBOR, treatment-naïve patients with nAMD were randomized to monthly or PRN ranibizumab (0.5 mg or 2.0 mg) for 24 months. Post hoc analyses included patients with ≥ 16 evaluable OCT images from month 3 onwards (after 3 monthly loading doses), and vision data at baseline and month 24. After month 3, CFT data were grouped into 3-month intervals through month 24, and “bounces” were counted for every ≥ 50-µm difference between the minimum and maximum CFT value within an interval, and between 2 consecutive intervals. Associations between bounces in CFT and vision outcomes at month 24 were compared between patients randomized to monthly versus PRN ranibizumab (0.5 mg and 2.0 mg arms pooled).

RESULTS Analyses included 849 patients randomized to monthly (n = 427) or PRN (n = 422) ranibizumab. By design, patients who received PRN injections experienced more bounces in CFT from months 3 through 24 than those treated monthly (Figure 1; mean [95% CI], 8.5 [8.0, 9.0] vs 3.4 [2.9, 3.9]). After adjusting for differences in baseline best-

corrected visual acuity (BCVA), mean (95% CI) vision gains from baseline at month 24 were similar between monthly- and PRN-treated patients with 0–3 bounces in CFT (+10.4 [8.6, 12.2] letters vs +10.3 [7.7, 12.9] letters). In patients with 4–21 bounces in CFT from months 3 through 24, adjusted mean (95% CI) BCVA gains in those who received monthly or PRN treatment decreased to +9.5 (7.1, 12.0) letters and +7.4 (5.7, 9.1) letters, respectively. When patients were stratified by bounce quartile, adjusted mean vision gains from baseline were smallest among the monthly and PRN subgroups with 11–21 bounces in CFT through month 24 (Figure 2).

CONCLUSION This post hoc analysis demonstrated a trend for numerically smaller vision gains among patients who exhibited greater fluctuations in CFT during the HARBOR trial. Further studies should assess whether early bounces in CFT may predict longer-term treatment responses, and may be used to optimize injection intervals and vision outcomes.

HUMAN RESEARCH Yes: Approved by institutional review board

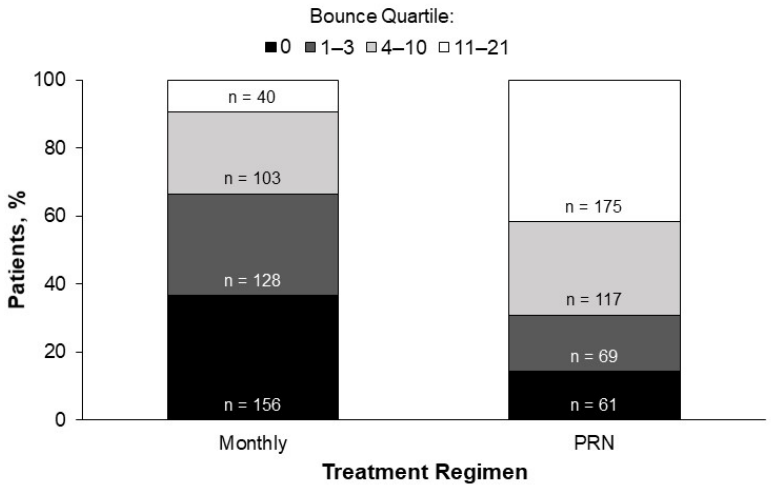


Figure 1. Distribution of patients across central foveal thickness (CFT) bounce quartiles, stratified by ranibizumab treatment regimen in HARBOR. Fluctuations in CFT were measured according to ≥ 50-µm "bounces" counted from months 3 through 24. PRN, as-needed.

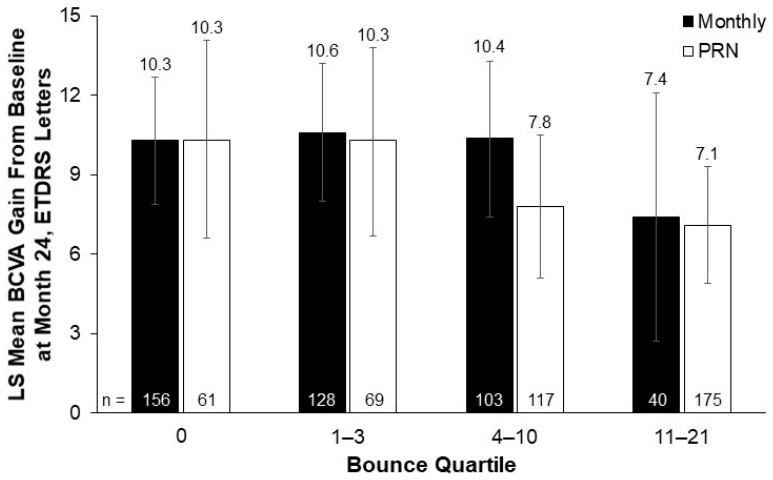


Figure 2. Adjusted mean vision gains with monthly or as-needed (PRN) ranibizumab treatment in HARBOR, stratified by central foveal thickness (CFT) bounce quartile. Fluctuations in CFT were measured according to ≥ 50-µm "bounces" counted from months 3 through 24; error bars represent 95% CI. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LS, least squares.

Anti-VEGF Resistant Subretinal Fluid Associated With Reduced Risk of Macular Atrophy and Better Vision: Drug-Induced Choroidal New Vessel Homeostasis?

- Marco A. Zarbin, MD, PhD
- Ivaylo Stoilov, MD
- Lauren Hill, BA, MS

OBJECTIVE To examine the relationship between subretinal fluid thickness, vision outcomes and development of macular atrophy in eyes with neovascular age-related macular degeneration treated with ranibizumab.

PURPOSE To evaluate the relationship between subretinal fluid (SRF) thickness, vision outcomes, and the development of macular atrophy (MA) in eyes with neovascular age-related macular degeneration (nAMD) treated with ranibizumab in the HARBOR clinical trial.

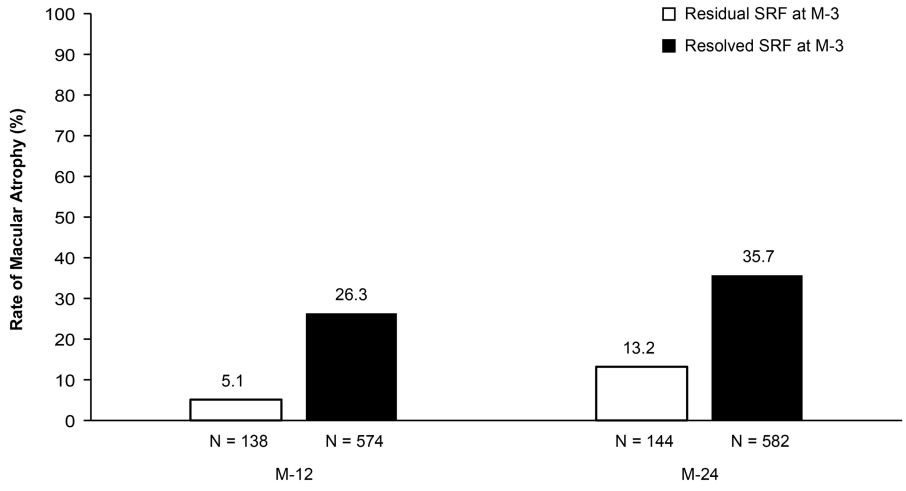
METHODS HARBOR (NCT00891735) was a phase 3, randomized trial of ranibizumab (0.5 mg and 2 mg PRN or monthly) in eyes with nAMD. Presence and thickness of SRF was determined by SD-OCT. Eyes were grouped according to SRF thickness: 0 µm, >0-50 µm, >50-100 µm, or >100 µm. Best corrected visual acuity (BCVA) was assessed using standard Early Treatment Diabetic Retinopathy Study (ETDRS) protocols. Presence of MA was determined from fluorescein angiograms and color fundus photographs by masked graders. All treatment arms were pooled, and the analysis limited to eyes with SRF at baseline (defined as screening, baseline, or week 1; n=785).

RESULTS At month(M)-12, ranibizumab-treated eyes with residual SRF had greater mean ETDRS BCVA compared to eyes with no SRF regardless of the SRF thickness: no SRF, 63.6 letters; >0-50 µm SRF, 71.2 letters; >50-100 µm SRF, 71.3 letters; >100 µm SRF, 69.2 letters. Mean BCVA values were similar at M-24. In eyes with no MA at baseline, the

presence of residual SRF at M-3 was associated with significantly lower rates of MA at M-12 and M-24 compared with eyes with resolved SRF at M-3. Specifically, the MA rate with residual vs resolved SRF at M-3 was 5.1% vs 26.3%, respectively, at M-12; and 13.2% vs 35.7%, respectively, at M-24. Similarly, in eyes with no MA at baseline, the presence of residual SRF at M-6 was also associated with significantly lower rates of MA at M-12 and M-24 compared with eyes with resolved SRF at M-6.

CONCLUSION In this analysis, SRF was not detrimental to vision outcomes over two years. In addition, rates of MA were significantly higher in the absence of SRF. We posit that persistent SRF during anti-VEGF treatment may be a sign of persistent choroidal new vessel perfusion with transudation, which may operate as an imperfect compensatory mechanism to maintain function in the degenerating macula.

HUMAN RESEARCH Yes: Approved by institutional review board



In the HARBOR trial, residual subretinal fluid during treatment of nAMD with ranibizumab is associated with a lower rate of developing macular atrophy compared with patient who did not have residual subretinal fluid.

Intravitreal Gene Therapy for Neovascular AMD With ADVM-022: Results of the Phase 1 OPTIC Trial

- Charles C. Wykoff, MD, PhD

OBJECTIVE To assess the safety and biological activity of a novel intravitreal anti-VEGF gene therapy in neovascular AMD.

PURPOSE A single-injection intravitreal gene therapy that durably expresses an intraocular anti-vascular endothelial growth factor (VEGF) agent could reduce repeated anti-VEGF injections and improve outcomes in neovascular AMD (nAMD). OPTIC is an ongoing phase 1 study assessing the safety, tolerability and efficacy of a single intravitreal injection of ADVM-022 in treatment-experienced patients with nAMD.

METHODS Multicenter, open-label, multiple cohort, dose-ranging study in patients with nAMD who have demonstrated a response to anti-VEGF therapy. Patients were administered an intravitreal injection of ADVM-022 at 6x10^11 vg/eye for cohort 1 (n=6) and at 2x10^11 vg/eye for cohort 2 (n=6). Incidence and severity of adverse events, change in best corrected visual acuity (BCVA), change in central subfield thickness (CST) and number of aflibercept rescue injections were evaluated.

RESULTS Patients in cohort 1 previously received frequent anti-VEGF injections (mean 6.2 injections in the preceeding 8 months) and had relatively good baseline BCVA (mean 65.8 ETDRS letters) with a mean baseline CST of 369.2µm prior to enrollment in OPTIC. Through week 24, there were no serious adverse events, no dose limiting toxicities and no non-ocular adverse events related to ADVM-022. Ocular inflammation was seen in all patients, occurred most frequently in the anterior segment, and was generally mild and manageable with topical steroids. BCVA was maintained with a mean change of -2.0 ETDRS letters (90% CI -9.1, 5.1). CST improved with a mean change of -52.7µm (90% CI -86.5, -18.8) and signs of CNV disease activity on OCT improved or stabilized in all patients. No rescue injections were given to any subject. Up to date data from the ongoing, open-label

OPTIC study will be presented including complete 52 week data from Cohort 1.

CONCLUSION ADVM-022 is designed to provide sustained therapeutic levels of aflibercept following a single intravitreal injection. Patients in cohort 1 of OPTIC treated with a single injection of ADVM-022 were able to maintain vision and improve anatomical outcomes without receiving any rescue aflibercept injections through week 24. Complete 52 week Cohort 1 data will be presented.

HUMAN RESEARCH Yes: Approved by institutional review board

OPTIC Phase 1 Baseline Demographics from Cohort 1 (n=6)

Baseline Characteristics:	**Value**
Dose of intravitreal injection ADVM-022, vg/eye	6x10^11
Mean age, years	79
Mean number of years since diagnosis, years	3.3
Mean number of prior anti-VEGF injections, n (range)	35.3 (7-109)
Mean number of anti-VEGF injections in 8 months prior to screening, n	6.2
Average annualized anti-VEGF injection frequency, n	9.3
Mean BCVA study eye, ETDRS letters Approximate Snellen equivalent	65.8 20/50
Mean CST study eye, µm	369

Ladder Phase 2 Trial of the Port Delivery System With Ranibizumab (PDS) End of Study Results

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- Steven Blotner, MS
- Natasha Singh, Pharm D
- Giulio Barteselli, Dr
- Shamika Gune, MD

OBJECTIVE To report the end of study results for the Ladder trial of the Port Delivery System with ranibizumab (PDS) for neovascular age-related macular degeneration (nAMD).

PURPOSE The Port Delivery System with ranibizumab (PDS) is an investigational drug delivery system designed for the continuous intravitreal release of ranibizumab through a permanent indwelling intraocular implant; the safety and efficacy of the PDS for the treatment of neovascular age-related macular degeneration (nAMD) were evaluated in the phase 2 Ladder trial.

METHODS The Ladder phase 2 trial (NCT02510794) compared the PDS with 3 different customized ranibizumab formulations with monthly intravitreal ranibizumab 0.5 mg. Patients with nAMD had a documented response to intravitreal anti-vascular endothelial growth factor treatment. The primary endpoint was time to first implant refill according to protocol-defined criteria assessed when the last enrolled patient completed the month (M) 9 visit. Secondary outcomes included mean change from baseline in best-corrected visual acuity (BCVA) and central foveal thickness (CFT). All patients continued on assigned study treatment until they were eligible to roll over into the Portal extension study (NCT03683251).

RESULTS Ladder evaluated 220 patients, with 58, 62, 59, and 41 patients in the PDS 10, 40, and 100 mg/mL and monthly intravitreal ranibizumab 0.5 mg arms, respectively. The mean time on study was 22.1M (range, 10.8M–37.6M) for all PDS patients. The median time to first required refill was 15.8M for the PDS 100 mg/mL arm. In PDS 100 mg/mL patients who met implant refill criteria at least once, the median time to first and second refills was consistent: first refill, 8.8M (n=31/59); second refill, 8.8M (n=19/31). At M22 in

the PDS 100 mg/mL and monthly ranibizumab 0.5 mg arms, respectively, the mean BCVA change from baseline was +2.9 and +2.7 letters. Mean CFT change from baseline excluding pigment epithelial detachment height was generally similar between the PDS 100 mg/mL and monthly ranibizumab 0.5 mg arms. No dose-related serious AEs were observed.

CONCLUSION Ladder end of study efficacy and safety outcomes were consistent with the primary analysis. PDS 100 mg/mL continuously maintained vision and anatomic outcomes through a mean time on study of 22M. The optimized implant insertion procedure and refill procedure were generally well tolerated. The PDS has potential to reduce high intravitreal treatment burden and improve real-world clinical outcomes.

HUMAN RESEARCH Yes: Approved by institutional review board