10/11/2021 11:10AM

Updated Safety and Efficacy Results From the Archway Phase 3 Trial of the Port Delivery System With Ranibizumab (PDS) for Neovascular AMD

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- Giulio Barteselli, MD
- Anne E. Fung, MD, FASRS
- Derrick Kaufman, Phd
- Sneha Makadia, PharmD, MPH
- Merce Morral, MD PhD
- Jeffrey R Willis, MD/PhD
- Shamika Gune, MD

OBJECTIVE To present updated results from the Sept 2020 data cut of the Archway phase 3 trial of the Port Delivery System with ranibizumab (PDS) for neovascular age-related macular degeneration (nAMD).

PURPOSE The PDS is an investigational drug delivery system for the continuous intravitreal delivery of a customized formulation of ranibizumab (RBZ) designed to address the unmet need to reduce the treatment burden in patients (pts) with nAMD. The Archway phase 3 trial evaluated the safety and efficacy of the PDS for nAMD, with the primary analysis focusing on results through week (W) 40.

METHODS Archway (NCT03677934) is a phase 3, randomized, active treatment–controlled trial. Pts with anti-VEGF–responsive nAMD were randomized 3:2 to treatment with the PDS with RBZ 100 mg/mL with fixed 24-week refill-exchanges (PDS Q24W) or intravitreal RBZ 0.5 mg injections every 4 weeks (monthly RBZ). The trial evaluated the noninferiority (NI) and equivalence of PDS Q24W versus monthly RBZ on a primary endpoint of best-corrected visual acuity (BCVA) change from baseline (BL) averaged over W36/40 (NI margin, –4.5 letters; equivalence margin, ±4.5 letters). Here, we present results through ≥ 48W of follow-up (2 complete PDS refill-exchange intervals) from the Sept 2020 data cut.

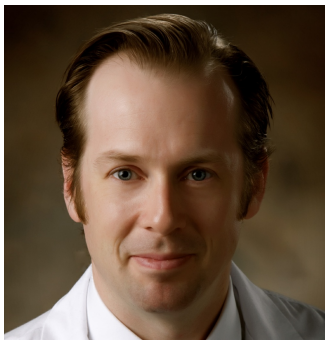
RESULTS 248 PDS Q24W and 167 monthly RBZ pts were treated in Archway. Change in adjusted mean BCVA score from BL averaged over W44/48 was 0.0 and +0.2 letters in the PDS Q24W and monthly RBZ arms, respectively. PDS Q24W was NI to monthly RBZ at W44/48, with a difference (95% CI) of −0.2 (−1.8, +1.3) letters between arms (equivalence not tested). Adjusted mean CPT change from BL results were consistent from the primary analysis through W48. 98.4% and 94.6% of PDS Q24W pts did not receive supplemental RBZ during the first or second refill-exchange intervals, respectively. Additional efficacy data to be presented. Through the Sept 2020 data cut, PDS Q24W pts received a mean total of 3.9 RBZ treatments over 77.9W compared with 19.5 RBZ treatments over 78.5W in monthly RBZ pts. PDS implant insertion and refill-exchange procedures were generally well tolerated and the ocular safety profile was generally unchanged from the primary analysis. Systemic safety findings were comparable across arms.

CONCLUSION Archway BCVA results for the average of W44/48 were consistent with the primary analysis, with PDS Q24W noninferior to monthly RBZ (equivalence not tested). Through a mean treatment duration of 78W, PDS Q24W pts received ~5x fewer RBZ treatments than monthly RBZ pts. PDS Q24W treatment was generally well tolerated, with a favorable benefit-risk profile.

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

10/11/2021 11:16AM

Pharmacokinetic Profile of the Port Delivery System With Ranibizumab in the Phase 3 Archway Trial



- John W. Kitchens, MD
- Shamika Gune, MD
- Mauricio Maia, PhD
- Han Ting Ding
- Matts Kågedal, PhD
- Katherine Maass

OBJECTIVE To characterize the pharmacokinetic (PK) profile of ranibizumab (RBZ) delivered via the Port Delivery System with RBZ (PDS) implant with fixed refill-exchanges every 24 weeks (Q24W).

PURPOSE The PDS is an investigational drug delivery system that includes a pars plana implant for continuous delivery of RBZ into the vitreous. In the phase 3 Archway trial (NCT03677934) in patients (pts) with neovascular age-related macular degeneration (N = 415), serum and aqueous humor (AH) samples were collected to characterize the PK profile of RBZ delivered via the PDS Q24W.

METHODS In the PDS with RBZ 100 mg/mL Q24W and intravitreal RBZ 0.5 mg injections every 4 weeks (Q4W) arms, serum PK samples were collected at specific time points from all pts, and at additional time points from pts at selected sites. In either arm, optional AH samples were collected at specific time points; serum samples were also collected at this time. PK-evaluable population included pts who did not receive RBZ as supplemental treatment in the study eye after implant insertion or in the fellow eye, or prior intravitreal bevacizumab treatment. RBZ concentrations were measured using validated enzyme-linked immunosorbent assays (lower limits of quantitation: serum, 15 pg/mL; AH, 20,000 pg/mL).

RESULTS In the PDS 100 mg/mL Q24W arm (number of pts [n] = 94), geometric mean (CV%) serum RBZ concentrations ranged from 419 (54%) pg/mL at week 4 to 340 (94%) pg/mL at week 24 (Figure 1). In the monthly RBZ arm (n = 79), the geometric mean serum RBZ concentrations ranged from 1880 (57%) pg/mL at 1–5 days after injection (Cmax) to 58.1 (171%) pg/mL at week 4 (Ctrough). The AH PK profile reflected the same trends seen in serum, with PDS 100 mg/mL Q24W (n = 42) maintaining concentrations above monthly

RBZ Ctrough (n = 46). Using a population PK model, the predicted vitreous humor concentrations of RBZ were estimated to decrease by half by 170 days after a refill-exchange procedure (Figure 2).

CONCLUSION The PDS continuously released RBZ over the Q24W refill-exchange interval, achieving steady concentrations. RBZ concentrations with PDS 100 mg/mL Q24W were within the range experienced with monthly RBZ injections. The AH PK profile was consistent with the serum PK profile.

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

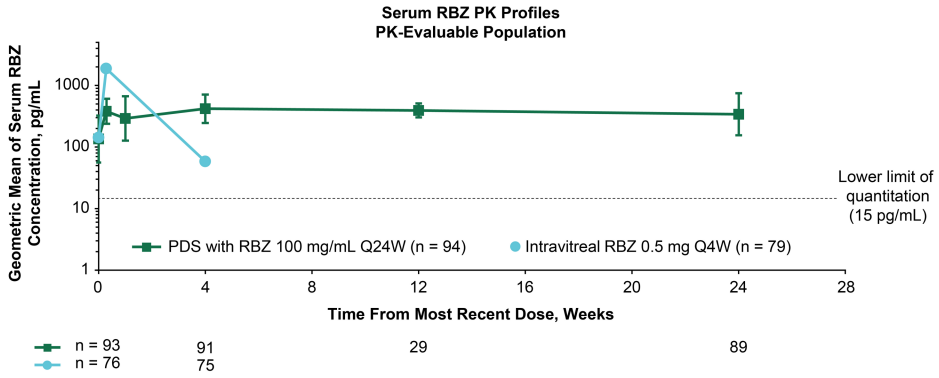


Figure 1. Serum RBZ PK profile showing geometric mean RBZ concentrations with PDS 100 mg/mL Q24W and monthly intravitreal RBZ 0.5 mg injections in the PK-evaluable population. Vertical bars represent the geometric mean */÷ geometric SD.

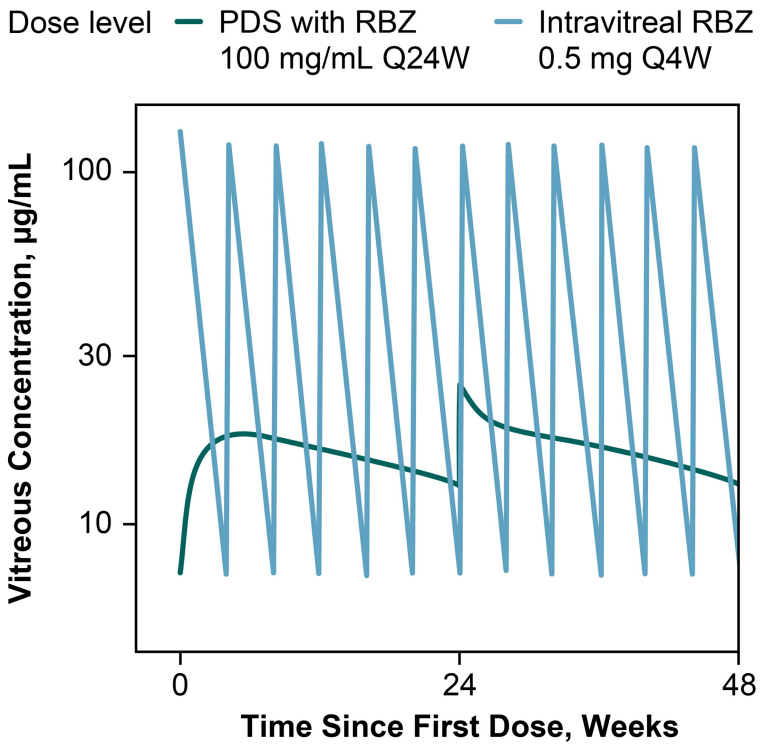


Figure 2. Prediction of vitreous humor concentrations of RBZ using a population PK model.

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Efficacy and Durability of Brolucizumab in Patients Being Transitioned From Prior Anti-VEGF Therapy

- Scott D Walter, MD, MSc
- Nicholas John Saba, MD

OBJECTIVE How effective is brolucizumab when wet AMD patients are transitioned from prior anti-VEGF therapy?

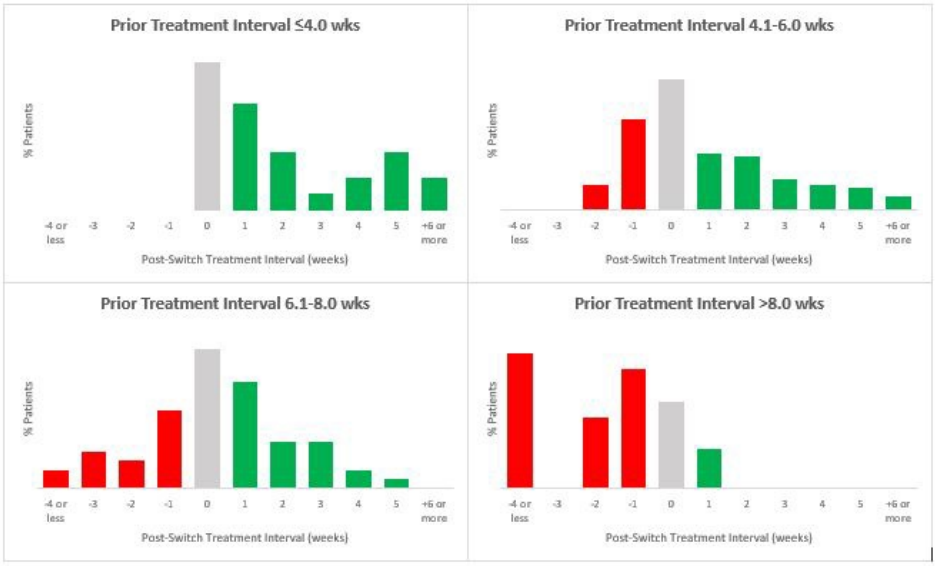
PURPOSE Clinical trials comparing brolucizumab to aflibercept demonstrated equivalent visual acuity outcomes, superior anatomic outcomes, and longer treatment intervals in treatment-naïve patients with wet AMD. In practice, many patients treated with brolucizumab are not treatment-naïve. This study evaluated the efficacy and durability of brolucizumab when transitioning from prior anti-VEGF therapy.

METHODS Retrospective consecutive case series of previously anti-VEGF treated eyes with wet AMD from a single private retina practice. The analysis included 530 eyes transitioned to brolucizumab between 10/1/2019 and 5/15/2020. The primary outcome measure was final visual acuity before and after transitioning to brolucizumab. Anatomic outcome measures included central subfield thickness (CST) and macular volume (MV) before and after the first brolucizumab injection, excluding OCT images with gross segmentation errors. Treatment intervals were compared on brolucizumab vs. prior anti-VEGF therapy. Data were collected and analyzed by non-masked investigators.

RESULTS 530 eyes with a history of aflibercept (78.8%), ranibizumab (48.2%), and/or bevacizumab (19.6%) injections were transitioned to brolucizumab. After a mean of 2.3 brolucizumab injections (range 1-8), there was no significant difference in visual acuity (-0.5 EDTRS letters, $p = 0.24$). Significant reductions in CST (-40.4 µm, $p<0.001$) and MV (-0.35 mm3 , $p<0.001$) were observed after the first brolucizumab injection. The average treatment interval was slightly longer with brolucizumab than with prior anti-VEGF therapy (+0.5 weeks, $p=0.001$).

CONCLUSION Eyes transitioning from prior anti-VEGF therapy to brolucizumab generally maintained visual acuity, while achieving significant improvements in anatomy and durability. While longer term follow-up is needed, this study suggests that some wet AMD patients may benefit when transitioned from prior anti-VEGF therapy.

IRB APPROVAL No — I **did not receive IRB approval** or a determination that the study/activity was exempt or that it did not require IRB approval. **Complete a Human Subject Research application** for review by the ASRS Human Research Committee. **Your abstract will not be considered without a completed application.** The ASRS HRC will review the information provided to determine whether the study qualifies as exempt or otherwise not requiring IRB approval. The ASRS HRC is not constituted as an IRB and thus cannot provide IRB approval for activities that require such.



Percent of eyes achieving longer or shorter treatment intervals after transitioning to brolucizumab, stratified by the prior anti-VEGF treatment interval

10/11/2021 11:30AM

Long-term Experience With Intravitreal Anti-VEGF Treatment in Patients With nAMD: Analysis of IRIS® (Intelligent Research in Sight) Registry Database

- Theodore Leng, MD, MS
- Vincent S Garmo, MHS
- Edward Neuberger, PharmD, MS, MBA
- Helene B. Fevrier, MSPH
- Andrew LaPrise
- Charles C Wykoff, MD, PhD, FASRS

OBJECTIVE To evaluate 6-year experience of intravitreal anti–vascular endothelial growth factor (VEGF) treatment in patients with neovascular age-related macular degeneration (nAMD) using the IRIS Registry.

PURPOSE Analyses of patient management and treatment outcomes based on routine clinical practice are often limited by the duration of the follow-up (F/U) period. This is the largest and longest F/U study known to date, where we evaluated intravitreal anti-VEGF treatment outcomes extending beyond 6 years in patients with nAMD from the IRIS Registry, the largest specialty clinical data registry.

METHODS In this retrospective observational study, data from patient eyes with nAMD treated with intravitreal anti-VEGF between July 1, 2013 and June 30, 2018 and with ≥ 2-year F/U in the IRIS Registry were included in the overall cohort. We evaluated the annual injection frequency, proportion of eyes treated with an anti-VEGF agent, switching patterns to and from off-label bevacizumab, and discontinuation patterns. Of the overall cohort, eyes with visual acuity (VA) readings at baseline and year 1 (VA data available ± 90 days from year 1) were separately analyzed for VA changes per year during F/U (corrected Snellen VA recordings converted to ETDRS letters). F/U data were collected until July 2020.

RESULTS The overall cohort included 254,655 eyes with ≥ 2-year F/U. In this cohort, the mean injection frequency was 6.1 injections in year 1, 5.2 in year 2, and 4.1–4.4 in years 3–6 (Figure 1). The proportion of eyes on aflibercept, bevacizumab, and ranibizumab changed

from 20%, 47%, and 16% at year 1 to 42%, 27%, and 24% at year 6, respectively. Anti-VEGFs were switched in 69,376 (27%) eyes; of these, 45,267 (65%) switched from bevacizumab to an on-label agent. Treatment was discontinued (defined as > 365 days without an anti-VEGF injection) in 121,544 (48%) eyes (mean [SD] time to discontinuation, 78 [69] weeks). The VA analysis cohort included 168,963 eyes. Of these, 23,470 eyes had ≥ 5 years of F/U (Table 1). VA at baseline and each annual F/U was generally higher for eyes with more F/U.

CONCLUSION This study evaluated real-world treatment patterns and VA outcomes of patients with nAMD with long-term F/U from the IRIS Registry. These findings showed that patients received relatively few anti-VEGF injections in years 3–6 and experienced high rates of therapy discontinuation. Given the size and inclusivity of the IRIS Registry, these findings could be generalized to the US population.

IRB APPROVAL Not applicable — I responded "No" to previous question regarding human subjects.

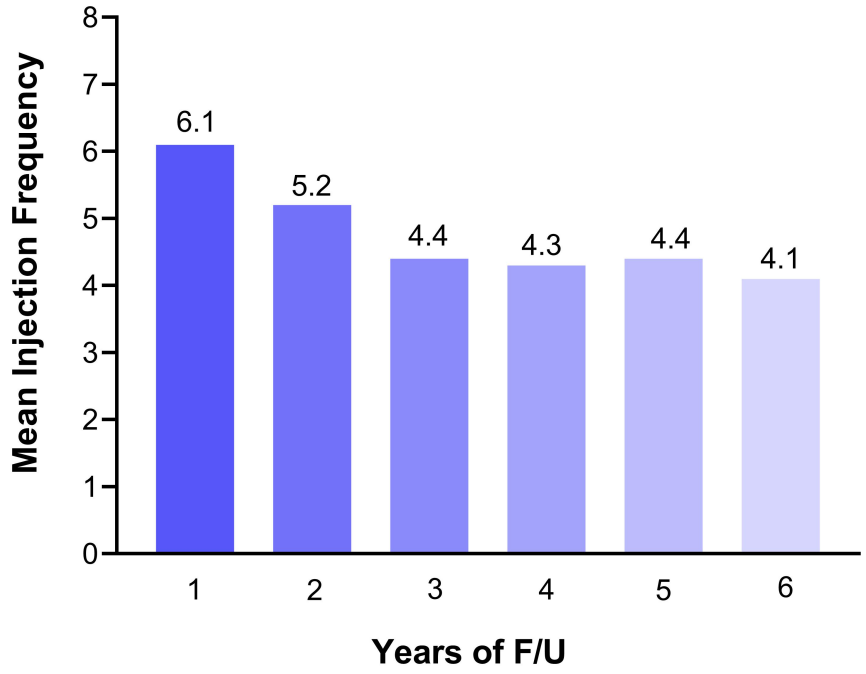


Figure 1. Mean Injection Frequency of Patient Eyes With nAMD That Were Included in the Overall Cohort

	Patient	VA (ETDRS), Mean (SD)						
	Eyes	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
VA at ≥ 1-year F/U	168,963	57.4 (21.0)	59.7 (21.8)	–	–	–	–	–
VA at ≥ 2-year F/U	142,255	58.3 (20.4)	61.0 (20.8)	58.7 (22.4)	–	–	–	–
VA at ≥ 3-year F/U	83,933	59.0 (19.9)	62.0 (20.0)	60.1 (21.4)	57.9 (22.6)	–	–	–
VA at ≥ 4-year F/U	45,117	59.8 (19.4)	62.9 (19.2)	61.4 (20.3)	59.5 (21.5)	57.3 (22.7)	–	–
VA at ≥ 5-year F/U	23,470	60.9 (18.8)	63.9 (18.4)	62.7 (19.3)	61.2 (20.3)	59.4 (21.4)	57.1 (22.6)	–
VA at ≥ 6-year F/U	8679	61.7 (18.7)	64.5 (18.1)	63.5 (18.8)	62.2 (19.9)	60.6 (20.8)	58.6 (22.1)	56.5 (22.8)

Table 1. VA (ETDRS) of Patient Eyes With nAMD That Were Included in the VA Analysis Cohort

10/11/2021 11:36AM

Apples and Oranges: "Real-World" Outcomes Differ From Clinical Trial Outcomes Because "Real-World" Patients Differ From Clinical Trial Patients

- Franco M. Recchia, MD

OBJECTIVE To compare the treatment and clinical outcomes of real-world nvAMD patients who would have qualified for Phase 3 trials with those of real-world nvAMD patients who would have been trial-ineligible.

PURPOSE Accurate knowledge of real-world outcomes is essential to health policy, practice management, and physician reimbursement. Conventional wisdom holds that real-world patients achieve outcomes inferior to what is expected from Phase 3 clinical trials. But this belief stems largely from registry studies that ignore underlying differences between real-world patients and clinical trial participants.

METHODS Clinical and imaging data of consecutive patients with new active nvAMD from a community-based tertiary retina practice were reviewed. Protocols from the HARBOR, VIEW-1, CATT, and LUCAS trials were applied to determine which patients would have been eligible for any of these trials ("trial-eligible" patients). Patients not meeting all study inclusion criteria were defined as "trial-ineligible." Primary outcome measures were visual acuity (VA) at 24 mos following diagnosis and number of anti-VEGF injections received over 12 and 24 mos. To replicate the methods from published Vestrum analyses, patients receiving ≥3 injections within 4 mos of diagnosis were identified for additional analysis.

RESULTS Clinical data and angiograms from 1239 eyes were analyzed. Only 589 eyes (48%) would have been eligible for CATT; 41% for LUCAS; 37% for HARBOR, and only 36% eligible for VIEW-1. Commonest reasons for ineligibility were lesion characteristics and prior anti-VEGF therapy. "CATT trial-eligible" eyes gained mean 8.7 ETDRS letters at 12 mos, after median 10 injections, and gained mean 7.8 ETDRS letters at 24 mos, with

median additional 7 injections. These results are comparable to what is expected from the CATT trial. Trial-ineligible eyes at 24 mos, by contrast, showed significantly worse median VA, were less likely to have improved VA, gained fewer ETDRS letters, were less likely to achieve 20/40 or better, were more likely to have 20/200 or worse, and received significantly fewer anti-VEGF injections. Even when applying Vestrum-analysis methodology, outcomes consistent with clinical trials were observed when analysis was limited to trial-eligible patients.

CONCLUSION Most nvAMD patients would not qualify for the trials that inform currents standards of care. Real-world outcomes DO mirror outcomes expected from clinical trials when only trial-eligible patients are analyzed. The pejorative implications of registry studies that real-world patients do worse than expected may be due to methodology that does not account for the heterogeneity of real-world patients.

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

10/11/2021 11:42AM

Geographic Access Disparities of Clinical Trials in Neovascular Age-Related Macular Degeneration in the United States

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- Anand Gopal, MD
- Devayu Parikh, BS
- Charlotte Shields
- Samir N Patel, MD
- John W Hinkle, MD
- James Sharpe
- Allen C Ho, MD
- Carl D. Regillo, MD
- Julia A. Haller, MD
- Yoshihiro Yonekawa, MD, FASRS

OBJECTIVE The objective of our study was to determine geographic and socioeconomic variables predictive of residential proximity to neovascular age-related macular degeneration (nAMD) clinical trial locations.

PURPOSE In recent decades, the expanding pipeline of clinical trials has offered new therapies to improve visual outcomes in nAMD. Including subjects from diverse backgrounds has important implications for data generalizability and improved access to innovative care. Understanding accessibility to clinical trials is imperative to address the disease burden of nAMD for all populations in the United States.

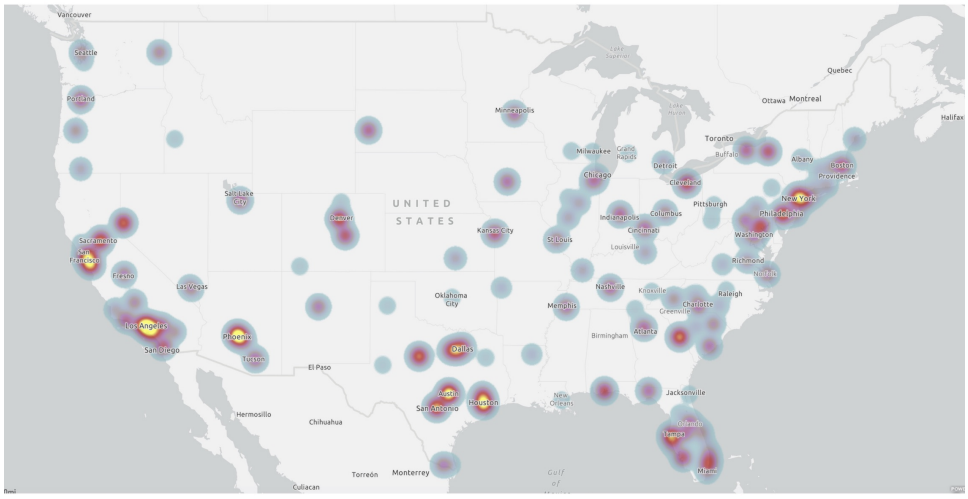
METHODS This was a cross-sectional, retrospective study, analyzing census-tract level data from public datasets and trial-level data from ClinicalTrials.gov. The primary outcome was driving distance (>60 miles) and time (>60 minutes) from the population-weighted United States (US) census tract centroid to the nearest clinical trial site, using geographic information systems software.

RESULTS There were 42 trials involving nAMD across 829 unique clinical trial sites in the

US. In multivariable regression, driving distance >60 miles was significantly associated with rural location [adjusted odds ratio [aOR] 5.54; 95% confidence interval [CI] 3.86-7.96, p<0.0001] and Midwest (aOR 2.30; 95% CI 1.21-4.38, p=0.01) and South (aOR 2.43; 95% CI 1.21-4.91, p=0.01) vs. Northeast, and some college or an Associates degree, as compared to a Bachelor's degree (aOR 1.02; 95% CI 1.01-1.04, p=0.0007) and (aOR 1.05; 95% CI 1.00-1.10, p=0.04), respectively. Lower odds of driving > 60 miles were associated with census tracts with a higher percentage of blacks (aOR 0.98; 95% CI 0.97-0.99, p<0.0001), Hispanics (aOR 0.97; 95% CI 0.95-0.99, p=0.002) and Asians (aOR 0.90; 95% CI 0.88-0.93, p<0.0001), as compared to whites, and a lower percentage of the population <200% of the federal poverty level (FPL). Time traveled >60 minutes had similar predictors in regression modelling.

CONCLUSION There are geographic disparities in access to clinical trial sites for nAMD in the US. While proximity to urban centers is beneficial for efficiency and retention of subjects, our study identifies populations with a high travel burden to sites, which may contribute to under-representation. More research is needed to characterize the current state of generalizability of clinical trials in nAMD.

IRB APPROVAL Not applicable — I responded "No" to previous question regarding human subjects.



Heat map of geographic distribution of active clinical trial sites in neovascular age-related macular degeneration in the United States, with start year of 2017. Warmer colors signify a higher number of clinical trial sites.

10/11/2021 11:48AM

Treatment Patterns and Visual and Health Function in Neovascular Age-Related Macular Degeneration (nAMD): Medicare Current Beneficiary Survey Analysis

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- Arshad M. Khanani, MD, MA, FASRS
- Vincent S Garmo, MHS
- Ibrahim M Abbass, RPh, PhD
- Alicia Menezes
- Carmen Ng, PhD
- Xiaohui Zhao
- Tania Banerji, MPH
- Keiko Wada
- Aimee Near, MPH
- Gary Michael Oderda, PharmD MPH
- Diana Brixner
- Joseph Biskupiak, PhD, MBA

OBJECTIVE To characterize treatment patterns, perceived visual functioning, and health functioning of patients with nAMD receiving intravitreal injection (IVI) of anti–VEGF monotherapy.

PURPOSE This is the first time use of the Medicare Current Beneficiary Survey (MCBS) to understand anti-VEGF treatment patterns, perceived visual functioning, and health functioning related to activities of daily living (ADL) and instrumental ADL (iADL) over time.

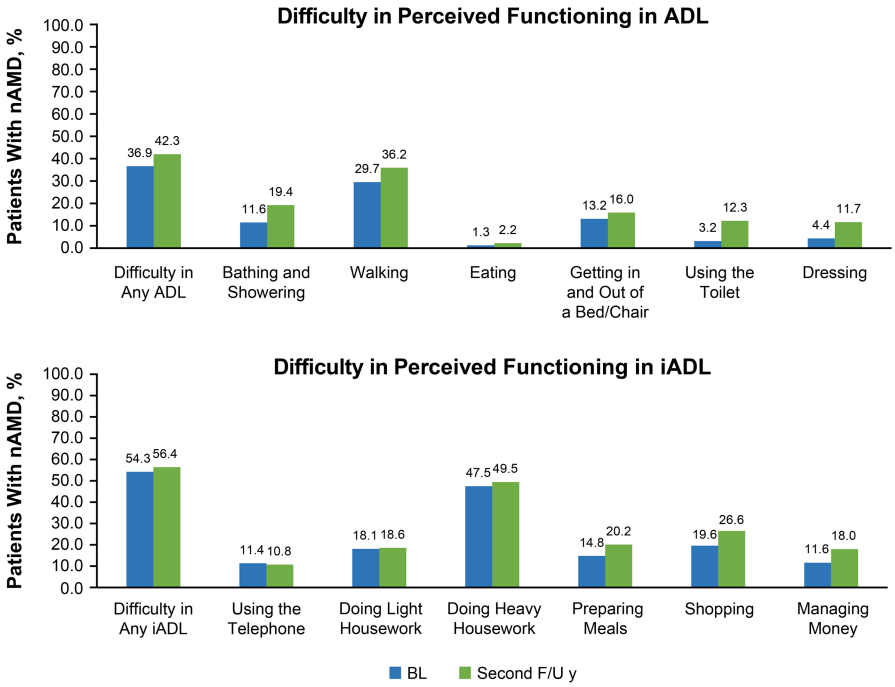
METHODS This retrospective study used pooled 3-year longitudinal data from the MCBS linked with Medicare fee-for-service claims in 2006–2013 and 2015–2018. Community-dwelling beneficiaries diagnosed with nAMD and receiving ≥ 1 anti-VEGF IVI at baseline (BL), and with full-year Medicare Part A and B enrollment for 3 years (BL + 2 follow-up [F/U] years), were identified. Those with other vision-threatening diseases and living in

long-term care facilities at BL or with health maintenance organization enrollment in the 3-year period were excluded. BL characteristics, anti-VEGF persistence (≥ 6 IVIs in 1 year) at F/U, as well as perceived function in vision, ADL, and iADL at BL + F/U, were evaluated.

RESULTS Of 161 nAMD beneficiaries (mean (SE) age, 82.6 (0.6) years; 61.0% female), the majority were non-Hispanic White (97.0%). In the first and second F/U years: (i) 35.9% and 30.5% of patients were 'persistent' on anti-VEGF treatment; (ii) patients received a mean (SE) of 4.2 (0.3) and 3.7 (0.3) injections, and had 7.9 (0.3) and 6.8 (0.3) clinic visits; and (iii) mean (SE) interval between consecutive injections/visits was 8.7 (0.3)/7.3 (0.3) and 8.4 (0.4)/8.2 (0.4) weeks, respectively. The proportion of patients reporting trouble seeing or blindness at BL, first, and second F/U years was 30.6%, 32.9%, and 27.6%, respectively. Overall, 68.6% of patients reported similar or better function in the second F/U year versus BL. However, a higher proportion of patients experienced difficulty in all ADL and most iADL in the second F/U year versus BL (Figure). ADL with greater changes were dressing and using the toilet; iADL with greater changes were preparing meals, shopping, and managing money.

CONCLUSION Only 1/3 of Medicare beneficiaries were 'persistent' with anti-VEGF monotherapy each year. Overall, 2/3 of patients treated with anti-VEGF at BL reported similar or better visual function after 2 years. However, more patients experienced difficulty in ADL and iADL at 2 years. Future research exploring how nAMD-related factors impact overall functioning is warranted.

IRB APPROVAL Not applicable — I responded "No" to previous question regarding human subjects.



Difficulty in perceived functioning in ADL and iADL.