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

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Key Clinical Question

What is the pharmacokinetic (PK) profile of ranibizumab delivered via the Port Delivery System with ranibizumab (PDS) implant with fixed refill-exchanges every 24 weeks (PDS Q24W) in patients with neovascular age-related macular degeneration (nAMD)?

Introduction

- The PDS is an innovative drug delivery system that includes a pars plana implant for continuous delivery of ranibizumab into the vitreous[1,2]
- It is approved by the US Food and Drug Administration for the treatment of nAMD in adults who have previously responded to ≥ 2 anti–vascular endothelial growth factor (VEGF) injections[1]
- In the phase 3 Archway trial (NCT03677934) in patients with nAMD, serum and aqueous humour samples were collected to characterise the PK profile of ranibizumab delivered via the PDS Q24W[3]

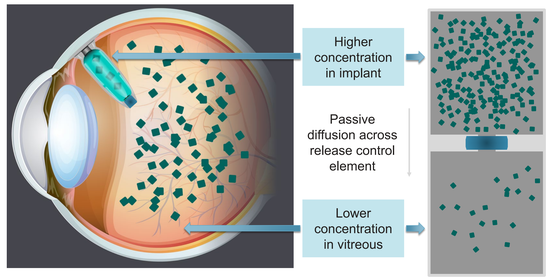
Methods

- In the Archway trial, patients with nAMD were randomised to PDS Q24W or intravitreal ranibizumab 0.5 mg injections every 4 weeks (monthly ranibizumab)[3]
- Serum PK samples were collected at randomisation and at weeks 4, 24, 36 and 96, with additional samples taken at selected sites and timepoints
- Optional aqueous humour samples were collected at randomisation and at weeks 24, 28, 48, 52, 72, 76 and 96
- Ranibizumab concentrations were measured using a validated enzyme-linked immunosorbent assay

Conclusions

- PDS is long lasting over 24 weeks
  - The PDS continuously releases ranibizumab over the Q24W treatment interval at steady concentrations
- PDS is comparable with intravitreal delivery
  - Ranibizumab concentrations with PDS Q24W are within the range experienced with monthly intravitreal ranibizumab 0.5 mg injections
- PDS has consistent PK profiles
  - Aqueous humour PK profiles were consistent with serum PK profiles
- PDS maintained vision while reducing treatment burden through continuous delivery of ranibizumab

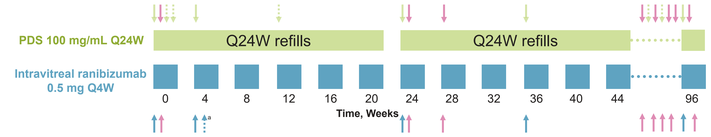
1. PDS Mechanism of Continuous Delivery: Passive Diffusion



- Pars plana implant is a refillable intraocular reservoir for ranibizumab
- Enables continuous drug delivery into the vitreous
- Mediated by passive diffusion along a concentration gradient
- PDS serum PK profile reflects implant release rate because implant release is the rate-limiting step

Diagram for illustrative purposes only.
PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic.

2. Serum and Aqueous Humour PK Samples Collected Throughout Archway



Serum sampling in all patients: Randomisation; weeks 4, 24, 36 and 96

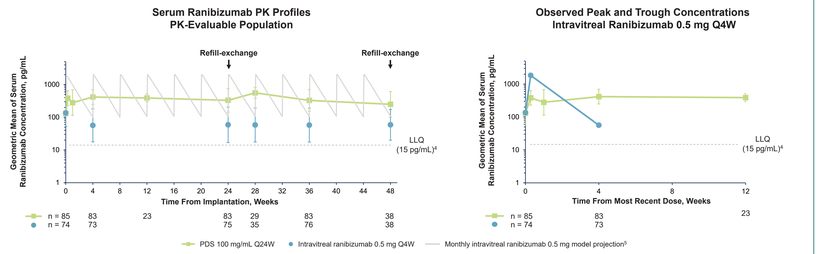
Serum sampling at selected sites: PDS arm: days 2 and 7; weeks 12, 48 and 72. Monthly ranibizumab: 1–5 days after an injection

Optional aqueous humour sampling: Randomisation; weeks 24, 28, 48, 52, 72, 76 and 96; serum samples were also collected at these times

Concentrations were measured using a validated ELISA with lower limits of quantification of 15 pg/mL[4] for serum and 20,000 pg/mL for aqueous humour

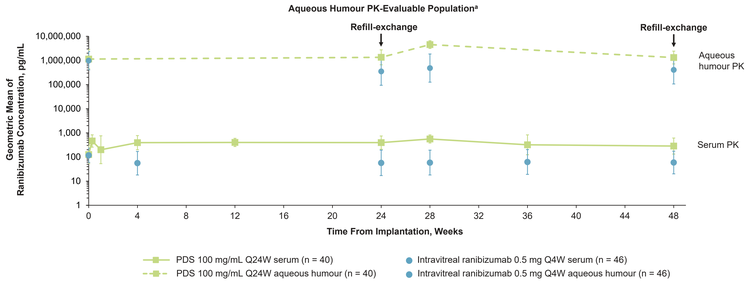
Archway, NCT03677934.
[a]Samples were collected monthly from the ranibizumab arm at 1–5 days after an injection.
ELISA, enzyme-linked immunosorbent assay; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; Q4W, every 4 weeks; Q24W, every 24 weeks.

3. Mean Ranibizumab Concentrations Were Steady and Continuous Over the Refill Interval With PDS 100 mg/mL Q24W



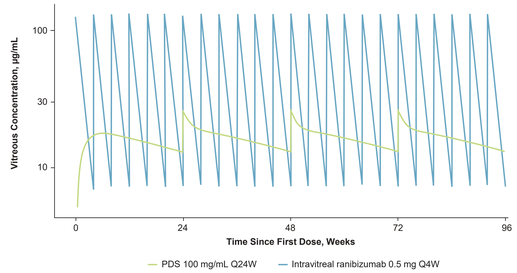
Vertical bars represent the geometric mean ± geometric SD. PK-evaluable population included patients who did not receive ranibizumab as supplemental treatment in the study eye after implant insertion or in the fellow eye, or prior intravitreal bevacizumab treatment.
Figure generated based on updated population PK analysis (including data from study FVF4579g).
LLQ, lower limit of quantification; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; Q4W, every 4 weeks; Q24W, every 24 weeks.

4. Aqueous Humour PK Profiles Were Consistent With Serum PK Profiles



Archway, NCT03677934. Vertical bars represent the geometric mean */÷ geometric SD.
[a] A subset of patients in the PK-evaluable population with ≥ 1 aqueous humour sample.
PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; Q4W, every 4 weeks; Q24W, every 24 weeks.

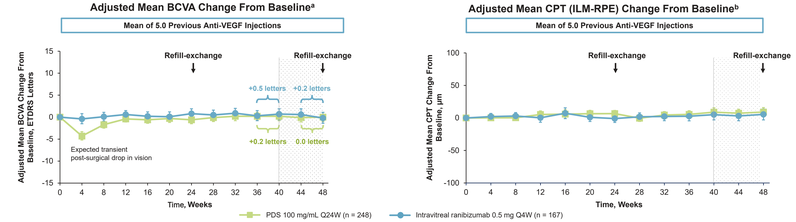
5. Predicted Vitreous Humour Concentrations of PDS 100 mg/mL Q24W Were in the Range of Intravitreal Ranibizumab 0.5 mg Q4W



- Population PK model based on final data from the phase 2 Ladder trial and validated with data from Archway
- Compartmental structure with compartments for the implant, vitreous and serum

Ladder, NCT02510794; Archway, NCT03677934.
PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; Q4W, every 4 weeks; Q24W, every 24 weeks.

6. PK Findings Support the Durable BCVA and CPT Outcomes Observed Throughout Archway



PDS Q24W was non-inferior and equivalent to monthly ranibizumab at the average of weeks 36 and 40 (primary endpoint)[c] and non-inferior[c] at the average of weeks 44 and 48

PDS Q24W and monthly ranibizumab results were comparable through weeks 40 and 48

Archway, NCT03677934. CPT defined as retinal thickness in the centre of the fovea measured between the ILM and the inner third of the RPE layer. [a] Adjusted means from a MMRM analysis through week 48. Adjusted means estimated using a MMRM with adjustment for change from baseline in BCVA as the response and included terms for treatment group, visit, treatment-by-visit interaction and baseline BCVA (< 74 vs ≥ 74 ETDRS letters). [b] Adjusted means from a MMRM analysis through week 40. MMRM adjustment for change from baseline in CPT score as the response and included terms for treatment group, visit, treatment-by-visit interaction and baseline BCVA (< 74 vs ≥ 74 ETDRS letters). Vertical bars represent 95% CI. 95% CI is a rounding of 95.03% CI; the type 1 error was adjusted for interim safety monitoring. [c] Equivalence not assessed per protocol. BCVA, best-corrected visual acuity; CPT, centre point thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; MMRM, mixed-effect model for repeated measures; PDS, Port Delivery System with ranibizumab; PK, pharmacokinetic; Q4W, every 4 weeks; Q24W, every 24 weeks; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

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Financial Disclosures

- JM: Annexon, Apellis, Cell Cure Neurosciences, EyeBio, Genentech, Inc., Iveric Bio, Kodiak Sciences, Lineage Cell Therapeutics, MacuLogix, Notal Vision, Novartis, ReNeuron, Roche
- SG, MMaia, HTD, MK, KFM: Employee: Genentech, Inc.
- MMorral: Employee: F. Hoffmann-La Roche Ltd.

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 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 Stephen Craig, PhD, CMPP, of Envision Pharma Group