Port Delivery System With Ranibizumab (PDS) for Continuous Treatment in Diabetic Retinopathy (DR) Without Centre-Involved Diabetic Macular Edema (CI-DME): 2-Year Data From the Phase 3 Pavilion Trial

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Disclosures

Author Disclosures

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- KT: Employment: F. Hoffmann-La Roche Ltd.
- PL : Employment: Genentech, Inc.

Study and Product Disclosures

- The Port Delivery System with ranibizumab (PDS) has been approved by the US Food and Drug Administration for the treatment of nAMD in adults who have previously responded to ≥ 2 anti-VEGF injections. Please note that the PDS has not been approved for use outside of the United States
- **The US Food and Drug Administration has issued a boxed warning for the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab[1]**
- This study includes research conducted on human subjects
- Institutional Review Board approval was obtained prior to study initiation
- Funding was provided by Genentech, Inc., a member of the Roche Group, for the study and third-party writing assistance, which was provided by Jeannine Delwiche, PhD, of Envision Pharma Group

nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; VEGF, vascular endothelial growth factor. 1. Susvimo [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2022.

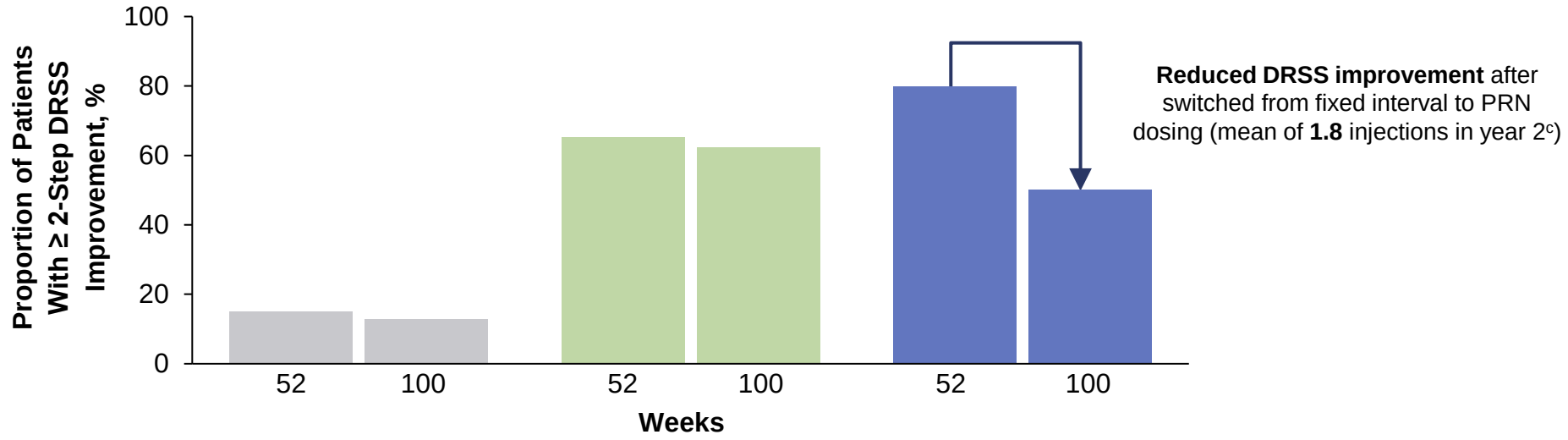
Anti-VEGF Treatment Can Improve Diabetic Retinopathy in terms of DRSS

PANORAMA Trial[1]

Moderately severe to severe NPDR without CI-DME, **DRSS level 47–53**, BCVA ≥ 20/40

Sham | IVT aflibercept Q16W[a] | IVT aflibercept Q8W, with switch to PRN dosing in year 2[b]

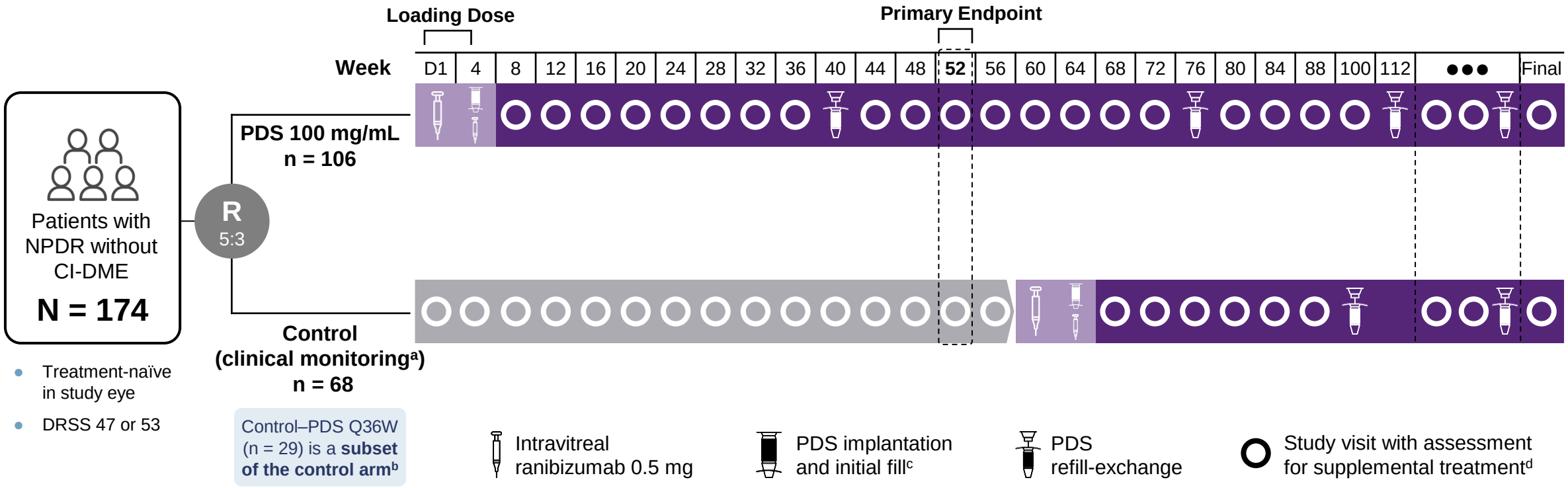
≥ 2-Step DRSS Improvement



Can the **clinical benefits** of intravitreal anti-VEGF monotherapy be achieved with **reduced treatment burden?**

[a] After 3 initial monthly doses and one 8-week interval. [b] After 5 initial monthly doses. [c] Mean number of injections in the IVT aflibercept Q8W/PRN arm was 1.8 in year 2 (week 52 –100). BCVA, best-corrected visual acuity; CI-DME, center-involved diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale; IVT, intravitreal; NPDR, nonproliferative diabetic retinopathy; PRN, pro re nata (as needed); Q8W, every 8 weeks; Q16W, every 16 weeks; VEGF, vascular endothelial growth factor. 1. Brown DM et al. *JAMA Ophthalmol*. 2021;139(9):946-955.

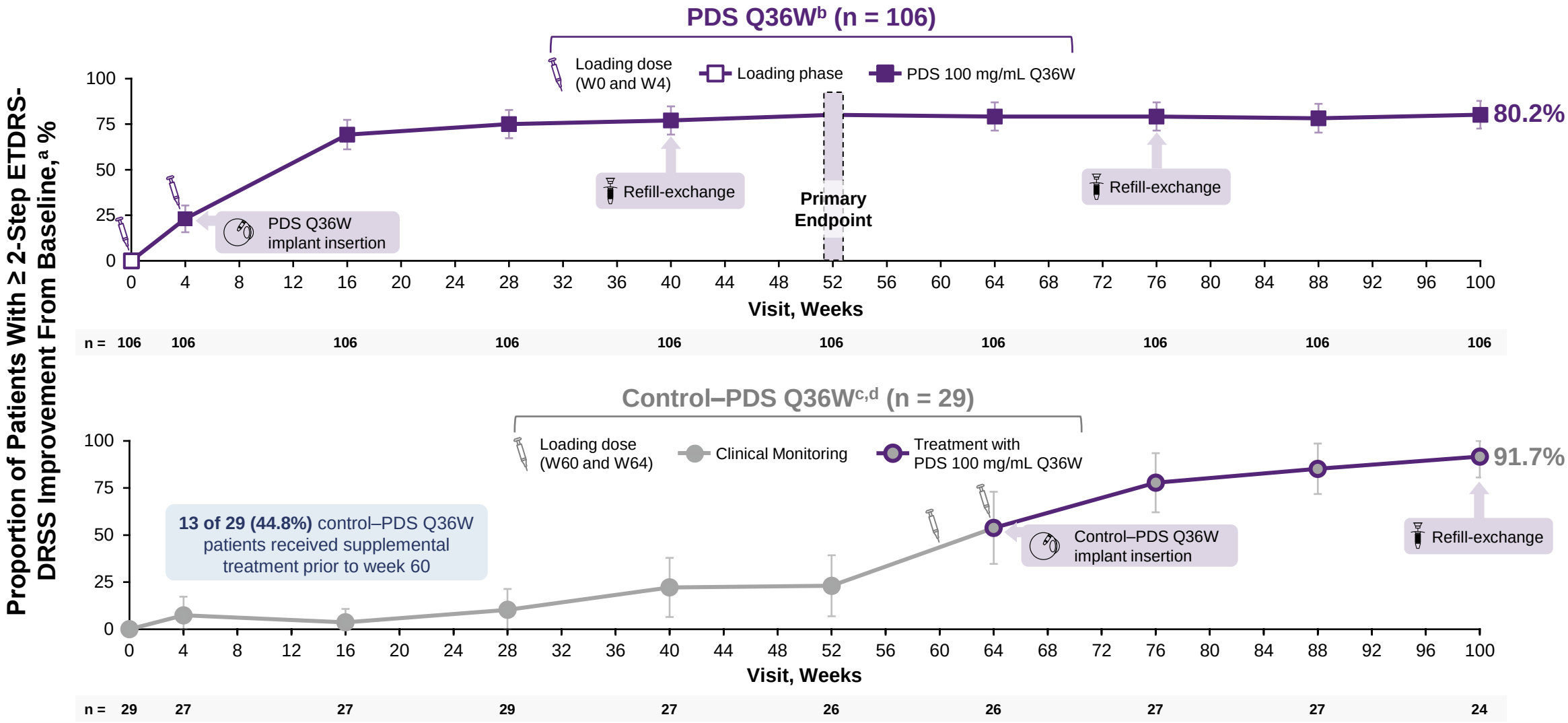
Pavilion Phase 3 Trial: Designed to Evaluate the Efficacy, Safety, and Pharmacokinetics of PDS Q36W for Nonproliferative DR



Primary Endpoint **Superior efficacy of PDS Q36W compared with control,** based on proportion of patients who achieve ≥ 2-step ETDRS-DRSS improvement from baseline at week 52

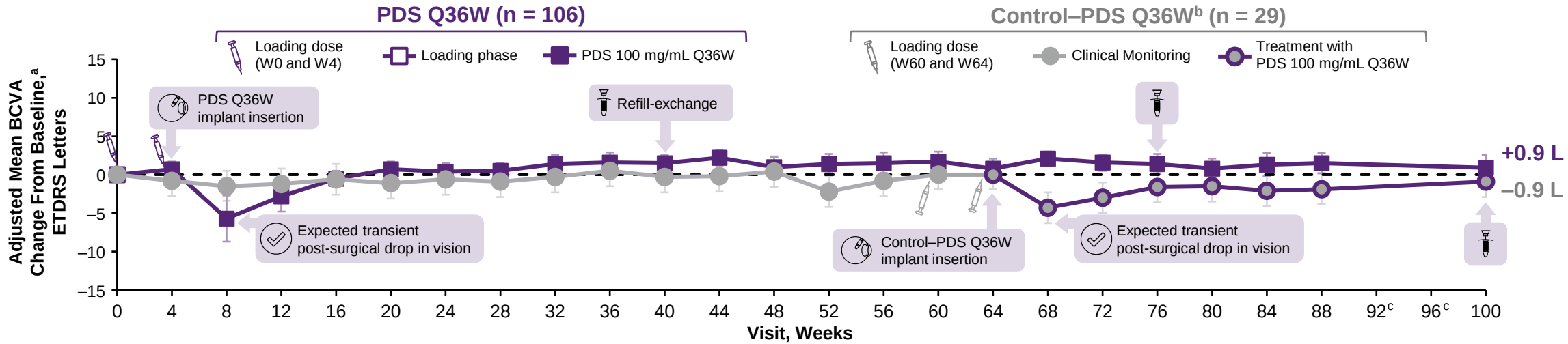
Pavilion clinical trial [NCT04503551]. [a] Study visits Q4W for observation and comprehensive clinical monitoring through week 60. [b] Control–PDS Q36W arm is a subset of control arm (29 of 68 control arm patients were implanted prior to the surgery pause and included in the control–PDS Q36W arm). [c] The PDS implant was surgically inserted 1–14 days after the second loading dose; additional visits for safety assessments 1 and 7 days after implant insertion procedure. [d] Patients were eligible to receive supplemental treatment with intravitreal ranibizumab 0.5 mg at each Q4W visit before week 60 (control), or at any non–refill-exchange visit (PDS Q36W) if any of the following criteria were met in the study eye as assessed by investigator: i) presence of CI-DME (CST ≥ 325 µm on SD-OCT; ii) development of PDR or ASNV. ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic macular edema; CST, central subfield thickness; D, day; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q36W, every 36 weeks; R, randomization; SD-OCT, spectral-domain optical coherence tomography.

PDS Q36W Maintained ≥ 2-Step DRSS Improvement Through Week 100 and Enabled Gains in Control–PDS Q36W Arm

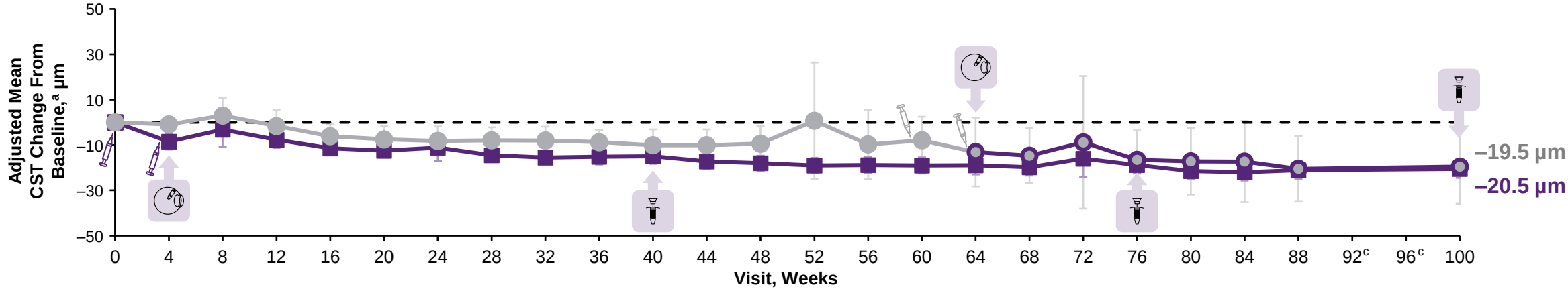


Pavilion clinical trial [NCT04503551]. ITT (PDS Q36W arm) and implanted comparator (control–PDS Q36W arm) populations. Vertical bars represent 95% CI. 95% CI is a rounding of 95.04% CI and estimates below 0% or above 100% are imputed as 0% or 100% respectively. [a] Baseline is the last available value on or prior to study day 1. [b] Patients who receive supplemental treatments, prohibited therapy, or PRP are considered nonresponders regardless of their observed outcome after the corresponding visit. Missing values not preceded by these intercurrent events are imputed using the last observation carried forward method. [c] All observed data are included in the analysis regardless of whether or not a patient has experienced an intercurrent event. Missing data are not imputed. [d] Control–PDS Q36W arm is a subset of control arm (29 of 68 control arm patients were implanted prior to the surgery pause and included in the control–PDS Q36W arm). CI, confidence interval; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intent-to-treat; PDS, Port Delivery System with ranibizumab; PRP, panretinal photocoagulation; Q36W, every 36 weeks; W, week.

BCVA Maintained and Sustained CST Decrease in Both Arms Following PDS Implantation Through Week 100



PDS Q36W n =	100	99	100	98	97	93	96	95	92	91	96	88	93	95	92	91	86	90	88	93	90	89	89		90
Control–PDS Q36W n =	29	28	28	29	28	28	28	29	29	27	27	26	27	26	27	29	28	28	26	28	27	27	29		28

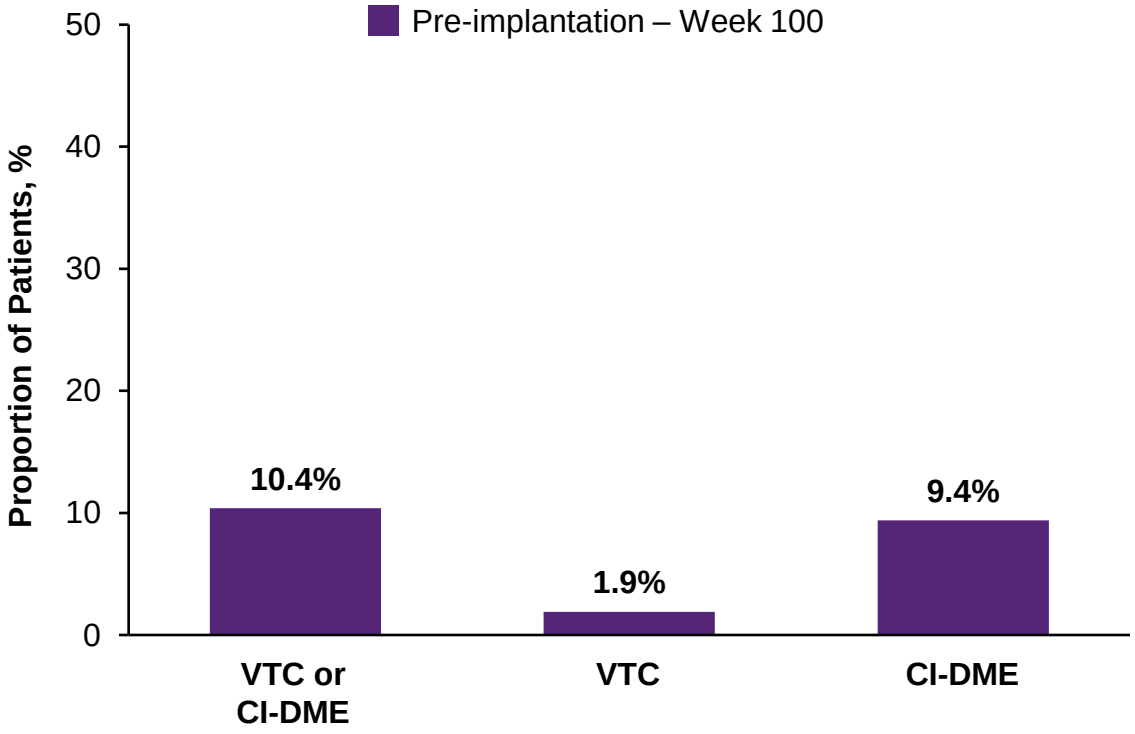


PDS Q36W n =	100	99	96	97	97	91	96	94	93	91	95	88	92	93	92	91	85	90	87	92	90	89	89		89
Control–PDS Q36W n =	29	28	28	29	27	28	28	29	29	27	26	26	27	25	27	29	28	28	26	28	27	27	29		27

Pavilion clinical trial [NCT04503551]. ITT (PDS Q36W arm) and implanted comparator (control–PDS Q36W arm) populations. For the MMRM analysis, the model adjusted for visit, baseline BCVA (upper graph) or baseline CST (lower graph) score (continuous), baseline ETDRS-DRSS level (47 vs 53), baseline intraretinal or subretinal fluid status (present vs absent). 95% CI is a rounding of 95.04% CI. All observed data are included in the analysis regardless of whether or not a patient has experienced an intercurrent event. Missing data are implicitly imputed by the MMRM model, assuming a MAR mechanism. [a] Baseline is the last available value on or prior to study day 1. [b] Control–PDS Q36W arm is a subset of control arm (29 of 68 control arm patients were implanted prior to the surgery pause and included in the control–PDS Q36W arm).). [c] No patient data for weeks 92 or 96 as visit frequency changed from Q4W to Q12W. BCVA, best-corrected visual acuity; CST, central subfield thickness; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intent-to-treat; MAR, missing at random; MMRM, mixed-effect model with repeated measures; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q12W, ever 12 weeks; Q36W, every 36 weeks; W, week.

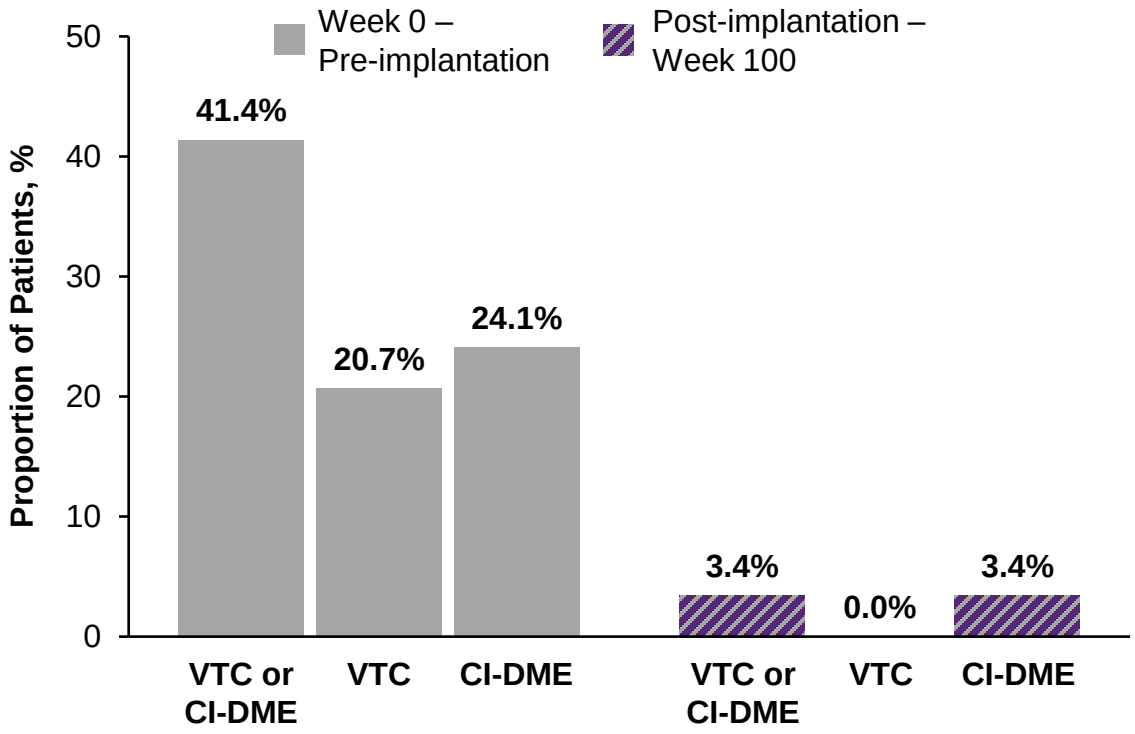
Following PDS Implantation, Proportion of Patients Developing CI-DME and/or Vision-Threatening Complications (PDR or ASNV) is Consistently Low

PDS Q36W (n = 106)



In **PDS Q36W** arm, proportion of patients who develop VTCs and/or CI-DME **consistently low** through week 100

Control–PDS Q36W[b,c] (n = 29)



In **control–PDS Q36W** arm, proportion of patients who developed VTCs and/or CI-DME **decreased after PDS implantation**

Pavilion clinical trial [NCT04503551]. ITT (PDS Q36W arm) and implanted comparator (control–PDS Q36W arm) populations. [a] Protocol-defined CST ≥ 325 µm. [b] Control–PDS Q36W arm is a subset of control arm (29 of 68 control arm patients were implanted prior to the surgery pause and included in the control–PDS Q36W arm). [c] Data is based on any instance of PDR or ASNV or CI-DME, within the defined interval. ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic macular edema; CST, central subfield thickness; ITT, intent-to-treat; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks, VTC, vision-threatening complication.

≥ 99% of Patients Treated With PDS Q36W Did Not Receive Supplemental Treatment Through Each Complete Refill-Exchange Interval

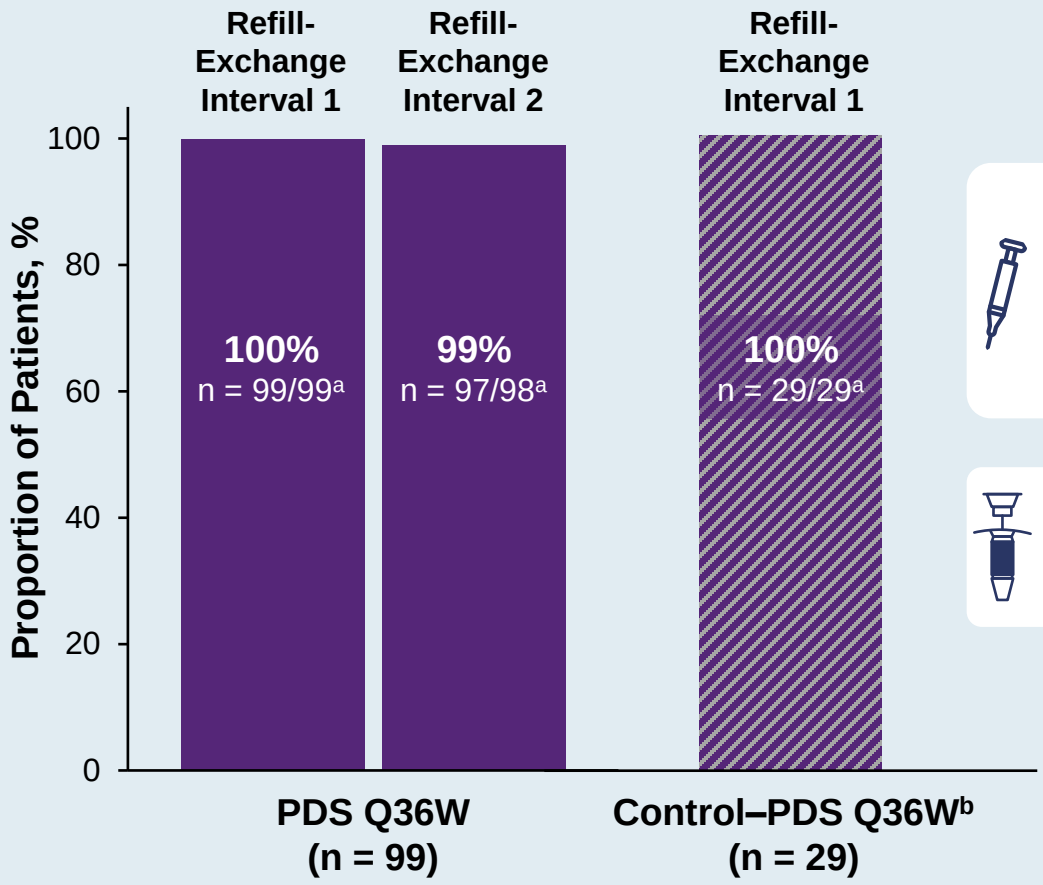
Supplemental Treatment Criteria

Presence of CI-DME, defined as CST ≥ 325 µm on SD-OCT as assessed by investigator

OR

Development of PDR or ASNV, as assessed by investigator

Proportion of Patients Who Did Not Receive Supplemental Treatment After PDS Implantation in Each Complete Refill-Exchange Interval



13 of 29 (44.8%) patients in **control–PDS Q36W arm** received supplemental treatment prior to receiving the implant

Refill-exchange intervals **every 36 weeks** following PDS implantation

Pavilion clinical trial [NCT04503551]. PDS safety population. [a] Number of patients who were assessed for the need of supplemental treatment at least once. [b] Control–PDS Q36W arm is a subset of control arm (29 of 68 control arm patients were implanted prior to the surgery pause and included in the control–PDS Q36W arm. ASNV, anterior segment neovascularization; CI-DME, center-involved diabetic retinopathy with diabetic macular edema; CST, central subfield thickness; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks; SD-OCT, spectral-domain optical coherence tomography.

Ocular Adverse Events of Special Interest

Ocular AESIs in Study Eye From Date of Implant Through CCOD

	All PDS 100 mg/mL Q36W (n = 128)	
	All	Serious[b]
Total number of AE, n	50	6
Total number of patients with ≥ 1 AE, n (%)	36 (28.1)	5 (3.9)
Cataract	19 (14.8)	1 (0.8)
Conjunctival bleb	5 (3.9)	0
Conjunctival erosion	3 (2.3)	1 (0.8)
Conjunctival retraction	2 (1.6)	0
Implant dislocation[a]	**0**	**0**
Endophthalmitis	**1 (0.8)**	**1 (0.8)**
Hyphema	3 (2.3)	0
Retinal detachment	1 (0.8)	1 (0.8)
Vitreous hemorrhage	12 (9.4)	2 (1.6%)

Data **pooled** from both study arms, including events after first loading dose

Patient Outcomes

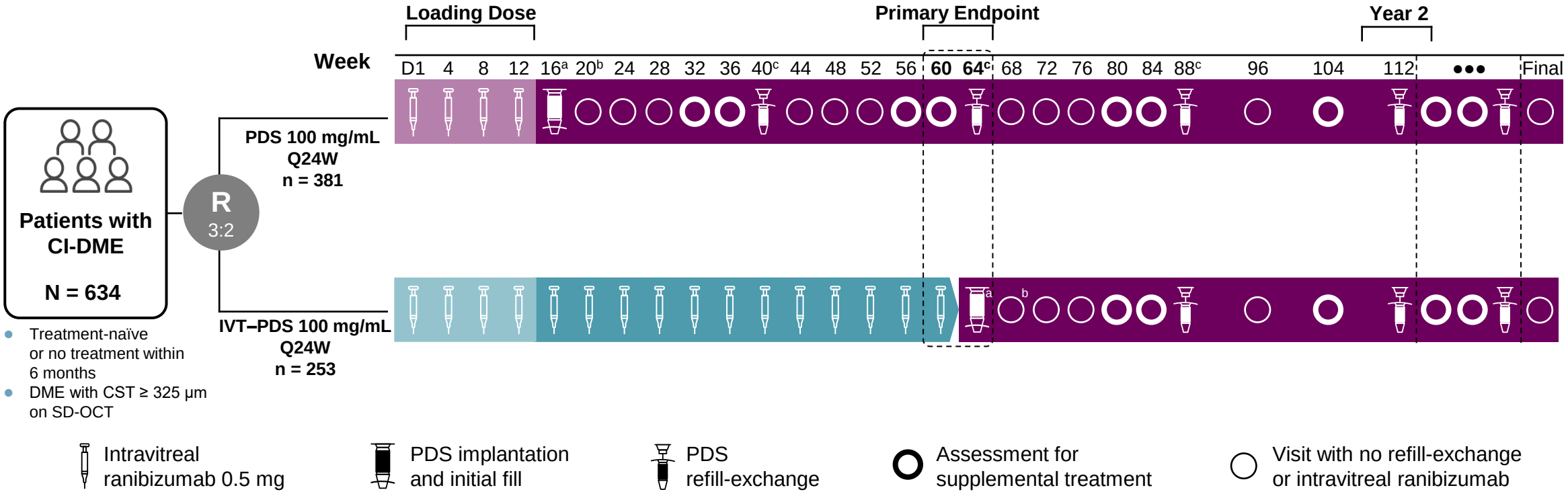
The endophthalmitis event had **resolved** within 20 days

The patient **received a refill-exchange** after successful resolution

The patient's BCVA **recovered** vision back to baseline (20/25 Snellen) after treatment for endophthalmitis

Pavilion clinical trial [NCT04503551]. PDS safety population. Ocular AESIs in study eye from PDS through CCOD (September 6, 2023). [a] "Implant dislocation" is reported in MedDRA as "device dislocation". [b] A serious ocular AESI is an ocular AESI that meets any of the seriousness criteria as defined in the protocol or as defined by ICH guidelines for Good clinical Practice. AE, adverse event; AESI, adverse event of special interest; BCVA, best-corrected visual acuity; CCOD, clinical cut-off date; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks.

PDS With Fixed Refill Exchange Intervals Every 24 Weeks Was Also Investigated in Patients With DME in the Pagoda Phase 3 Trial

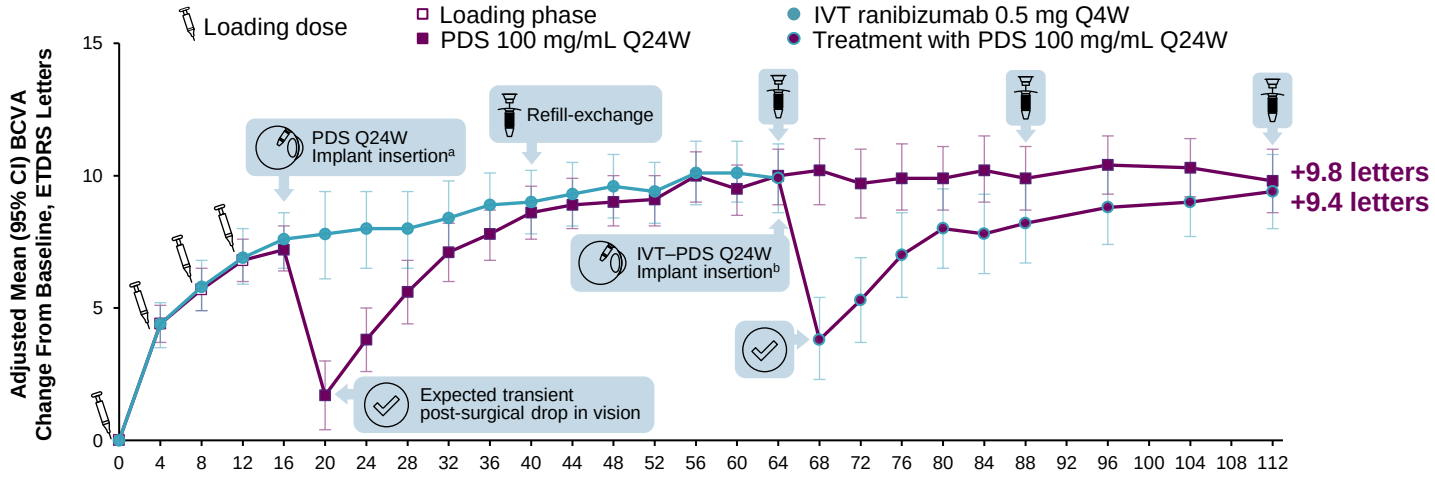


Primary Endpoint **Noninferiority of PDS Q24W** compared with monthly intravitreal ranibizumab 0.5 mg injections based on change in BCVA score from baseline averaged over Weeks 60 and 64

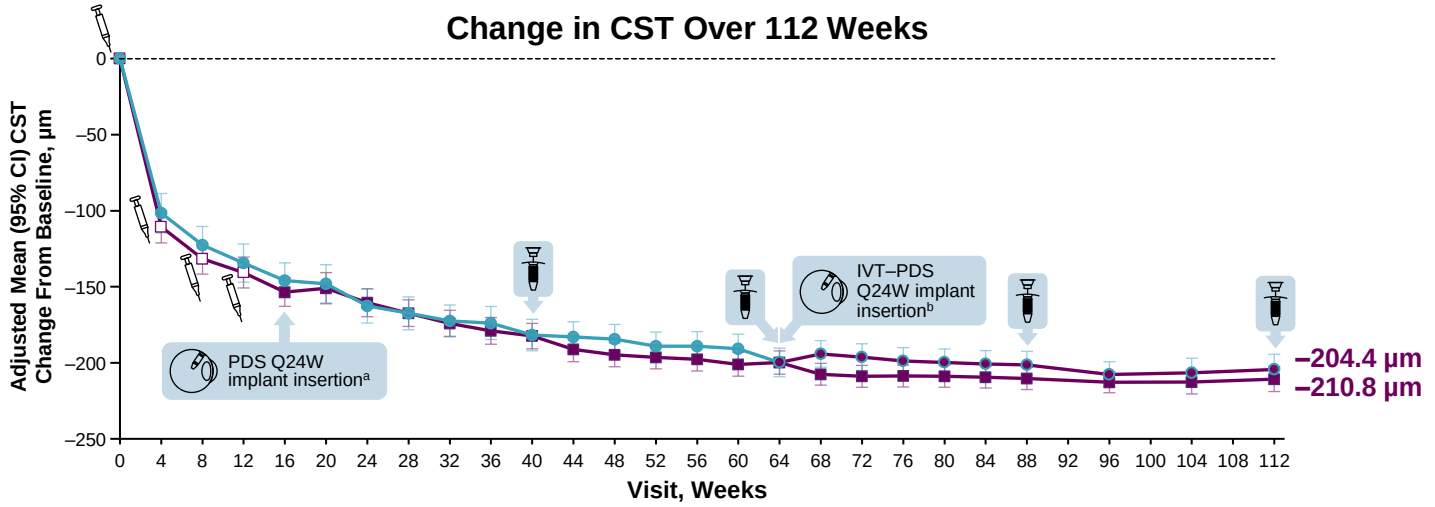
Pagoda clinical trial [NCT04108156]. Adjusted ITT population, patients randomized to PDS treatment who received an implant at week 16 or 20 (PDS arm) and patients randomized to intravitreal ranibizumab treatment who received an implant at week 64 or 68 (IVT–PDS arm). [a] Within 21–35 days since last intravitreal injection; additional visits for safety assessments 1 and 7 days after implantation. [b] Delayed PDS implantation and initial fill if week 16 (PDS Q24W arm) or week 64 (ranibizumab 0.5 mg Q4W arm) is not possible; additional loading dose required at week 16 or week 64; implant insertion procedure must happen within 28 ± 7 days since last intravitreal injection; additional visits for safety assessments 1 and 7 days after implantation. [c] Delayed PDS implantation and initial fill, if applicable. BCVA, best-corrected visual acuity; CI-DME, center-involved diabetic macular edema; CST, central subfield thickness; D, day; DME, diabetic macular edema; ITT, intention to treat; IVT, intravitreal treatment; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; R, randomization; SD-OCT, spectral-domain optical coherence tomography.

PDS Q24W Demonstrated Maintenance of Year 1 Vision and Anatomic Gains Over the Second Year of the Pagoda Phase 3 Trial Through Week 112

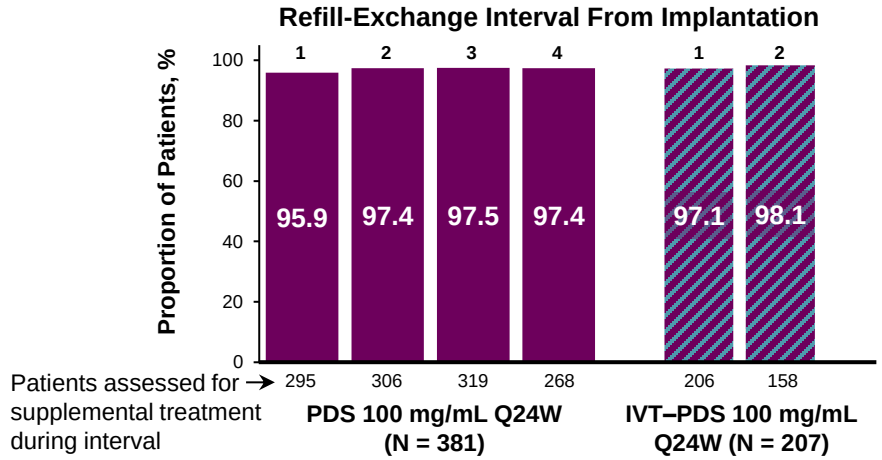
Change in BCVA Over 112 Weeks



Change in CST Over 112 Weeks



Proportion of Patients Who Did Not Receive Supplemental Treatment Through Week 112



Safety Highlights

	All PDS 100 mg/mL Q24W (n = 556)
Conjunctival erosion	12 (2.2)
Conjunctival retraction	7 (1.3)
Implant dislocation[c]	**1 (0.2)**
Endophthalmitis[d]	**4 (0.7)**
Retinal detachment	**4 (0.7)**
Vitreous hemorrhage	56 (10.1)

Pagoda clinical trial [NCT04108156]. Adjusted ITT population (BCVA and CST); ITT (PDS Q24W) and implanted comparator (IVT–PDS Q24W) populations (Supplemental), patients with a PDS implant were eligible for supplemental treatment at weeks 32, 36, 56, 60, 80, 84, 104, and 108; Safety population (Safety), ocular AESIs in the study eye from PDS from day 1 through CCOD (21 August 2023). [a] Due to extenuating circumstances, implant insertion may be delayed beyond week 16. If week 16 is not possible, additional loading dose required at week 16. Implant insertion procedure must happen within 28 ± 7 days since last intravitreal injection. [b] Due to extenuating circumstances, implant insertion may be delayed beyond week 64. If week 64 is not possible, additional loading dose required at week 64. Implant insertion procedure must happen within 28 ± 7 days since last IVT injection. [c] "Implant dislocation" is reported in MedDRA as "device dislocation. [d] A second episode of endophthalmitis was reported in 1 patient on November 28, 2023 (total of 5 events in 4 patients). All patients received the next scheduled refill-exchange as of the CCOD (August 21, 2023). The patient that had the second episode was resolving at the time of reporting (December 12, 2023). AESI, adverse event of special interest; BCVA, best-corrected visual acuity; CCOD, clinical cutoff date; CI, confidence interval; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ITT, intent-to-treat; IVT, intravitreal; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

PDS Demonstrated DR Severity Control and Maintenance Over 2 Years With 1 Refill-Exchange Every 9 Months

DRSS OUTCOMES MAINTAINED WITH PDS Q36W

PDS Q36W **maintained ≥ 2-step DRSS improvement** through week 100 and **enabled DRSS improvements** in control–PDS Q36W arm

DISEASE CONTROL MAINTAINED WITH PDS Q36W

Patients who develop VTCs and/or CI-DME **remained low** through week 100 in PDS Q36W arm, and **decreased after implantation** in control–PDS Q36W arm

NO NEW SAFETY SIGNALS

Updated safety data align with the primary analysis, with **no new safety signals** observed

PDS, the only continuous delivery system that has **demonstrated improvement and maintenance of DR severity in patients with DR without CI-DME** over 2 years, has the potential to provide long-term functionality and anatomic benefits with 1 refill-exchange every 9 months

Similar **positive results have been shown in patients with DME** over 2 years with 1 refill-exchange every 6 months

Pavilion clinical trial [NCT04503551]. CI-DME, center-involved diabetic macular edema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; PDS, Port Delivery System with ranibizumab; Q36W, every 36 weeks; SoC, standard of care; VTC, vision-threatening complications.

Thank You to All Participating Pavilion and Pagoda Investigators, Study Sites, and Patients