Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Details of the Ladder trial have been reported previously.[1,2] Briefly, patients with neovascular age-related macular degeneration (nAMD) were assigned randomly 3:3:3:2 to treatment with the Port Delivery System with ranibizumab (PDS) filled with ranibizumab 10 mg/mL (n = 58), 40 mg/mL (n = 62), or 100 mg/mL (n = 59), or monthly intravitreal ranibizumab 0.5 mg injections (n = 41) (Lucentis; Genentech, Inc., South San Francisco, CA). For PDS patients, implant refills were performed on a pro re nata (PRN) basis according to predefined criteria and assessed at each monthly visit.[1,2]

PPPQ Content Validation Study
The PDS Patient Preference Questionnaire (PPPQ) is a 3-item questionnaire that was developed to capture patient preference between treatment with the PDS and intravitreal injections of ranibizumab, along with the strength of preference and the reasons for preference.[3] To limit potential confounding factors, including different treatment settings or care providers for patients at different sites, patients were asked patients to think about the PDS treatment itself when making comparisons with intravitreal injections. The PPPQ was developed based on the literature and modified from questionnaires that were used to assess preference for intravenous vs subcutaneous drug administration in oncology settings.[4,5] To establish content validity, a small number of patients in the phase 2 Ladder trial were recruited to provide feedback on the relevance, clarity, and comprehensiveness of the PPPQ using qualitative interviews.[3]

Patient Sample for the PPPQ Content Validation Study
The PPPQ content validation study aimed to enroll 10 patients in Ladder. The PPPQ content validation study included PDS-treated patients from 6 study sites in the United States who were recruited for interviews based on availability, but also to ensure a mix of sex and geographic locations. To be eligible, patients had to have been treated after May 13, 2016, when the implant insertion procedure was optimized in Ladder.[1,2]

Patient Interviews
Patients were invited to participate in a 1:1 interview in person (patient's home or other neutral location) or via phone. A semistructured Interview Guide was used to administer the PPPQ and conduct cognitive debriefing on the questionnaire. Iterative changes were made to the Interview Guide and PPPQ based on patient feedback. All interviews were audio recorded for cross checking of details.

Expert Reviews
Several ophthalmologists experienced with intravitreal injections and the PDS reviewed the questionnaire and proposed revisions. Revisions were also reviewed by experts in outcomes research and clinical trial execution.

Evaluation of Patient Treatment Preference in Ladder Using the MacTSQ
Patients' treatment satisfaction was evaluated in Ladder using the Macular Disease Treatment Satisfaction Questionnaire (MacTSQ).[6] The MacTSQ was assessed in the PDS with ranibizumab 100 mg/mL with PRN refill-exchanges and monthly intravitreal ranibizumab 0.5 mg injection arms. Assessments were made at baseline and months 1, 6, and 9. MacTSQ total score and subscale scores were summarized using appropriate descriptive statistics based on the observed data. Treatment group means, differences, and associated 95% CIs were estimated with an analysis of variance model with randomized treatment as the independent variable.

eResults

PPPQ Content Validation Study Population
Eleven patients were interviewed and included in the PPPQ content validation study (herein described as the PPPQ content validation population; the eleventh patient was added to ensure data for at least the planned 10 patients were collected because the recording equipment failed for 1 patient). Baseline characteristics are shown in the **eTable 1**. The mean age was 78 years, 6 patients were female, and the mean duration of PDS treatment was 15.6 months. All patients included in Ladder had previously been treated with and responsive to intravitreal anti-VEGF treatment; the mean number of previous anti-VEGF injections was 2.9 for all PDS-treated patients.

PPPQ Testing and Validation
Most patient interviews (n = 7) were conducted in person and 4 were conducted by phone. The draft PPPQ for content validity assessment is shown in **eFigure 1A**. Each section was assessed for clarity, relevance, and comprehensiveness. PPPQ version 1 (**eFigure 1A**) was used for interviews 1 to 5, version 2 for interviews 6 to 11, and version 3 for interviews 10 and 11. The final version of the PPPQ is shown in **eFigure 1B**, with revisions highlighted.

Regarding the PPPQ context statement and instructions, patients provided their understanding of the terms used. The meaning of macular degeneration came across clearly. However, there was confusion about the meaning of "intravitreal injection," with 5 patients having difficulty defining the term or mixing it up with implant refills, so it was revised for PPPQ version 3 to "a shot or injection in your eye" and further clarified to "injection in your eye" for the final version. Most patients were clear about the definition of the PDS refill and how it related to the implant. "Treatment setting" was mainly understood to be the place to see a doctor; however, 3 patients were confused by the term and thought it related to the treatment itself, so it was changed to "doctor's office" for the final version. Patients' understanding of the 3 PPPQ items was also reviewed, including the following items. Item 1: this question was revised to remove "all things considered" for the final revised PPPQ to leave a simpler and clearer question based on review by the outcomes research experts. Item 2: there were no changes for the question or response options regarding strength of preference. Item 3: patients seemed to understand the question, although 1 (patient 9) could not define "emotionally distressing" and so the term was revised to "less worry or nervousness" for version 3. The second response option was simplified to "requires less time for treatment" and the 2 terms "less discomfort during treatment" and "less discomfort following treatment" were combined to 1 simpler term ("less discomfort") for version 2. In addition, although patients understood the response options, 2 patients declined to choose a second reason and 3 would have chosen more than 2 reasons; therefore, an amendment was made to the final PPPQ so that rather than choosing the 2 main reasons, patients were asked to choose all that applied from the list of 5 reasons.

Overall, with some minor modifications for clarity, patients thought the PPPQ questions were understandable, clear, and relevant.

Treatment Preference and Strength of Preference in the PPPQ Content Validation Population

Ten of the 11 patients who participated in the PPPQ content validation study preferred treatment with the PDS compared with intravitreal injections of ranibizumab (**eFigure 2A**). Patients who had only 1 refill-exchange procedure had more difficulty deciding if they had a preference for PDS or intravitreal injection; however, most expressed a clear preference. Patients had no difficulty in remembering their previous intravitreal injection treatment, as well as more recent treatments, including the PDS (even if it was >10 months before the interview). In addition, most recalled specifically when they received the PDS.

Of the 10 patients who expressed a preference for the PDS, 8 reported a "very strong" preference, 1 reported a "fairly strong" preference, and the other was "not very strong" (**eFigure 2B**); the most frequently cited reasons for their preference were "fewer treatments" and "less discomfort". For the 1 patient who expressed a preference for intravitreal injections, the strength of preference was very strong (**eFigure 2B**); this patient reported that "they're faster and they're over" with regard to intravitreal injections. The 2 main reasons given by this patient for preference were "less discomfort" and "less worry or nervousness."

Of the 11 patients evaluated for the PPPQ, 5 (45%) had bilateral nAMD. Of these, all 5 expressed a preference for PDS and 4 stated that their preference for PDS was "very strong." Reasons for preference for the PDS were "fewer treatments", reported by 3 patients; "requires less time for single treatment visit", reported by 2 patients; and "less emotionally distressing" and "less discomfort", reported by 1 patient each (1 patient only reported 1 reason as "requires less time" but did state that all reasons applied).

Patient Treatment Preference in Ladder Using MacTSQ

All patients in the PDS 100 mg/mL (n = 59) and monthly intravitreal ranibizumab 0.5 mg injection (n = 41) arms in Ladder were included in the analysis for MacTSQ. In both treatment arms, patients had high overall treatment satisfaction with both treatments as observed in both MacTSQ total and subscale scores at month 1 (**eFigure 3** and **eTable 3**). High treatment satisfaction continued at months 6 and 9 in both treatment arms. Treatment satisfaction was also high for PDS patients with and without ocular SAEs (**eTable 4**). There were no ocular SAEs in the monthly intravitreal ranibizumab 0.5 mg injection arm (**eTable 4**).

eReferences

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eTable1. Baseline Characteristics and Demographics for the PPPQ Content Validation Population

Characteristic	PPPQ Content Validation Population (N = 11)
Age, y	
Mean (SD)	78 (8.7)
Range	63-95
Sex, n (%)	
Female	6 (55)
Male	5 (45)
Geographic location, n	
Austin	3
Cincinnati	3
Reno	2
Salt Lake City	1
Santa Ana	1
Tampa	1
Duration of PDS treatment, mo[a]	
Mean (SD)	15.6 (2.6)
Range	11-20
Bilateral nAMD, n (%)[a]	
Yes	5 (45)
No	6 (55)

[a]Time of PDS treatment and bilateral disease were self-reported.
Abbreviations: nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; PPPQ, PDS Patient Preference Questionnaire.

eTable 2. MacTSQ Overall Treatment Satisfaction and Subscale Scores From Archway for the PDS 100 mg/mL q24w (n = 248) and Intravitreal Ranibizumab 0.5 mg q4w Injection (n = 167) Arms for Patients With and Without Ocular SAEs

	Patients With Ocular SAEs				Patients Without Ocular SAEs			
	PDS 100 mg/mL q24w		Intravitreal Ranibizumab 0.5 mg q4w		PDS 100 mg/mL q24w		Intravitreal Ranibizumab 0.5 mg q4w	
	n	Mean	n	Mean	n	Mean	n	Mean
Week 40								
Overall treatment satisfaction score	12	64.8	2	63.0	225	68.2	157	66.2
Treatment convenience, information provision, and general satisfaction subscale score	12	33.6	2	34.0	222	34.7	156	34.1
Impact of treatment subscale score	12	31.5	2	29	225	33.5	157	32.0

The overall MacTSQ score is on a scale of 1 to 72, with scores of at least 60 indicating high satisfaction. Each MacTSQ subscale is on a scale of 1 to 36, with scores of at least 30 indicating high satisfaction.

Abbreviations: MacTSQ, Macular Disease Treatment Satisfaction Questionnaire; PDS, Port Delivery System with ranibizumab; q4w, every 4 weeks; q24w, every 24 weeks; SAE, serious adverse event.

eTable 3. Difference in MacTSQ Overall Treatment Satisfaction Subscale Scores From Ladder for the PDS 100 mg/mL PRN (n = 59) and Monthly Intravitreal Ranibizumab 0.5 mg Injection (n = 41) Arms

	PDS 100 mg/mL PRN		Monthly Intravitreal Ranibizumab 0.5 mg		Difference (95% CI)
	n	Mean	n	Mean	
Month 1					
Overall treatment satisfaction score	59	67.3	41	65.3	2.0 (–1.1 to 5.1)
Treatment convenience, information provision, and general satisfaction subscale score	57	34.2	41	34.1	0.1 (–1.2 to 1.4)
Impact of treatment subscale score	59	32.9	41	31.1	1.8 (–0.2 to 3.8)
Month 6					
Overall treatment satisfaction score	51	69.0	41	67.0	2.0 (–0.0 to 4.0)
Treatment convenience, information provision, and general satisfaction subscale score	51	34.8	41	34.5	0.3 (–0.6 to 1.1)
Impact of treatment subscale score	53	34.2	41	32.5	1.7 (–0.4 to 3.1)
Month 9					
Overall treatment satisfaction score	52	69.0	36	67.7	1.3 (–0.5 to 3.2)
Treatment convenience, information provision, and general satisfaction subscale score	50	34.8	36	34.9	–0.2 (–0.9 to 0.6)
Impact of treatment subscale score	52	34.2	36	32.8	1.5 (0.2 to 2.8)

The overall MacTSQ score is on a scale of 1 to 72, with scores of at least 60 indicating high satisfaction. Each MacTSQ subscale is on a scale of 1 to 36, with scores of at least 30 indicating high satisfaction.
Abbreviations: MacTSQ, Macular Disease Treatment Satisfaction Questionnaire; PDS, Port Delivery System with ranibizumab; PRN, pro re nata.

eTable 4. MacTSQ Overall Treatment Satisfaction and Subscale Scores From Ladder for the PDS 100 mg/mL PRN (n = 179) and Monthly Intravitreal Ranibizumab 0.5 mg Injection (n = 41) Arms for Patients With and Without Ocular SAEs

	Patients With Ocular SAEs	Patients Without Ocular SAEs

	PDS 100 mg/mL PRN		Monthly Intravitreal Ranibizumab 0.5 mg		PDS 100 mg/mL PRN		Monthly Intravitreal Ranibizumab 0.5 mg	
	n	Mean	n	Mean	n	Mean	n	Mean
Month 1								
Overall treatment satisfaction score	9	59.1	-	-	165	67.7	41	65.3
Treatment convenience, information provision, and general satisfaction subscale score	9	31.3	-	-	165	34.5	41	34.1
Impact of treatment subscale score	9	27.8	-	-	165	33.2	41	31.1
Month 6								
Overall treatment satisfaction score	7	67.6	-	-	157	68.5	41	67.0
Treatment convenience, information provision, and general satisfaction subscale score	7	33.9	-	-	157	34.6	41	34.5
Impact of treatment subscale score	7	33.7	-	-	157	33.9	41	32.5
Month 9								
Overall treatment satisfaction score	7	67.0	-	-	147	68.0	36	67.7
Treatment convenience, information provision, and general satisfaction subscale score	7	34.9	-	-	147	34.5	36	34.9
Impact of treatment subscale score	7	32.1	-	-	147	33.5	36	32.8

The overall MacTSQ score is on a scale of 1 to 72, with scores of at least 60 indicating high satisfaction. Each MacTSQ subscale is on a scale of 1 to 36, with scores of at least 30 indicating high satisfaction.

Abbreviations: MacTSQ, Macular Disease Treatment Satisfaction Questionnaire; PDS, Port Delivery System with ranibizumab; PRN, pro re nata; SAE, serious adverse event.

eFigure 1. Draft (A) and Final (B) PPPQ for Content Validity Assessment.

Text in red in (B) indicates final changes compared with version 1 of the PPPQ. PDS indicates Port Delivery System with ranibizumab; and PPPQ, PDS Patient Preference Questionnaire.

A

You have now been treated with a drug for macular degeneration in two different ways:

1. through a needle injected into the back part of your eye, called an intravitreal injection, and
2. through a device implanted in your eye, called a Port Delivery System, with a refill procedure once every six months.

Please answer the following questions about your treatment experiences and your preferences.

Think about the treatment itself, rather than the treatment setting or care provider. There are no right or wrong answers.

1) All things considered, which method of administration did you prefer?
☐ Intravitreal injections ☐ Port Delivery System ☐ No preference

2) If you have a preference for one of the administration routes, how strong is this preference?
☐ Very strong ☐ Fairly strong ☐ Not very strong

3) If you have a preference for one of the administration routes, what are the TWO main reasons for your preference?
☐ Less emotionally distressing
☐ Requires less time for a single treatment visit
☐ Less discomfort during treatment
☐ Less discomfort following treatment
☐ Fewer treatments
☐ Other reason

B

You have now been treated with a drug for macular degeneration in two different ways:

1. through an injection in your eye, called an intravitreal injection, and
2. through a device implanted in your eye, called a Port Delivery System, with a refill procedure once every six months.

Please answer the following questions about your treatment experiences and your preferences.

Think about the treatment itself, rather than the doctor's office or care provider. There are no right or wrong answers.

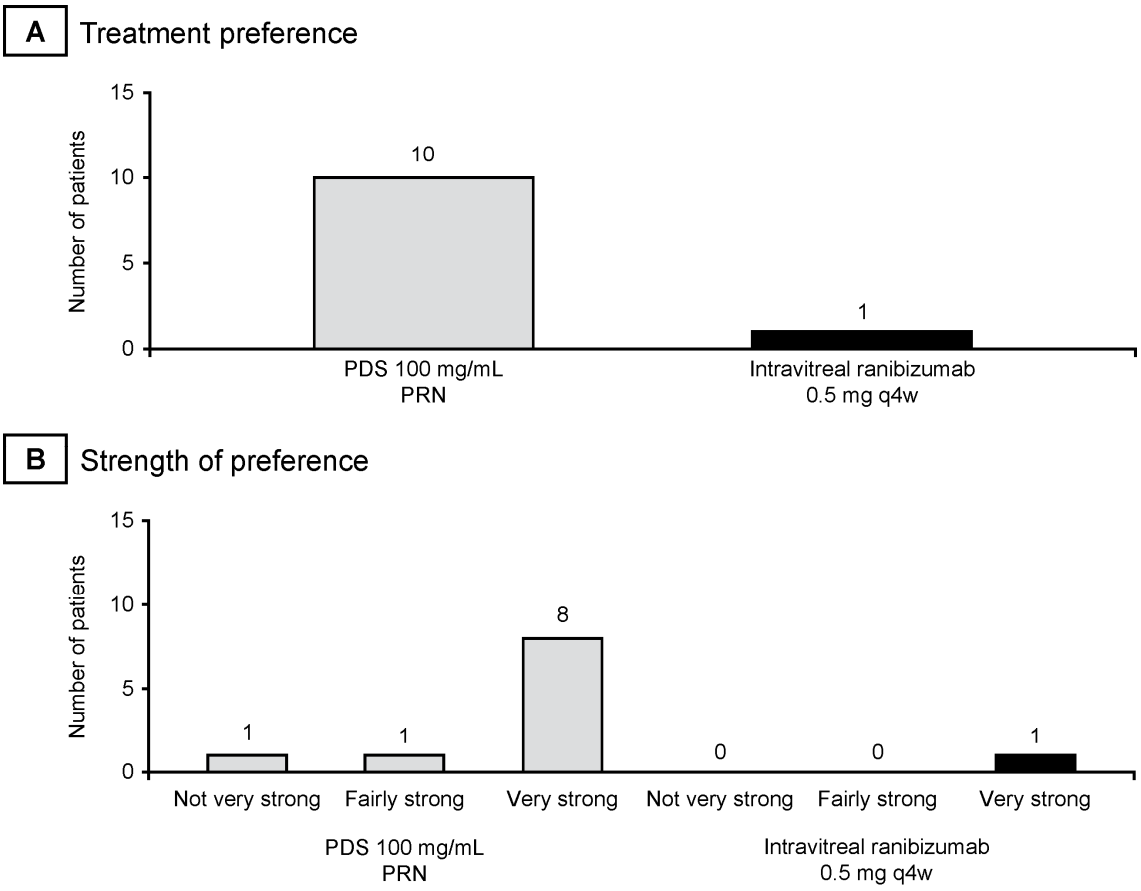
1) Which method of administration did you prefer?
☐ Intravitreal injections ☐ Port Delivery System ☐ No preference

2) If you have a preference for one of the administration routes, how strong is this preference?
☐ Very strong ☐ Fairly strong ☐ Not very strong

3) If you have a preference for one of the administration routes, what are the main reasons for your preference?
Please choose all that apply:
☐ Less worry or nervousness
☐ Requires less time for treatment
☐ Less discomfort
☐ Fewer treatments
☐ Other reason

eFigure 2. Treatment Preference (A) and Strength of Preference (B) for the PPPQ (PPPQ Content Validation Population; n = 11).

PDS indicates Port Delivery System with ranibizumab; PPPQ, PDS Patient Preference Questionnaire; PRN, pro re nata..



eFigure 3. MacTSQ Overall Treatment Satisfaction (A) and Subscale Scores (B) From Ladder for the PDS 100 mg/mL PRN (n = 59) and Monthly Intravitreal Ranibizumab 0.5 mg Injection (n = 41) Arms.

Error bars represent the 95% CI. The overall MacTSQ score is on a scale of 1 to 72, with scores of at least 60 indicating high satisfaction. Each MacTSQ subscale is on a scale of 1 to 36, with scores of at least 30 indicating high satisfaction. MacTSQ indicates Macular Disease Treatment Satisfaction Questionnaire; PDS, Port Delivery System with ranibizumab; and PRN, pro re nata.