Port Delivery System With Ranibizumab in Patients With Diabetic Macular Oedema: Primary Analysis Results of the Phase 3 Pagoda Trial

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On behalf of the Pagoda Investigators

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Key Clinical Question

To present the primary analysis on efficacy and safety from the Phase 3 PAGODA trial with the Port Delivery System with ranibizumab (PDS)

Introduction

- The limitations of intravitreal anti-VEGF therapy are that frequent monitoring and injections are required which impose a high treatment burden and lead to poor treatment adherence in patients. Higher number of injections are known to correlate with vision improvement[1]
- Continuous delivery of ranibizumab using the PDS offers a treatment strategy for DMO that maintains the clinical benefits of intravitreal anti-VEGF therapy while reducing overall treatment and visit burden
- The PDS 100mg/mL with fixed Q24W refill-exchanges has the potential to reliably maintain long-term vision gains with ≤ 2 refill-exchanges per year
- The Phase 2 LADDER[2] and Phase 3 ARCHWAY[3] trials demonstrated that the PDS 100 mg/mL was generally well tolerated and effective in patients with nAMD, providing vision outcomes equivalent to monthly ranibizumab injections with fewer treatment interventions

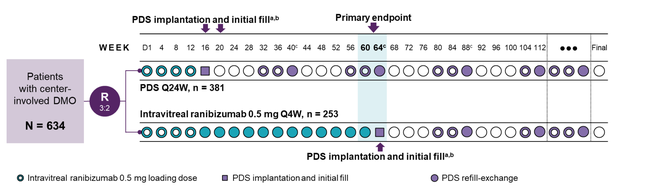
Methods

- PAGODA (NCT04108156) is a phase 3 multicenter, randomized, active treatment–controlled, non-inferiority clinical trial to evaluate the efficacy, safety, and pharmacokinetics of the PDS Q24W compared with intravitreal ranibizumab 0.5 mg injections every 4 weeks (monthly ranibizumab) in patients with DMO
- The primary efficacy objective was to evaluate non-inferiority in efficacy based on change in BCVA from baseline averaged over weeks 60 and 64
- The primary safety objective was to evaluate safety and tolerability based on incidence, severity, and duration of AEs and AESIs
- The primary pharmacokinetic objective was to characterize serum PK profile based on serum concentrations over time and estimated PK parameter values
- Pagoda began in September 2019 and is currently ongoing. Final study visit is week 120

Conclusions

- PDS Q24W was noninferior to ranibizumab 0.5 mg injections Q4W in BCVA change from baseline averaged over weeks 60 and 64
- Continuous delivery of ranibizumab 100 mg/mL with PDS refilled Q24W resulted in visual and anatomic outcomes comparable to ranibizumab 0.5 mg Q4W injections including:
  - Comparable and clinically significant improvements in CST and DRSS
- >95% of PDS patients did not receive supplemental treatment in each treatment interval through week 64
- PDS was generally well tolerated and ocular AESIs were well understood and manageable
- No cases of endophthalmitis or retinal detachment were reported in PDS Q24W patients in this study duration
- The safety profile showed a trend towards a reduction in ocular AESI and ocular SAEs compared to a similar study period in nAMD[3]

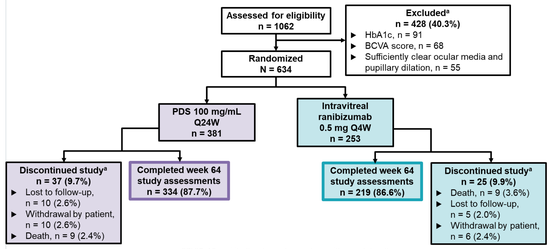
1.Pagoda Phase 3 Trial: Designed to Evaluate Efficacy, Safety, and Pharmacokinetics of PDS Q24W for DMO



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

Every 24-week interval consists of visits X, Y, and Z, with an 8-week interval between each visit until the final visit at end of study: visit X: 8 weeks post refill-exchange; visit Y: 16 weeks post refill-exchange; visit Z: PDS refill-exchange.
[a] PDS 100 mg/mL Q24W (n = 381): implantation and initial fill at baseline (visit 1). Intravitreal ranibizumab 0.5 mg Q4W (n = 253): intravitreal ranibizumab 0.5 mg Q4W at baseline (visit 1) and every 4 weeks thereafter; additional 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. [b] Delayed PDS implantation and initial fill, if applicable. Protocol updates in response to COVID-19 pandemic include patients to continue on monthly ranibizumab and undergo implantation at first allowable opportunity (week 40, 64, 88, etc); minimum 4 loading doses required before implantation (and the last injection within 21–35 days of implantation); safety assessment visits required at days 1 and 7 after implantation; implantation may be delayed 4 weeks , from week 40 to 44 or 64 to 68, under extenuating circumstances, similar to the implant delay allowed at week 20. BCVA, best-corrected visual acuity; COVID-19, coronavirus disease 2019; D, day; DMO, diabetic macular oedema; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; R, randomization.

2.Patient Disposition Through Week 64



COVID-19 had limited impact on data quality and integrity
Robustness of the primary endpoint analysis was assessed through supplementary and sensitivity analyses

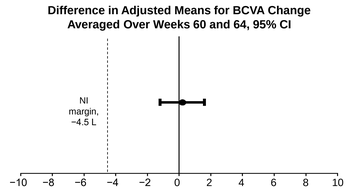
[a] Top 3 reasons by patient numbers included. BCVA, best-corrected visual acuity; COVID-19, coronavirus disease 2019; HbA1c, glycated hemoglobin; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

3.Baseline Ocular Characteristics of the Study Eye Were Generally Well Balanced Across Study Arms

Characteristic	PDS 100 mg/mL Q24W (n = 381)	Intravitreal Ranibizumab 0.5 mg Q4W (n = 253)
BCVA letter score (letters), mean (SD)	65.4 (11.3)	65.1 (11.4)
≥ 64 letters (20/50 Snellen or better) (%)	246 (64.6)	166 (65.6)
CST (µm), mean (SD)	484.9 (133.2)	483.7 (121.8)
ETDRS-DRSS status,[a] n (%)		
DRSS level < 47 NPDR	222 (58.3)	139 (54.9)
DRSS level 47–53 NPDR	132 (34.6)	95 (37.5)
DRSS level ≥ 60 PDR	20 (5.2)	12 (4.7)
Time since first diagnosis of DMO (months), mean (SD)	15.9 (22.9)	17.9 (37.7)
Prior intravitreal anti-VEGF treatment for DR with or without DMO, n (%)	13 (3.4)	9 (3.6)
Lens status:[b] phakic, n (%)	278 (73.0)	186 (73.5)

[a] 7 patients in each arm had baseline DRSS unable to be graded, so totals do not add up to 100%. [b] Lens Status can be phakic, pseudophakic, aphakic or other. No patients reported aphakic or other.BCVA, best-corrected visual acuity; CST, central subfield thickness; DMO, diabetic macular oedema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Score; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; VEGF, vascular endothelial growth factor.

4.Pagoda Primary Endpoint Met: PDS Q24W Was Noninferior to Ranibizumab 0.5 mg Q4W in BCVA Change From Baseline Averaged Over Weeks 60 and 64

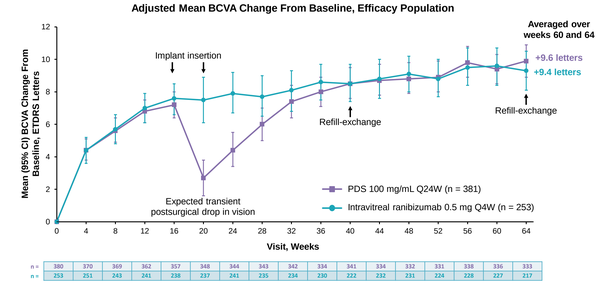


Adjusted Mean Change From Baseline in BCVA Score, (95% CI)	Averaged Over Weeks 60 and 64
PDS 100 mg/mL Q24W	9.6 (8.7, 10.5)
Intravitreal ranibizumab 0.5 mg Q4W	9.4 (8.3, 10.5)
Difference in adjusted means	**0.2 (−1.2, 1.6)**

An equivalence test was not pre-planned. With 95% confidence, the difference in mean change in BCVA was between -1.2 and 1.6 letters. With this tight confidence interval, we consider the difference was clinically equivalent.

Efficacy population. Horizontal bars represent 95% CI. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; L, letters; NI, noninferiority; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

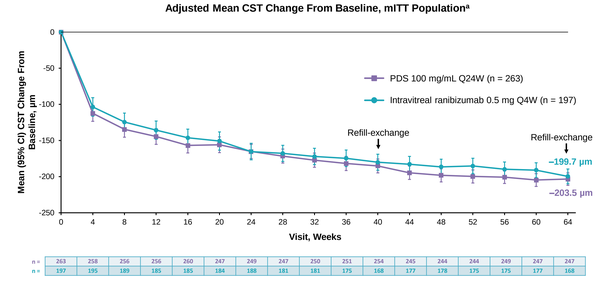
5.PDS Q24W Resulted in Robust Vision Gains Comparable to Ranibizumab 0.5 mg Q4W Through Week 64



n =	380	370	369	362	357	348	344	343	342	334	341	334	332	331	338	336	333
n =	253	251	243	241	238	237	241	235	234	230	222	232	231	224	228	227	217

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

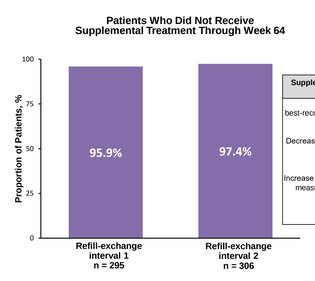
6.PDS Q24W Resulted in Robust CST Reductions Comparable to Ranibizumab 0.5 mg Q4W Through Week 64



n =	263	258	256	256	260	247	249	247	250	251	254	245	244	244	249	247	247
n =	197	195	189	185	185	184	188	181	181	175	168	177	178	175	175	177	168

[a] The mITT population comprised of all patients in the in the efficacy population with the exclusion of all patients in the randomization blocks consisting of PDS patients noncompliant to the protocol-defined PDS insertion schedule due to sponsor-initiated surgery pause.
CST, center subfield thickness; mITT, modified intent-to-treat population; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

7.>95% of PDS Q24W Patients Did Not Receive Supplemental Treatment Through Each Refill-Exchange Interval



Supplemental Treatment Criteria, Assessed at 2 Visits Before Refill-Exchange
Decrease of ≥ 15 letters from the best-recorded BCVA in the study due to the presence of DMO
OR
Decrease of ≥10 letters from the day 1 visit BCVA score, due to the presence of DMO
OR
Increase of ≥ 150 µm in CST on SD-OCT from the lowest CST measurement in the study, due to the presence of DMO
OR
Development of high-risk PDR[a]

[a] Development of high-risk PDR, as defined by any of the following criteria: Any vitreous or preretinal haemorrhage, neovascularization at disc ≥ 1/3 disc area, neovascularization elsewhere ≥ 1/2 disc area within an area equivalent to the mydriatic ETDRS 7 fields.BCVA, best-corrected visual acuity; CST, central subfield thickness; DMO, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks.
SD-OCT, spectral-domain optical coherence tomography.

8.PDS Treatment Was Generally Well Tolerated Through Week 64

	PDS 100 mg/mL Q24W (n = 320)	Intravitreal Ranibizumab 0.5 mg Q4W (n = 314)
	Overall	Overall
Total number of AE, n	1915	1387
Total number of patients with ≥ 1 AE, n (%)	316 (98.8)	264 (84.1)
Ocular AEs: study eye	294 (91.9)	140 (44.6)
Nonocular AEs	221 (69.1)	221 (70.4)
Deaths	4 (1.3)	12 (3.8)
Ocular AESIs in study eye	88 (27.5)	28 (8.9)
APTC events	11 (3.4)	22 (7.0)

Safety population.AE, adverse event; AESI, adverse event of special interest; APTC, Antiplatelet Trialists' Collaboration; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

9.Ocular AESIs Were Well Understood and Manageable No Cases of Endophthalmitis or Retinal Detachment Were Reported in the PDS Q24W Arm After Implantation Through Week 64

	PDS 100 mg/mL Q24W (n = 320)		Intravitreal Ranibizumab 0.5 mg Q4W (n = 314)	
	Overall		Overall	
	All	Serious	All	Serious
Total number of AE, n	110	12	34	2
Total number of patients with ≥ 1 AE, n (%)	88 (27.5)	9 (2.8)	28 (8.9)	2 (0.6)
Cataract	35 (10.9)	1 (0.3)	23 (7.3)	1 (0.3)
Conjunctival bleb	25 (7.8)	4 (1.3)	0	0
Conjunctival erosion	6 (1.9)	5 (1.6)	0	0
Conjunctival retraction	4 (1.3)	1 (0.3)	0	0
Implant dislocation*	1 (0.3)	1 (0.3)	0	0
Endophthalmitis	0	0	1 (0.3)	1 (0.3)
Hyphema	6 (1.9)	0	0	0
Retinal detachment	0	0	0	0
Vitreous hemorrhage	31 (9.7)	1 (0.3)	5 (1.6)	0

One case of septum dislodgement was reported as a device deficiency in the PDS arm through week 64
*Implant dislocation" is reported in MedDRA as "device dislocation".

Safety population.AE, adverse event; AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

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References

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2. Campochiaro P et al. Ophthalmology 2019 Aug;126(8):1141-1154
3. Holekamp NM et al. Ophthalmology. 2022 Mar;129(3):295-307

Financial Disclosures

- AMK: Consultant: Abbvie, Adverum Biotechnologies, AGTC, Alimera Sciences, Allergan, Apellis Pharmaceuticals, Arrowhead, Pharmaceuticals, AsclepiX Therapeutics, Aviceda Therapeutics, Bausch & Lomb , BroadWing Bio, Cholgene Therapeutics, 4D Molecular Therapeutics, Eyepoint Pharmaceuticals, Frontera Therapeutics, Gemini Pharmaceuticals, Genentech, Graybug Vision, Gyroscope Therapeutics, Iveric Bio, Janssen Pharmaceuticals, Kato Pharmaceuticals, Kartos Therapeutics, Kodiak Sciences, Kriya Therapeutics, Ocular Therapeutix, Oculis, Ocuterra, Opthea, Oxurion, Novartis, Perfuse, PolyPhotonix, Ray Therapeutics, Recens Medical, Regeneron Pharmaceuticals, REGENXBIO, Roche, Stealth Biotherapeutics Therapeutics, Thea Pharma, UNITY Biotechnology, Vanotech; Research Support: Adverum Biotechnologies, Annexon Biosciences, Apellis Pharmaceuticals, AsclepiX Therapeutics, 4D Molecular Therapeutics, Gemini Pharmaceuticals, Genentech, Graybug Vision, Gyroscope Therapeutics, Iveric Bio, Janssen Pharmaceuticals, Kodiak, Neurotech, NGM Biopharmaceuticals, Novartis, Ocular Therapeutix, Oculis, Ocuterra, Opthea, Oxurion, Recens Medical, REGENXBIO, Roche, UNITY Biotechnology, Speaker: Abbvie, Apellis, Genentech, Novartis; Financial support: Aviceda Therapeutics, PolyPhotonix, Recens Medical
- VM, CQR, SG, SD, AB, MR, PL: Employee: Genentech, Inc.
- PAC: Grants or Contracts: Ashvattha, Sanofi/Genzyme, Mallinckrodt, Oxford Biomedica, REGENXBIO; Consulting: Asclepix, Ashvattha, Bausch + Lomb, Catawba Research, Celanese, Clearside, Cove, Exgenesisbio, Gyroscope, Wave Life Sciences; Payment or Honoraria: Allegro, Asclepix, Ashvattha, Bausch + Lomb, Catawba Research, Celanese, Clearside, Exgenesisbio, Exonate, Genentech/Roche, Gyroscope, Merck & Co., Perfuse, Wave Life Sciences; Stock/Stock Options: Cove, Allegro, Graybug

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 / Roche/Genentech has voluntarily recalled the PDS (Susvimo) Ocular Implant and Insertion Tool Assembly, including the ranibizumab drug vial and initial fill needle (lot numbers 34991B8 and 3523071), which are sold together, and paused implantations including in ongoing global clinical trials
- 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 ranibizumab1
- This study includes research conducted on human subjects
- Institutional Review Board approval was obtained prior to study initiation
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