Patient Preference and Treatment Satisfaction With a Port Delivery System for Ranibizumab vs Intravitreal Injections in Patients With Neovascular Age-Related Macular Degeneration
A Randomized Clinical Trial

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**IMPORTANCE** The port delivery system (PDS) with ranibizumab has demonstrated noninferior and equivalent efficacy compared with monthly intravitreal injections of ranibizumab, an anti–vascular endothelial growth factor (VEGF) agent, in patients with neovascular age-related macular degeneration (nAMD), but evaluating patient preference is important to help inform clinical decision-making.

**OBJECTIVE** Evaluate treatment satisfaction for ranibizumab delivered via PDS vs intravitreal injections as well as patient preference among those assigned to PDS.

**DESIGN, SETTING, AND PARTICIPANTS** Archway was a phase 3 randomized active-comparator open-label clinical trial conducted at 78 sites in the US. Patients 50 years and older with nAMD diagnosed within 9 months of screening with a documented response to anti-VEGF therapy were included. Of 619 patients screened, 418 were enrolled; 415 were included in the primary analysis and 234 were included in the secondary exploratory analysis. The Archway study ran from September 12, 2019, through primary readout on May 22, 2020.

**INTERVENTIONS** Patients were randomized 3:2 to PDS with ranibizumab, 100 mg/mL, with fixed refill exchanges every 24 weeks or intravitreal ranibizumab injections, 0.5 mg, every 4 weeks.

**MAIN OUTCOMES AND MEASURES** Treatment satisfaction was measured using the Macular Disease Treatment Satisfaction Questionnaire in the PDS and intravitreal injection arms at week 40. Patient preference was assessed using the content-validated PDS Patient Preference Questionnaire (PPPQ), which measured the proportion of patients in the PDS arm with monthly monitoring who preferred treatment with the PDS at week 40 over previous intravitreal injections or concurrent fellow-eye injections. Both outcomes were exploratory end points.

**RESULTS** The mean (SD) age of participants at baseline was 75.0 (7.9) years; 234 participants (59%) were women and 162 (41%) were men. At week 40, differences in overall treatment satisfaction scores were minimal for the PDS and intravitreal injection arms (mean, 68.0; 95% CI, 67.4-68.6; n = 237 and mean, 66.1; 95% CI, 64.9-67.3; n = 159, respectively; difference, 1.9; 95% CI, 0.7-3.1). A total of 234 of 248 patients (94.4%) in the PDS arm were included in the PPPQ analysis. At week 40, almost all patients in the PDS arm preferred treatment via PDS (218 of 234 [93.2%]) vs previous intravitreal injections (3 of 234 [1.3%]), including 172 of 234 (73.5%) with a very strong preference for the PDS. In patients who received concurrent fellow-eye injections (n = 78), 72 (92.3%) preferred the PDS.

**CONCLUSIONS AND RELEVANCE** Although PDS treatment was preferred by almost all patients assigned to PDS over previous intravitreal injections, both delivery methods have high treatment satisfaction. These findings provide further evidence for the PDS as a meaningful alternative treatment option for patients with nAMD.

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Since the introduction of anti–vascular endothelial growth factor (VEGF) agents, treatment outcomes for patients with neovascular age-related macular degeneration (nAMD) have transformed, shifting from managing vision loss to patients achieving vision gain or stabilization. However, optimal long-term anti-VEGF therapy involves frequent injections and monitoring, which contribute to a high management burden and associated noncompliance, and ultimately result in lower visual acuity gains than observed in controlled clinical trials.

The port delivery system with ranibizumab (PDS) is an innovative drug delivery system that has been approved by the US Food and Drug Administration for the treatment of nAMD in adults who have previously responded to at least 2 anti-VEGF injections. The PDS includes a surgically placed permanent indwelling and refillable ocular implant that provides continuous release of a customized formulation of ranibizumab. The PDS is refilled with ranibizumab in an in-clinic setting approximately every 6 months and, compared with the requirement for frequent intravitreal injections, has the potential to lead to a reduction in treatment frequency and monitoring visits. The phase 3 Archway trial evaluating PDS with ranibizumab, 100 mg/mL with fixed refill exchanges every 24 weeks, vs intravitreal ranibizumab, 0.5 mg injections every 4 weeks, demonstrated that continuous ranibizumab delivery via PDS had equivalent visual acuity efficacy to monthly ranibizumab injections and a generally well-tolerated safety profile.

As in other medical fields, the patient voice is becoming increasingly valuable in clinical decision-making in ophthalmology because traditional efficacy measures do not fully assess all aspects of treatment that are important to patients (eg, quality of life, symptoms, costs, ease of treatment, and treatment satisfaction). Although the PDS is a new treatment for nAMD, a disease for which many other treatment options exist, the drug-device combination and surgical nature of the PDS, with its unique surgical and device-related risks, distinguish it from other options involving intravitreal injections.

When new treatments become available, clinicians may take account of patient preferences. To quantify this, it is necessary to prospectively evaluate patient preference, strength of preference, and reasons for preference using standardized and validated instruments. Patient-reported outcome measures offer clinicians the ability to capture patient views in aspects of treatment beyond efficacy measures. The Macular Disease Treatment Satisfaction Questionnaire (MacTSQ) is a validated patient-reported outcome measure that has been used to measure treatment satisfaction for injections of anti-VEGF agents in patients with nAMD in both clinical trials and clinical practice settings. However, other specific and validated patient-reported outcome measures in patients with nAMD are lacking, and opportunities to inform clinical decision-making incorporating the views of patients have been limited.

Patients who receive their preferred treatment (ie, through shared decision-making, choice, or assessed preferences) may have higher treatment satisfaction rates, increased adherence and compliance, and superior clinical outcomes. The potential for fewer visits and reduced treatment burden with the PDS vs intravitreal injections may influence patient choice. To evaluate patient preference between PDS and intravitreal injections, a PDS Patient Preference Questionnaire (PPPQ) was developed based on the previously reported Patient Preference Questionnaire. We report treatment satisfaction with the PDS vs intravitreal injections as measured by the MacTSQ in the phase 3 Archway trial and the phase 2 Ladder trial. In addition, among the patients in the PDS arms, we report the PPPQ whereby we evaluated patient preference in the for the PDS vs intravitreal anti–VEGF injections. To further assess the patient voice in our PDS trials, we also report development and content validity of the PPPQ in a subpopulation of patients in Ladder.

### Methods

#### Study Design and Participants

The Archway study ran from September 12, 2019, through primary readout on May 22, 2020. Details of the primary analysis of Archway have been published. Briefly, Archway was a phase 3 randomized visual assessor-masked active-comparator open-label trial of the PDS for patients nAMD conducted at 78 sites in the US. The trial adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with International Conference on Harmonisation E6 Guidelines for Good Clinical Practice and applicable local, state, and federal laws. All trial sites received institutional review board approval before trial initiation and all patients provided written informed consent before enrollment. Participants were compensated for their travel expenses.

Patients were 50 years and older with nAMD-related neovascular lesions involving the macula diagnosed in the study eye within 9 months of screening. Patients had to have received at least 3 previous anti–VEGF intravitreal injections (ranibizumab, bevacizumab, or aflibercept) within 6 months of screening and demonstrated response to anti-VEGF therapy. Study eye exclusion criteria have been previously reported and included history of surgical or therapeutic treatment for nAMD other than ranibizumab or prior participation in a clinical trial involving anti-VEGF agents.

Patients were assigned randomly 3:2 to receive ranibizumab either every 24 weeks via the PDS or monthly via intravitreal injection. Implant insertion at day 1 and refill-exchange procedures...
at 24 weeks were performed as detailed previously. Patient monitoring in both treatment arms occurred monthly, and criteria for supplemental treatment in the PDS arm has been described previously. Details of Ladder have been reported previously and are summarized in the eMethods in Supplement 3.

Patient-Reported Outcomes, End Points, and Statistical Analyses

The MacTSQ was used to evaluate patient-reported treatment satisfaction with ranibizumab delivered via the PDS for 40 weeks compared with monthly ranibizumab as an exploratory end point in Archway. The MacTSQ was assessed at baseline and week 40 before any other study procedures were conducted. The MacTSQ provides a total score and 2 subscale scores. MacTSQ total score ranges from 0 to 72, where a score of at least 60 indicates high satisfaction; the 2 subscales are the Information Provision and Convenience and the Impact of Treatment. Both subscale scores range from 0 to 36, with a score of at least 30 indicating high satisfaction. MacTSQ scores were summarized using appropriate descriptive statistics based on observed data. For patients who discontinued the study early and were administered the MacTSQ at the early termination visit, the last assessment available before week 40 was used in the analysis. The MacTSQ was also used to assess treatment satisfaction in the PDS and intravitreal injection groups in the phase 2 Ladder trial. Details of assessment of treatment satisfaction in Ladder are provided in the eMethods in Supplement 3. To assess impact of the experience of ocular serious adverse events (SAEs) on treatment satisfaction, subgroup analyses were performed for patients with and without ocular SAEs in both Archway and Ladder.

Patient preference was assessed using the PPPQ in Archway to evaluate patient preference for treatment delivered via the PDS vs previous intravitreal injections as an exploratory end point. The 3-item PPPQ captures a patient’s preference for treatment, the strength of their preference, and reasons for their preference (eFigure 1 in Supplement 3). Development and content validation of the PPPQ in a subpopulation in Ladder are described in the eMethods in Supplement 3. The PPPQ content validation study included 11 patients (eTable 1 in Supplement 3), 10 of whom (90.9%) preferred the PDS vs 1 (9.1%) who preferred intravitreal injections (eFigure 2A in Supplement 3). Trained study site personnel administered the PPPQ at week 40 (before any other study procedures) to patients in the PDS arm, all of whom had received at least 3 anti-VEGF injections before day 1. Assessment of the PPPQ at week 40 was to coincide with assessment of the primary end point in Archway. Patients were asked to compare the experience of PDS treatment with intravitreal anti-VEGF treatment. For patients who discontinued the study early and were administered the PPPQ at the early termination visit, the last assessment available before week 40 was used in the analysis. A subgroup analysis was carried out in patients with bilateral nAMD in the PDS arm who received at least 1 anti-VEGF intravitreal injection in the fellow eye within the study through week 40. Additionally, to assess impact of the experience of ocular SAEs on patient preference, a subgroup analysis was performed for patients with and without ocular SAEs. Strength of preference and reasons for preference with the PPPQ were summarized descriptively.

Results

MacTSQ

The mean (SD) age of participants at baseline was 75.0 (7.9) years; 234 participants (59%) were women and 162 (41%) were men. All patients in Archway were included in the analysis.
of MacTSQ at baseline (248 in the PDS arm; 167 in the monthly injection arm). In both the PDS and monthly injection arms, patients had high overall treatment satisfaction, with MacTSQ total scores of at least 60 and subscale scores of at least 30 in both treatment arms at baseline (Figure 1). At week 40, high total treatment satisfaction scores were observed in the PDS (mean, 68.0; 95% CI, 67.4-68.6; n = 237 and mean, 66.1; 95% CI, 64.9-67.3; n = 159, respectively; difference, 1.9; 95% CI, 0.7 to 3.1) (Figure 1 and Table). Subscale scores also showed high treatment satisfaction in both arms. Treatment satisfaction was high for both treatment methods in patients with and without ocular SAEs (eTable 2 in Supplement 3).

High treatment satisfaction was also observed with PDS and monthly intravitreal injections throughout Ladder8,10 and in patients with and without ocular SAEs in the PDS arm (eResults, eTables 3 and 4, and eFigure 3 in Supplement 3).

PPPQ
PPPQ was evaluated only in patients assigned to the PDS arm. A total of 234 of 248 patients (94.4%) completed the PPPQ and were included in the analysis (Figure 2). As reported in our primary analysis of Archway,9 almost all patients in the PDS group (218 of 234 [93.2%]) preferred treatment via PDS at week 40 vs intravitreal injections (3 of 234 [1.3%]); 13 patients (5.6%) had no preference for either regimen. Most patients in the PDS group (172 of 234 [73.5%]) had a very strong preference for PDS (Figure 3). The most common reasons cited for preference for PDS were fewer treatments (175 of 218 [80.3%]), less discomfort (164 of 218 [75.2%]), and less worry or nervousness (117 of 218 [53.7%]) (Figure 4).

Results from the subgroup analysis in patients with bilateral nAMD in the PDS group (n = 78 [33.3%]) who received at least 1 anti-VEGF intravitreal injection in the fellow eye through
Discussion

Systematic evaluation of patient preference is emerging as an important factor in determining the most appropriate treatments, especially when different treatments show equivalent efficacy. Objective cohort preference data are increasingly helpful to physicians, patients, and health care systems in determining treatment choices. Archway was the first phase 3 trial of the PDS; it demonstrated that longer-acting anti-VEGF treatment via the PDS provided equivalent visual acuity efficacy, with some safety concerns unique to the PDS, compared with monthly intravitreal anti-VEGF injections. To better understand the patient experience in Archway and Ladder, we used the MacTSQ to measure treatment satisfaction for patients treated with the PDS vs patients treated with intravitreal injections. Patients in both Archway and Ladder reported not only a high overall treatment satisfaction for both the PDS and intravitreal injections, but post hoc analyses did not demonstrate a difference in treatment satisfaction between treatment methods. Another clinical trial in patients with nAMD using the MacTSQ to assess treatment satisfaction after injection of anti-VEGF agents showed that visual acuity gains were an important determinant of patient satisfaction. In Archway, visual acuity was equivalent between the PDS and intravitreal injections arms and may have led to similar outcomes for treatment satisfaction. However, when using the MacTSQ to assess treatment satisfaction in patients with nAMD in a clinical practice setting, visual acuity gains were found to be less important, and patients’ perception of satisfaction was more related to aspects of their care and disease process, including in-clinic service, quality of life, and duration of disease. These findings indicate that the patient’s experience of treatments is likely to differ depending on setting and may encompass other aspects besides efficacy.

Here, using the content-validated PPPQ with patients assigned to the PDS arm, we found that 93.2% of patients preferred treatment with ranibizumab delivered via the PDS vs only 1.3% of patients who preferred intravitreal injections. In addition, we found that most patients (73.5%) in the PDS group had a very strong preference for the PDS, with the most common reasons for PDS preference being fewer treatments, less discomfort, and less worry or nervousness. This is unsurprising because many patients receiving repeated intravitreal injections report discomfort and anxiety arising from fear of discomfort, and fear and anxiety are commonly given reasons for nonadherence among patients receiving intravitreal anti-VEGF injections. We found that a similarly high proportion of patients preferred the PDS vs intravitreal injections in the subpopulation of patients with bilateral disease who received concurrent intravitreal injections in the fellow eye. These findings in Archway were consistent with the results from our earlier PPPQ content validation study.

Given the concerns associated with the safety profile of the PDS, we performed a subgroup analysis for patients with and without ocular SAEs to assess whether preference for the PDS was driven by those without serious complications. Although patient preference for the PDS was lower in patients with ocular SAEs vs those without, most patients (75.0%) with ocular SAEs preferred PDS treatment. These data further contextualize the overall strong patient preference for the PDS observed in Archway.

Patient-reported outcome measures provide a unique opportunity to aid clinical development because they capture aspects of treatment that are important to patients and generate standardized outcomes that can be used to inform treatment decision-making. However, there is a need for specific and validated instruments in patients with nAMD to accurately capture the patient’s voice. The PPPQ was developed, and its content was validated using a subpopulation of patients with nAMD who completed Ladder. The aim of developing the PPPQ was to provide clinicians with a robust and standardized method of assessing patient preference for the PDS. After minor modifications to the PPPQ based on feedback in the PPPQ content validation study, we successfully demonstrated the content validity of the PPPQ.

Long-term and frequent use of intravitreal anti-VEGF injections is associated with substantial burden to patients, caregivers, and health care professionals. Other studies evaluating patient preference for different anti-VEGF treatments in clinical practice settings showed that the main factor in patient treatment preference was impact on visual
acuity. However, treatment burden (eg, frequency and length of visits and costs to patients and health care professionals) was another important consideration. One study comparing pro re nata vs monthly injections with ranibizumab in patients with nAMD reported that a higher proportion of patients favored a less burdensome pro re nata regimen over monthly injections (53% vs 38%, respectively). Another analysis of anti-VEGF regimens in patients with nAMD reported a preference for treat-and-extend (46%), followed by pro re nata (44%), and fixed (4%) anti-VEGF regimens, thereby reducing the burden for patients and caregivers and use of health care resources. These studies highlight the unmet need for improvements in the treatment approach for patients with nAMD. In addition, these findings suggest that patients may prefer less burdensome treatment regimens. Evidence from other treatment settings suggest that saving time and less frequent injection regimen are key reasons underlying patient preference.

Limitations
In addition to the open-label study design, there are several limitations of this investigation that could affect interpretation of results. In Archway, the PPPQ was assessed at week 40 in patients who were diagnosed with nAMD within 9 months of screening and who were responsive to anti-VEGF therapy. Further studies are required to evaluate patient preference with longer-term disease, with longer-term follow-up, and in a clinical practice setting. This is particularly important in patients with nAMD because nAMD is a life-long condition. Patients’ preference for treatment may vary during the course of the disease and be influenced by factors outside those that can be controlled in a clinical trial. Another potential limitation of the current study is the risk of bias. Patients who were open to receiving a surgical procedure agreed to participate in Archway. Further, because patients with the PDS were asked to recall their previous experience with intravitreal injections (ie, before PDS implantation at baseline), results at week 40 may suffer from recall bias. However, because results from the 33.3% of patients with bilateral disease who received intravitreal injections in the fellow eye through week 40 showed that a similarly high proportion of patients (more than 90%) preferred the PDS vs intravitreal injections, the potential impact of this bias on patient preference is assumed to be minimal. Neither Archway nor Ladder was designed to evaluate the number of visits required for monitoring patients treated via PDS. The potential role of decreased monitoring cannot be assessed in this study because patients in the PDS arm came in for monthly visits. Future studies may determine the optimal visit schedule for patients treated with the PDS and investigate the potential of the PDS to reduce the treatment and monitoring burden among patients with nAMD. Another important consideration is assessment of real-world economics of any treatment; hence, appropriate evaluations of preference for the PDS accounting for economics are warranted, and will be feasible in the future given recent approval of the PDS.

Conclusions
Although PDS treatment was preferred over previous intravitreal injections by almost all patients assigned to the PDS, both delivery methods had high treatment satisfaction. Using the content-validated PPPQ in patients with nAMD only assigned to the PDS in Archway, we found that continuous delivery of ranibizumab via the PDS was preferred by almost all patients in the PDS group vs intravitreal injections. Preference for the PDS was supported by findings in patients with bilateral nAMD who received concurrent intravitreal injections in the fellow eye. Most patients assigned to the PDS who experienced ocular SAEs preferred treat-
Treatment Satisfaction With PDS vs Intravitreal Ranibizumab in Patients With nAMD

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