10/11/2021 8:00AM

Assessment of Central Subfield Thickness Fluctuations and Impact on Vision in Archway Phase 3 Trial of the Port Delivery System With Ranibizumab (PDS)

- Chirag D. Jhaveri, MD, FASRS
- Steven Blotner
- Shamika Gune, MD

OBJECTIVE To characterize central subfield thickness (CST) fluctuations and their potential impact on vision outcomes in the Archway trial of the Port Delivery System with ranibizumab (PDS)

PURPOSE The PDS is an investigational drug delivery system for the continuous intravitreal delivery of ranibizumab (RBZ) that was evaluated for the treatment of neovascular age-related macular degeneration (nAMD) in the Archway phase 3 trial. In anti-VEGF–treated patients (pts) with nAMD, understanding the impact of retinal thickness fluctuations on vision outcomes is of great interest.

METHODS Archway (NCT03677934) compared PDS with RBZ 100 mg/mL with fixed 24-week refill-exchanges (PDS Q24W) vs intravitreal RBZ 0.5 mg every 4 weeks (monthly RBZ) in nAMD. Post hoc analyses included pts with ≥7 study visits with evaluable OCT images over 40 weeks and BCVA data at baseline and week 40. CST was measured from internal limiting membrane to Bruch's membrane. A fluctuation was defined as a change in CST ≥50 µm in either direction. Fluctuation score was determined using the cumulative changes in µm of CST measurements over 40 weeks; changes <50 µm were considered clinically insignificant and not included. Associations between CST fluctuations and vision outcomes at week 40 were analyzed.

RESULTS Analyses included 243 PDS Q24W and 163 monthly RBZ pts. Through week 40, 78.2% and 79.1% of pts in the PDS Q24W and monthly RBZ arms, respectively, did not

experience any CST fluctuations ≥50 µm. In pts who experienced CST fluctuations ≥50 µm, the mean number of fluctuations through week 40 was 1.8 in the PDS Q24W arm and 2.3 in the monthly RBZ arm; the cumulative mean CST change in µm through week 40 was 181.2 µm and 232.7 µm in the PDS Q24W and monthly RBZ arms, respectively. Mean (95% CI) BCVA change from baseline at week 40 in PDS Q24W vs monthly RBZ pts, respectively, was −1.6 (−3.6, 0.3) vs −1.0 (−3.4, 1.4) letters in pts who experienced CST fluctuations ≥50 µm through week 40 and +1.1 (0.0, 2.1) vs +1.0 (−0.2, 2.3) letters in pts who did not experience any CST fluctuations ≥50 µm through week 40.

CONCLUSION In Archway, nearly 80% of pts did not experience any clinically significant CST fluctuations ≥50 µm through week 40, and vision outcomes at week 40 were comparable in pts with or without fluctuations in both treatment arms. Overall, continuous delivery of RBZ with PDS Q24W resulted in stable retinal thickness in the vast majority of pts, and robust vision, regardless of fluctuation status.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/11/2021 8:06AM

Analysis of Retinal Fluid and Vision Outcomes in the Archway Phase 3 Trial of the Port Delivery System With Ranibizumab (PDS) in Patients With nAMD

- Arshad M. Khanani, MD, MA, FASRS
- Steven Blotner
- Shamika Gune, MD
- Merce Morral, MD PhD

OBJECTIVE To describe the relationship between retinal fluid and vision outcomes in the Archway trial of the Port Delivery System with ranibizumab (PDS) in neovascular age-related macular degeneration (nAMD).

PURPOSE The PDS is an investigational drug delivery system for the continuous delivery of ranibizumab (RBZ) into the vitreous, evaluated for the treatment of nAMD in the phase 3 Archway trial. This analysis aims to determine the incidence of subretinal fluid (SRF) and/or intraretinal fluid (IRF) from baseline to week 40 in Archway and assess vision outcomes based on presence, type, and location of fluid.

METHODS Archway (NCT03677934) is a visual assessor–masked trial comparing PDS with ranibizumab 100 mg/mL with fixed 24-week refill-exchanges (PDS Q24W) with intravitreal RBZ 0.5 mg every 4 weeks (monthly RBZ) in the treatment of nAMD, with patients randomized 3:2, respectively. This post hoc analysis comprised patients from Archway with SRF/IRF presence/absence data at baseline. Presence of retinal fluid was assessed using OCT at each monthly visit, independently graded for SRF or IRF. Analysis outcomes included proportion of patients with either SRF or IRF (and SRF and/or IRF in the center 1 mm) and best-corrected visual acuity (BCVA) in study eyes in the presence/absence of SRF/IRF up to week 40.

RESULTS Percentage of patients with either SRF or IRF was similar between the PDS Q24W and monthly RBZ treatment arms at baseline (47.6% [118/248] vs 50.9% [85/167]) and week 40 (50.6% [120/237] vs 48.4% [77/159]). Vision outcomes were comparable

between treatment arms, regardless of presence/absence of any retinal fluid, including presence/absence of SRF in the center 1 mm (SRF 1 mm); mean (95% CI) BCVA change (ETDRS letters) from baseline at week 40 with PDS Q24W vs monthly RBZ: absence of SRF 1 mm, +0.9 (−0.1, 1.9; n = 182) vs +0.6 (−0.6, 1.8; n = 137); presence of SRF 1 mm, +0.2 (−1.6, 2.0; n = 51) vs +1.0 (−1.7, 3.8; n = 21). BCVA vision outcomes were also comparable between the PDS Q24W and monthly RBZ arms in the absence of IRF in the center 1 mm (IRF 1 mm): +0.8 (−0.1, 1.7; n = 216) vs +1.0 (−0.0, 2.0; n = 147), but appeared to be slightly reduced in the monthly RBZ arm in the presence of IRF 1 mm: PDS Q24W, +0.1 (−3.6, 3.8; n = 17); monthly RBZ, −3.5 (−11.8, 4.7; n = 11).

CONCLUSION In Archway, incidence of retinal fluid was generally similar in the PDS Q24W and monthly RBZ treatment arms and remained consistent over time. Vision outcomes were generally comparable in both treatment arms. Continuous delivery of RBZ with PDS Q24W maintained vision outcomes, regardless of the presence or absence of retinal fluid.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/11/2021 8:10AM

Faricimab in Neovascular Age-Related Macular Degeneration: Week 48 Efficacy, Safety, and Durability Results From the Phase 3 TENAYA and LUCERNE Trials

- Karl G. Csaky, MD, PhD
- Carlos Quezada-Ruiz, MD
- Jane Ives, MSc
- Karen Basu, PhD
- David Silverman, MSc, MBChB

OBJECTIVE To assess efficacy, safety, and durability of faricimab, a dual angiopoietin (Ang)-2 and VEGF-A inhibitor, in patients with neovascular age-related macular degeneration (nAMD).

PURPOSE Dual Ang-2 and VEGF-A inhibition with faricimab, a bispecific antibody designed for intraocular use, may promote vascular stability, resulting in improved durability and long-term outcomes beyond anti-VEGF monotherapy for nAMD. The phase 3 TENAYA and LUCERNE trials were designed to assess efficacy, safety, and durability of faricimab up to Q16W compared with aflibercept Q8W in patients with nAMD.

METHODS TENAYA (NCT03823287) and LUCERNE (NCT03823300) are randomized, active comparator–controlled, 112-week, global, phase 3, noninferiority trials of faricimab in nAMD. Patients were randomized 1:1 to faricimab 6.0 mg up to Q16W (based on protocol-defined disease activity assessments at weeks 20 and 24) or aflibercept 2.0 mg Q8W. The primary endpoint was mean change in BCVA from baseline averaged over weeks 40, 44, and 48. Other endpoints included the proportion of patients receiving faricimab Q16W, Q12W, and Q8W; the proportion of patients gaining or avoiding a loss of ≥ 15 ETDRS letters from baseline; change in CST from baseline; and the incidence and severity of adverse events.

RESULTS In total, 1329 patients with nAMD were enrolled in TENAYA (N = 671) and LUCERNE (N = 658). Baseline characteristics were generally well balanced across treatment arms. Both trials met their primary endpoint of noninferiority in mean change in BCVA from baseline averaged over weeks 40, 44, and 48 with faricimab up to Q16W (+5.8 and +6.6 ETDRS letters in TENAYA and LUCERNE, respectively) compared with aflibercept Q8W (+5.1 and +6.6 ETDRS letters). 79.7% and 77.8% of patients in TENAYA and LUCERNE, respectively, were on ≥ Q12W dosing intervals at week 48, with 45.7% and 44.9% of patients on a Q16W dosing interval. Reductions in CST from baseline averaged over weeks 40, 44, and 48 with faricimab up to Q16W (−136.8 and −137.1 µm in TENAYA and LUCERNE, respectively) were comparable to aflibercept Q8W (−129.4 and −130.8 µm). In both trials, faricimab was well tolerated; intraocular inflammation event rates were low and no cases of vasculitis or occlusive retinitis have been reported.

CONCLUSION Faricimab administered at up to Q16W demonstrated non-inferior vision

gains to aflibercept Q8W in patients with nAMD, with ~80% of patients on ≥ Q12W and ~45% on Q16W fixed dosing intervals at week 48. Reductions in CST were meaningful and faricimab was well tolerated. Results at week 48 were consistent across both the TENAYA and LUCERNE trials.

IRB APPROVAL Yes — *IRB Approval Letter may be requested.*

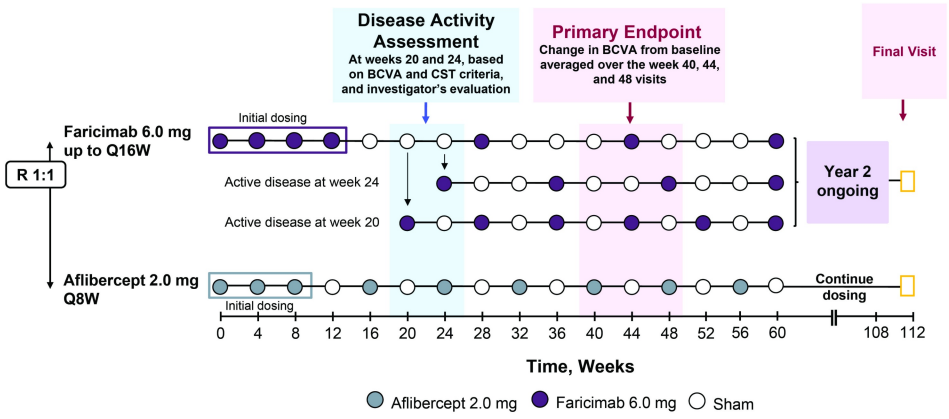


Figure 1. TENAYA and LUCERNE trial design. BCVA, best-corrected visual acuity; CST, central subfield thickness; Q8W, every 8 weeks; Q16W, every 16 weeks; R, randomization.

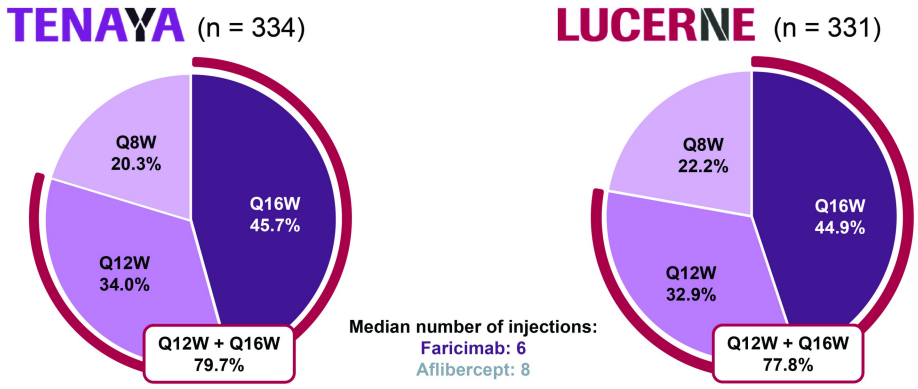


Figure 2. Proportion of patients in the faricimab arm receiving Q8W, Q12W, or Q16W dosing at week 48 of TENAYA (left) and LUCERNE (right). Analyses included patients completing week 48 study visit (ITT population). ITT, intent-to-treat; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.

10/11/2021 8:16AM

Prospective Longitudinal Study: Fluid Quantification From Daily Self-imaging With Home OCT in Neovascular Age-Related Macular Degeneration (NV-AMD)

- Jeffrey S. Heier, MD
- Nancy M. Holekamp, MD

OBJECTIVE To evaluate the performance of a self-operated home OCT system quantifying retinal fluid in patients with NV-AMD

PURPOSE To evaluate the longitudinal performance of the Home OCT System comprising an SD-OCT device for self-imaging at home, telemedicine infrastructure for automated data upload, and deep learning algorithm (NOA) for fluid quantification. The aims were to study the system's performance in daily image acquisition and automated analysis and to characterize the dynamics of retinal fluid exudation in NV-AMD

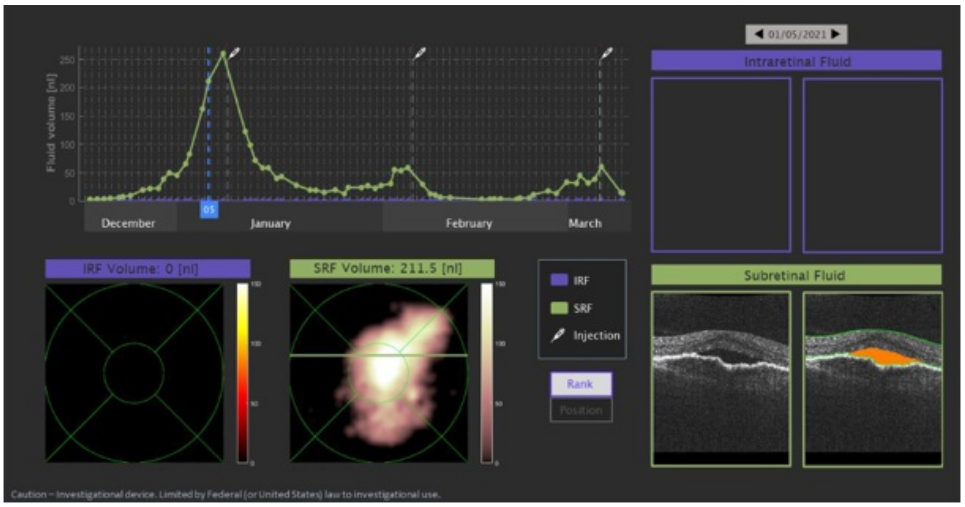
METHODS Prospective observational longitudinal study for 3 months of 15 NV-AMD patients under anti-VEGF therapy in routine clinical practice. Fellow AMD eyes were also monitored. At the time of abstract submission, 10/15 subjects enrolled and will complete enrollment and follow-up by the time of ASRS. Participants performed daily self-imaging at home. Scans were automatically uploaded to the Cloud. Images underwent evaluation separately by the NOA, human expert graders, and the investigators (NH, JH). Main outcome measures included daily self-imaging completion; acquisition time; image quality; agreement between automated and human grading of retinal fluid; temporal dynamics of fluid volume

RESULTS 8 patients, mean age 74, 62.5% females, VA range 20/20 to 20/125, self-imaged 15 eyes, 11 diagnosed with NV-AMD and 4 with dry-AMD. The subjects were enrolled for a median of 73.5 days, self-imaged on average in 49 of these days (82%), and on some days more than once, for a total of 810 self-images. Of these, 93% had satisfactory quality. The

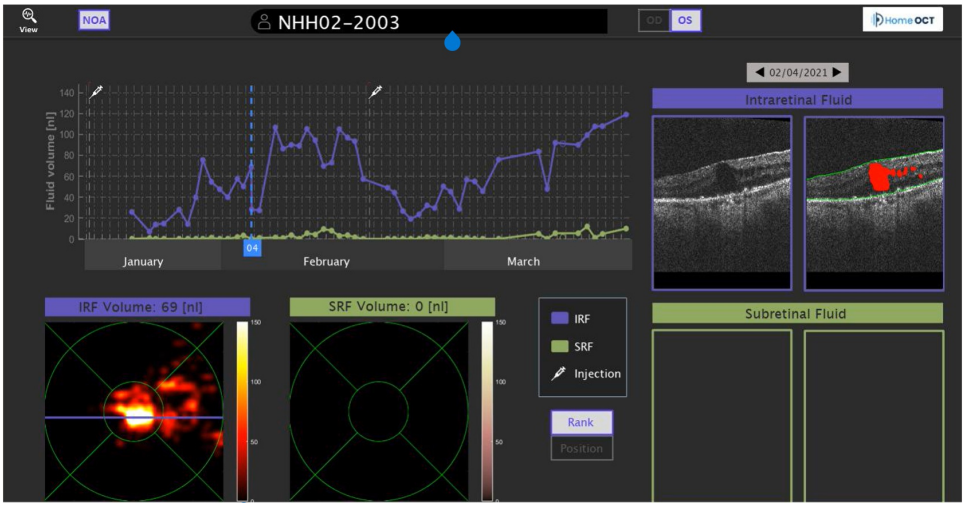
median (IQR) self-image duration was 49 (19.4) seconds. For any fluid presence, the NOA agreed with human grading in 94% of cases, 99% for IRF and 91% for SRF. Cases of fluid falsely identified by NOA were limited on average to very small volume of less than 1 nL of any fluid type. Graphical trajectories of fluid volume over the study period revealed wide variation in the dynamics of fluid exudation in terms of volume, type, retinal location, and treatment response. Examples shown in Figures 1 & 2.

CONCLUSION The analysis suggests that daily self-imaging generated images of satisfactory quality for human grading and automated analysis of fluid volume over time permitting a novel paradigm of monitoring. Home OCT may allow personalized retreatment decisions with fewer clinic visits especially in conjunction with longer acting drugs and sustained release systems. Completed study results will be presented.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.



Fluid volume trajectory (ID NHH01-1001), VA: 20/40, age 76 y/o, 81 days in study. Observed fast increase in centrally located SRF with fast treatment response however incomplete fluid resolution. Second injection resulted in complete resolution, with recurrence 2 weeks later to a similar volume and repeat resolution after another injection.



Fluid volume trajectory (ID NHH02-2003), VA: 20/20, age 75 y/o age, 60 days in study. Gradual increase of IRF with incomplete

resolution following an injection, and recurring increase in centrally located prominent IRF.

10/11/2021 8:32AM

Subretinal Delivery of RGX-314 for Neovascular AMD: End of Study Phase I/IIa Results

- Lejla Vajzovic, MD, FASRS

OBJECTIVE To evaluate the final safety and efficacy data for RGX-314 in patients previously treated with intravitreal anti-VEGF for neovascular AMD through two years, and additional long-term follow up data.

PURPOSE Frequent anti-VEGF injections have been shown to reduce the risk of blindness in clinical trials. Real world evidence shows patients lose visual acuity over time due to a high treatment burden of current anti-VEGF injections. RGX-314 is designed as a single gene therapy intervention utilizing an AAV8 vector to deliver a transgene for a soluble anti-VEGF fab to produce continuous anti-VEGF therapy.

METHODS This Phase I/IIa trial is evaluating five doses of RGX-314 administered via transvitreal subretinal delivery. Assessments of safety and efficacy are being conducted out to 2 years, and measurements include: ocular and systemic adverse events, RGX-314 aqueous protein level, vision, central retinal thickness, and additional anti-VEGF injections needed post-RGX-314. Patients are then encouraged to enroll in a Long-Term Follow-Up (LTFU) study to assess safety and efficacy for up to a total of five years after RGX-314 administration. In the LTFU study, visits are scheduled every 6 months for the first year and then annually until end of study, and patient management is per physician discretion.

RESULTS Cohorts 1 - 5 have completed enrollment (n=42). As of January 22, 2021, RGX-314 has been generally well-tolerated with 20 serious adverse events (SAEs) reported in 13 patients, including one possibly drug-related SAE of significant decrease in vision in Cohort 5. A durable treatment effect was observed with stable visual acuity, decreased retinal thickness, and reductions in anti-VEGF injection burden in patients in Cohorts 4 and 5 at 1.5 years post RGX-314 administration. A long-term treatment effect over 3 years was

demonstrated in the LTFU study for Cohort 3 with a mean improvement in vision (+12 letters) and stable retinal thickness. This cohort saw a reduction of 66.7% from the mean annualized injection rate during the 12 months prior to administration of RGX-314, and 50% of patients (3/6) remain anti-VEGF injection-free over three years. Updated data will be presented.

CONCLUSION In the 42 subjects with nAMD, subretinal administration of RGX-314 has been generally well-tolerated and initial results out to three years show potential for a one-time administration of RGX-314 to provide sustained clinical outcomes with improved visual acuities, decreased retinal thickness and reduced treatment burden in the treatment of nAMD.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/11/2021 8:38AM

Suprachoroidal Delivery of RGX-314 for Neovascular AMD: Initial Results From the Phase II AAVIATE Study

- Mark R. Barakat, MD

OBJECTIVE To evaluate the safety, tolerability, and efficacy of RGX-314 by suprachoroidal delivery in patients previously treated with intravitreal anti-VEGF injection for neovascular AMD (nAMD).

PURPOSE Optimal treatment of nAMD requires frequent anti-VEGF injections. RGX-314, a single gene therapy utilizing an AAV8 vector to deliver a soluble anti-VEGF fab transgene, has shown sustained anti-VEGF levels with subretinal delivery in an ongoing Phase I/IIa trial. Preclinical studies suggest that suprachoroidal RGX-314 may also lead to meaningful anti-VEGF production.

METHODS AAVIATE is a Phase II trial that will evaluate the efficacy, safety, and tolerability of suprachoroidal delivery of RGX-314 at two doses (2.5x1011GC/eye and 5x1011GC/eye) using the SCS Microinjector, an in-office route of administration. The trial will enroll 40 patients with severe wet AMD, and patients are randomized to receive RGX-314 or monthly 0.5 mg ranibizumab intravitreal injections at a 3:1 ratio. Safety and efficacy assessments are being conducted with the Primary Endpoint at Week 40 and followed through Week 52. Measurements include: adverse events, best corrected visual acuity (BCVA), central retinal thickness (CRT), and additional anti-VEGF injections needed post-RGX-314.

RESULTS Cohort 1 has completed enrollment (n=20) and cohort 2 is enrolling. As of December 31, 2020, suprachoroidal delivery of RGX-314 is reported to be generally well-tolerated. Updated safety and efficacy data will be presented, and a thermal imaging video from the AAVIATE trial will be presented to demonstrate drug delivery by this route of administration.

CONCLUSION RGX-314 has the potential to provide sustained clinical outcomes in the treatment of nAMD with a one-time treatment administered in-office. This treatment may deliver advantages over conventional treatments that require life-long intraocular injections, typically repeated every four to 12 weeks in frequency, to maintain efficacy.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/11/2021 8:42AM

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

- Dante Joseph Pieramici, MD
- David S. Boyer, MD
- Arshad M. Khanani, MD, MA, FASRS
- Charles C Wykoff, MD, PhD, FASRS
- Brandon G. Busbee, MD
- Carl D. Regillo, MD
- Carl J Danzig, MD
- Brian C. Joondeph, MD, MPS, FACS
- James C. Major, MD, PhD FACS FASRS
- Szilárd Kiss, MD
- Carol Hoang, PharmD, MBA
- Adam Turpcu, PhD
- Carol Chung, PhD
- Aaron Osborne, MBBS, MRCOphth

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

PURPOSE A single-injection intravitreal gene therapy that durably expresses intraocular anti-vascular endothelial growth factor (VEGF) could reduce the need for repeated anti-VEGF injections and improve outcomes in nAMD. OPTIC is an ongoing phase 1 study assessing the safety, tolerability and efficacy of aflibercept-expressing ADVM-022 through 104 weeks in treatment-experienced patients with nAMD.

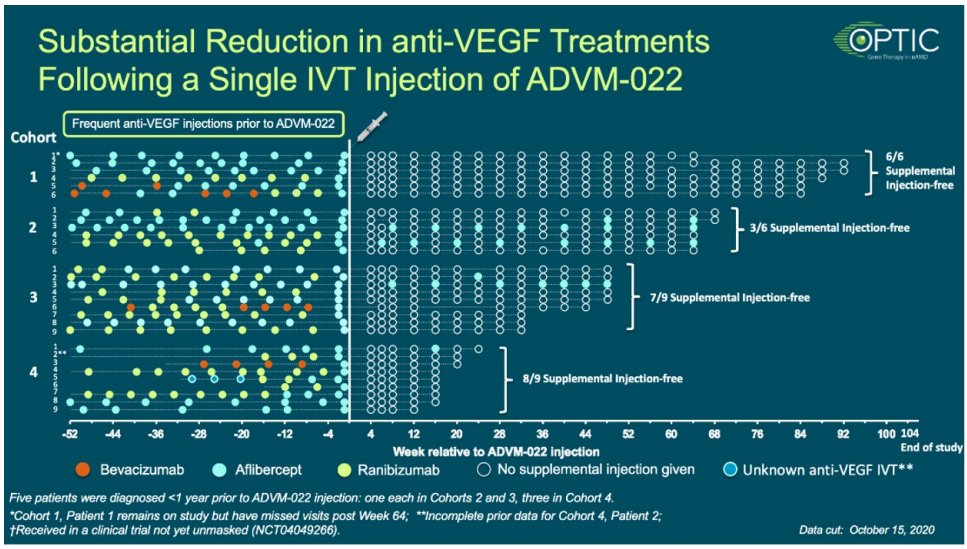
METHODS Multicenter, open-label, multiple cohort, dose-ranging study in patients with nAMD who have demonstrated a response to anti-VEGF therapy. Patients were administered a single intravitreal injection of ADVM-022 at 6x10^11 vg/eye for cohorts 1 (n=6) and 4 (n=9) and at 2x10^11 vg/eye for cohorts 2(n=6) and 3 (n=9). 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 As of October 15 2020, median follow-up was 86 weeks (C1), 64 weeks (C2), 48

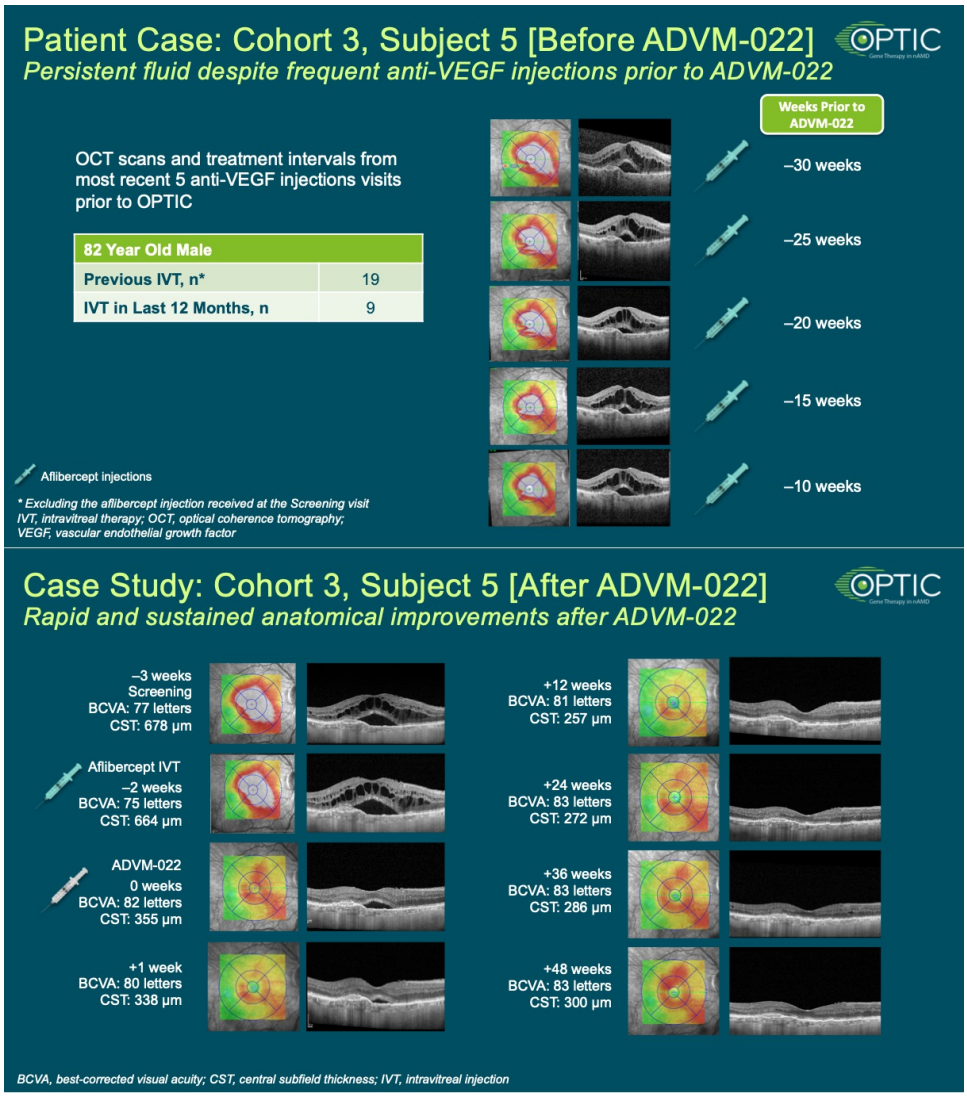
weeks (C3) and 16 weeks (C4). All patients received frequent anti-VEGF injections12 months prior to receiving ADVM-022 (mean 7.1–9.2 injections) with relatively good baseline BCVA (mean 65.0–65.9 ETDRS letters). ADVM-022 continues to be well tolerated with a favorable safety profile. All ADVM-022-related ocular adverse events were mild (78%) to moderate (22%). When observed, ocular inflammation predominantly affecting the anterior segment was responsive to steroid eye drops. No cases of retinal involvement or vasculitis were reported. 14/15 patients receiving high dose and 10/15 patients receiving low dose remained supplemental anti-VEGF injection free; mean annualized anti-VEGF injection frequency was reduced by 99% (high dose) and 85% (low dose) after ADVM-022. For C1–3, BCVA was maintained with a mean change of -2.5 to +0.2 ETDRS letters, and CST improved with a mean change of -19.7 to -132.7 µm.

CONCLUSION ADVM-022 is designed to provide continuous stable expression of aflibercept following a single intravitreal injection. Over 80% of patients with nAMD treated with a single injection of ADVM-022 in OPTIC have not needed any supplemental anti-VEGF injections up to 92 weeks follow-up. ADVM-022 has the potential to reduce treatment burden and improve long term patient vision outcomes.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.



Swimmer Plot of Supplemental Anti-VEGF injections administered in Cohorts 1-4.



Patient Case: Prior to ADVM-022, patient required frequent anti-VEGF injections to maintain vision, OCT scans show persistent fluid despite anti-VEGF treatment. After a single intravitreal injection of ADVM-022 low dose 2x10^11 vg/eye, rapid and sustained anatomical improvements.

10/11/2021 8:56AM

Maximum Consecutive Fluid Free Months and Its Association With Visual and Anatomical Outcomes in nAMD: A Post-Hoc Analysis From HAWK and HARRIER

- David A. Eichenbaum, MD, FASRS
- David M. Brown, MD
- Arshad M. Khanani, MD, MA, FASRS
- Marta Figueroa, MD, PhD
- Ian McAllister, MBBS, FRANZCO
- Augustinus Laude, MBChB, MSc, FRCSEd (Ophth), FAMS (Ophth)
- Guru Prasad
- Shuhan Tang
- Benjamin Gmeiner
- Andreas Clemens
- Eric Souied, Dr

OBJECTIVE To assess the effect of maximal consecutive retinal fluid-free months on the visual and anatomic outcomes of neovascular age-related macular degeneration (nAMD) patients in the HAWK and HARRIER trials

PURPOSE Retinal fluid is an important biomarker of disease activity in nAMD. Resolving retinal fluid and maintaining a dry retina is a common clinical goal of anti-vascular endothelial growth factor (VEGF) therapy. Here we assess the impact of absolute retinal fluid-free duration and its association with visual and anatomic outcomes of patients in HAWK and HARRIER.

METHODS 96-week data from the brolucizumab 6 mg and aflibercept 2 mg groups of the Phase III HAWK and HARRIER studies were pooled for the current treatment agnostic analysis. Patients were categorized based on the maximum consecutive number of months they remained fluid free after the anti-VEGF loading phase (from Week 12 to 96), with a fluid-free month (FFM) defined as the absence of sub-retinal fluid and intraretinal fluid. The categories were as follows: category 1: 0 FFMs ('never dry'); category 2: 1–3 FFMs; category 3: 4–9 FFMs; category 4: 10–21 FFMs ('dry for a long period of time'); category 5: 22 FFMs ('always dry'), with category 1 used as a reference for statistical comparison

purposes.

RESULTS At Week 96, patients in categories 4 and 5 had a least square mean (95% CI) best corrected visual acuity (BCVA) gain of 7.8 (4.5, 11.2) letters and 8.0 (4.3, 11.7) letters, respectively, compared with patients in category 1 ('never dry' [who gained 0.2 (-2.88, 3.30) letters from baseline]). At Week 96, the least square mean (95% CI) central subfield thickness (CSFT) of patients in categories 4 and 5 was -121.8 µm (-143.7, -99.8) and -127.8 µm (-152.2, -103.4) lower, respectively, compared with patients in category 1 ('never dry' [whose CSFT decreased by -86.2 µm (-106.0, -66.0] from baseline]).

CONCLUSION In comparison with patients who were 'never dry' after anti-VEGF loading, nAMD patients in HAWK and HARRIER who were 'always dry' or 'dry for a long period of time' had better visual and anatomic outcomes at study end, and greater reduction of CSFT throughout. These findings suggest that longer absolute fluid-free periods have a positive impact on visual and anatomic outcomes in nAMD patients.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

10/11/2021 9:00AM

Real World Experience of Brolucizumab for Persistent Macular Fluid in Neovascular Age-Related Macular Degeneration After Prior Anti-VEGF Treatments

- Rehan M. Hussain, MD
- Sumit P Bhatia, MD
- Kevin H Patel, MD
- Nicolas A Yannuzzi, MD
- Seenu M. Hariprasad, MD
- Siya Huo, MD

OBJECTIVE What are the anatomic and visual outcomes of wet AMD eyes with persistent fluid that are treated with brolucizumab after previous treatment with aflibercept and bevacizumab?

PURPOSE The HAWK and HARRIER trials established that brolucizumab resulted in greater resolution of fluid compared to aflibercept in treatment-naive wet AMD patients, but there is limited data on anatomic and visual acuity results of eyes switched to brolucizumab after previous treatment with anti-VEGF therapy.

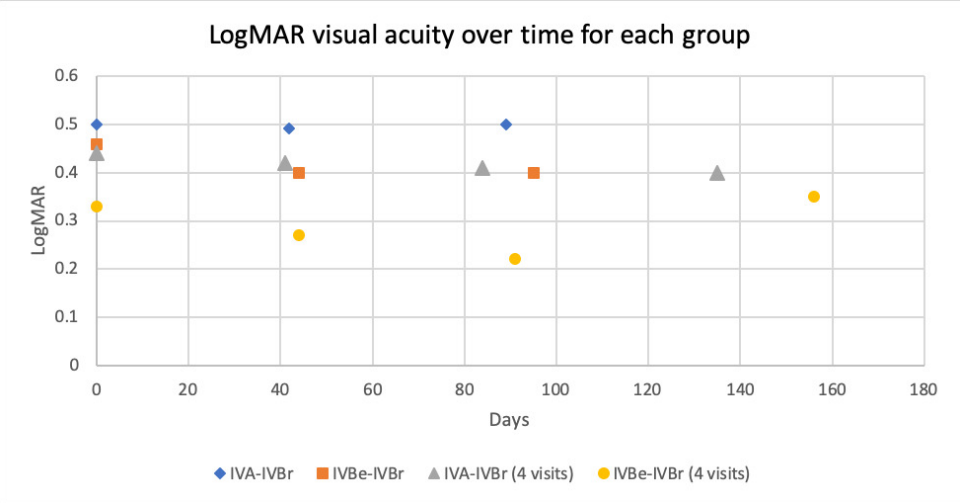
METHODS This is a retrospective case series of wet AMD eyes switched to broluczimab for persistent fluid after at least 3 prior anti-VEGF injections. Aflibercept was the last treatment for 48 eyes (IVA-IVBr group) and bevacizumab for 10 eyes (IVBe-IVBr group). Exclusion criteria included other causes of macular exudation, such as diabetic macular edema or retinal vein occlusion. The best corrected visual acuity (BCVA), central subfield thickness (CSFT) and presence of intraretinal or subretinal fluid (IRF/SRF) were recorded at each visit. Snellen visual acuity was converted to logMAR. A paired t-test was performed on the CSFT and logMAR at various intervals.

RESULTS For both groups, last injection was a mean of 6 weeks prior to first IVBr. In the IVA-IVBr group, mean CSFT improved from 340 to 305 mm ($p<0.001$) after one IVBr when checked a mean of 6 weeks later; 31% of eyes had no fluid, 42% had reduced fluid, 25% had

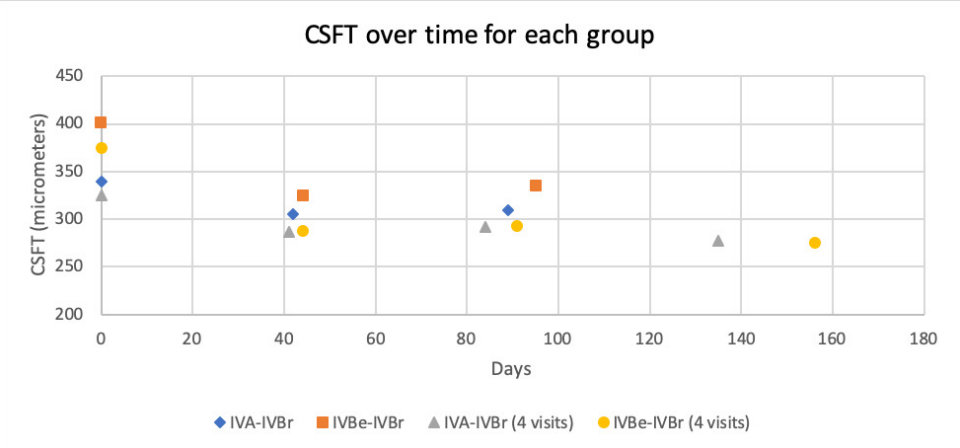
stable fluid, and 2% had increased fluid. In 25 eyes that completed a series of 3 IVBr, mean CSFT improved from 325 to 277 mm (p=0.001); 24% of eyes had no fluid at last follow up. In the IVBe-IVBr group mean CSFT improved from 401 to 325 mm (p=0.009) after one IVBr when checked a mean of 6 weeks later; 30% of eyes had no fluid and 70% had reduced fluid. In 4 eyes that completed a series of 3 IVBr, mean CSFT improved from 375 to 275 mm (p=0.001); 50% of eyes had no fluid at last follow up. Mean logMAR at baseline and fourth visit was 0.44 and 0.40 for the IVA-IVBr group (p=0.35), and 0.33 and 0.35 (p=0.39) in the IVBe-IVBr group respectively.

CONCLUSION In wet AMD eyes previously treated with IVA and IVBe, switching to IVBr significantly reduced persistent IRF/SRF while keeping similar treatment frequency. Visual acuity did not significantly change at any point in the study for either group.

IRB APPROVAL No — I received a determination that the study/activity qualified for **exempt status or that it did not require IRB approval** from an IRB or another authorized oversight body *(IRB Exemption Letter may be requested)*.



Scatterplot showing the mean best corrected visual acuity (LogMAR) for each visit after switching to brolucizumab. There was no statistically significant change in mean logMAR for any of the groups in this study.



Scatterplot showing the mean central subfield thickness (CSFT) for each visit after switching to brolucizumab. For both the

IVA-IVBr and IVBe-IVBr groups, there was a statistically significant reduction in CSFT after the first and second IVBr. For both subgroups that completed a series of 3 IVBr, there was further reduction of CSFT after the third IVBr.

10/11/2021 9:04AM

Key Pearls of Conjunctival and Tenon's Capsule Handling During the Implant Insertion Procedure for the Port Delivery System With Ranibizumab (PDS)

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OBJECTIVE To report key pearls from the optimization of conjunctival and Tenon's capsule handling required for successful Port Delivery System with ranibizumab (PDS) implant insertion procedure outcomes.

PURPOSE The PDS is an investigational drug delivery system designed for continuous intravitreal release of a customized formulation of ranibizumab through a surgically implanted, refillable ocular implant. Key pearls from optimizing conjunctival and Tenon's capsule handling during the PDS implant insertion procedure are reported here.

METHODS The phase 2 Ladder (NCT02510794) trial and phase 3 Archway (NCT03677934) trial compare the PDS with monthly intravitreal ranibizumab 0.5 mg for treatment of neovascular age-related macular degeneration. The ongoing PDS extension trial, Portal (NCT03683251), is evaluating the long-term safety and tolerability of the PDS 100 mg/mL. Experiences during the implant insertion procedures in these trials have informed evolution of PDS surgical methodologies, with the goal of optimizing surgical outcomes.

RESULTS The implant insertion procedure has 7 major steps to ensure good surgical outcomes: conjunctival peritomy, implant preparation, scleral dissection, laser ablation of pars plana, pars plana incision, implant insertion, conjunctival and Tenon's capsule closure. Traction suture placement before peritomy aids in visualization of the superotemporal quadrant. A spacious ≥ 6 × 6-mm peritomy centered around the implant location is created to facilitate implant placement away from the radial relaxing incision and provide proper tissue coverage for the implant. Delicate handling and appropriate dissection of the conjunctiva and Tenon's capsule with nontoothed forceps during peritomy and closure is critical to preserve tissue integrity over the implant. Capturing both the conjunctiva and

Tenon's capsule and a slightly exaggerated anterior approximation when anchoring to the anterior limbus with scleral bites during closure are critical to account for physiologic retraction during wound healing.

CONCLUSION Proper handling of the conjunctiva and Tenon's capsule during the PDS implant insertion procedure is important to minimize complications. To maximize optimal surgical outcomes, the procedure requires careful attention to elements not emphasized in other vitreoretinal procedures. Mastering these elements is achievable by vitreoretinal surgeons and supports successful procedure and patient outcomes.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

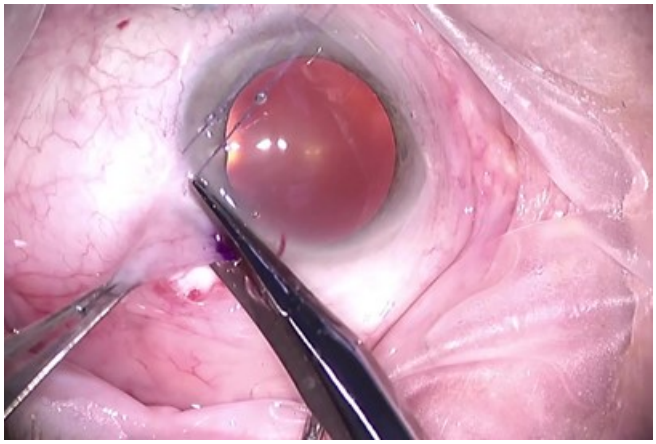


Figure 1. A surgical peritomy aided by a traction suture using delicate handling with nontoothed forceps and appropriate dissection and preservation of the conjunctiva and Tenon's capsule.

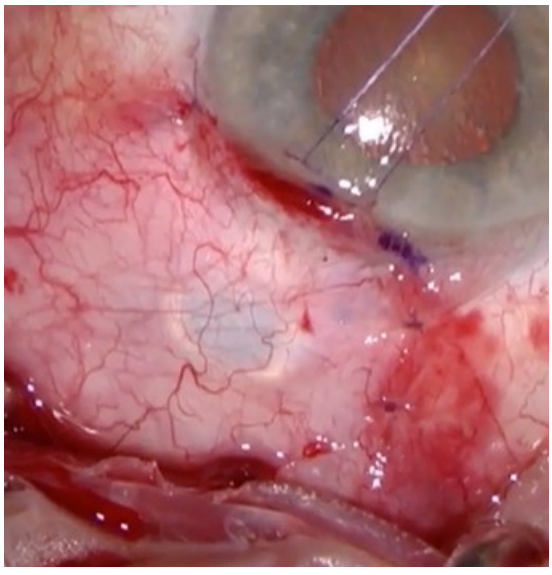
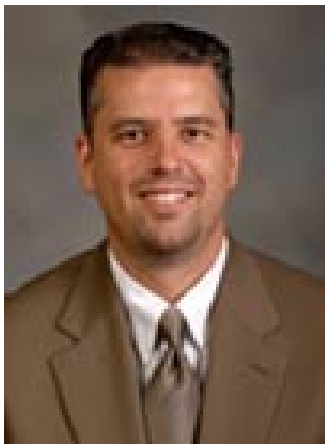


Figure 2. Demonstration of a proper closure, in which the conjunctival tissue has been secured taut against the anterior limbus, with minimal overhang and no gap at the limbus.

10/11/2021 9:08AM

Key Pearls of the Refill-Exchange Procedure for the Port Delivery System With Ranibizumab (PDS)



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OBJECTIVE To report key pearls from the optimization of the Port Delivery System with ranibizumab (PDS) refill-exchange procedure.

PURPOSE The PDS is an investigational drug delivery system designed for continuous intravitreal release of a customized formulation of ranibizumab through a surgically implanted, refillable ocular implant. Key pearls from the optimization of the PDS refill-exchange procedure are reported here.

METHODS The phase 2 Ladder (NCT02510794) trial and phase 3 Archway (NCT03677934) trial compare the PDS with monthly intravitreal ranibizumab 0.5 mg for treatment of neovascular age-related macular degeneration. The ongoing open-label PDS extension trial, Portal (NCT03683251), is evaluating the long-term safety and tolerability of the PDS 100 mg/mL. Experiences during the implant insertion and refill-exchange procedures in these trials have informed the evolution of PDS procedural methodologies, with the goal of optimizing procedure and patient outcomes.

RESULTS The PDS implant is refilled during a minimally invasive in-clinic refill-exchange procedure using the specially designed PDS refill needle. The refill needle is a 34G double cannula with a vented needle and fluid collection reservoir that enables exchange of the implant contents with fresh ranibizumab 100 mg/mL. The refill-exchange procedure is successfully performed with the retina specialist standing on the contralateral side of the study eye using a cotton-tipped applicator to stabilize the globe and minimize eye movement

(Figure 1). Proper patient positioning, visualization with magnification, and task lighting set the stage for success. A perpendicular approach, precise targeting into the septum center, and avoidance of twisting during the procedure is critical (Figure 2). The implant should be refilled slowly over ~5–10 seconds and the refill needle soft stop must remain in contact with the conjunctiva throughout the refill-exchange procedure.

CONCLUSION The PDS refill-exchange procedure represents a new development in vitreoretinal practice and requires a unique and precise skillset. Appropriate adherence to the refill-exchange procedure maximizes optimal outcomes. The PDS implant insertion and refill-exchange procedures have evolved and will continue to evolve as needed to support successful procedural and patient outcomes.

IRB APPROVAL Yes — *IRB Approval Letter may be requested*.

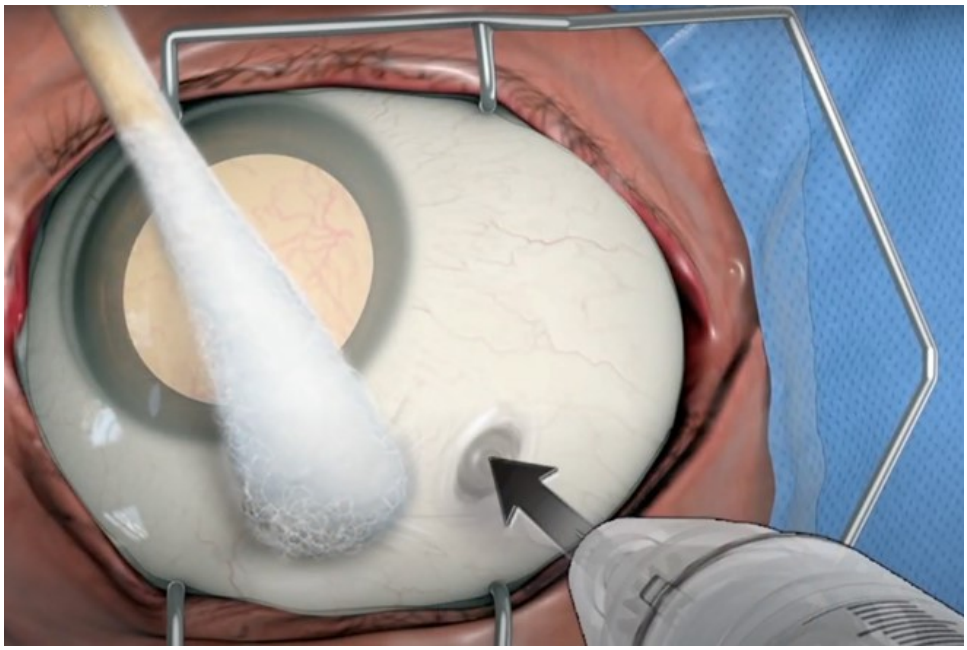

Figure 1. The surgeon's perspective, demonstrating good visualization, a perpendicular approach, targeting the center of the septum, and use of a cotton-tipped applicator in the other hand to stabilize the globe.

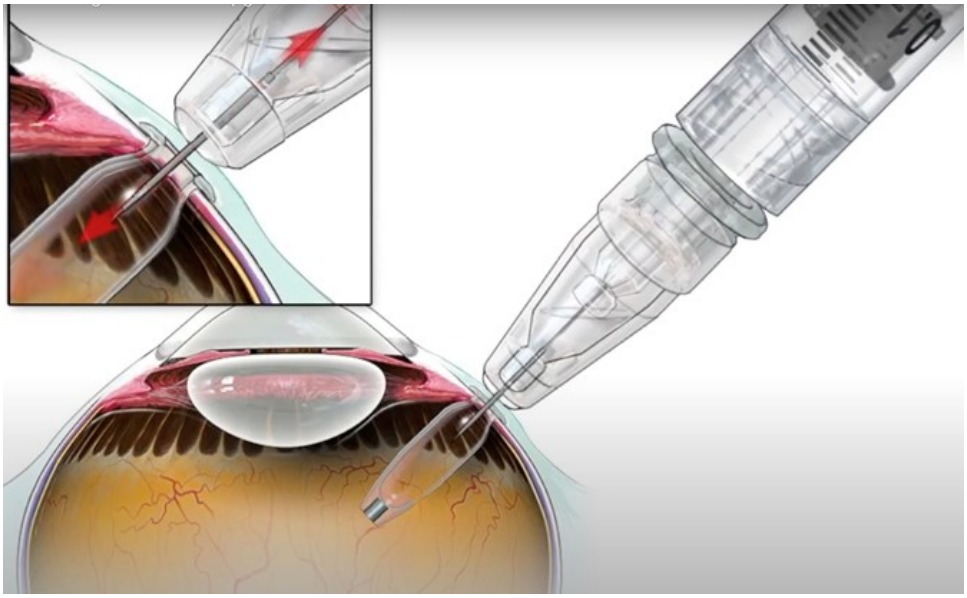

Figure 2. The refill-exchange procedure, highlighting the dual bore needle functioning and soft stop remaining in contact with the conjunctiva throughout the procedure, resulting in proper refill-exchange.