The Port Delivery System With Ranibizumab (PDS): A New Paradigm for Long-Acting Retinal Drug Delivery

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Purpose

To characterise ranibizumab release and refill-exchange efficiency of the Port Delivery System with ranibizumab (PDS)

Introduction

- The PDS is a US Food and Drug Administration–approved intraocular drug delivery system indicated for the treatment of patients with neovascular age-related macular degeneration (nAMD) who have previously responded to ≥ 2 intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor[1]
- The PDS implant is a permanent, indwelling device designed to continuously deliver a customised formulation of ranibizumab into the vitreous via passive diffusion[1,2]
- This innovative drug delivery system has the potential to reduce treatment burden in patients with retinovascular diseases[2]

Methods

- In vitro ranibizumab release rate at starting concentrations of 10, 40 and 100 mg/mL; active release rate of ranibizumab 100 mg/mL over multiple refill-exchange intervals; and retained ranibizumab within the implant over time were measured
- In the phase 3 Archway trial (NCT03677934), patients with nAMD were randomised to PDS with ranibizumab 100 mg/mL with fixed refill-exchanges every 24 weeks (PDS Q24W) or intravitreal ranibizumab 0.5 mg injections every 4 weeks (monthly ranibizumab)[3]

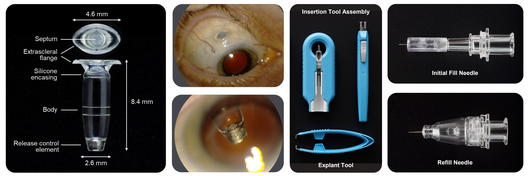
Conclusions

- The PDS continuously and reproducibly delivers ranibizumab over a period of ≥ 6 months while maintaining potency
  - Release rate changes gradually, from ~17 µg/day to ~4 µg/day, due to continuously decreasing ranibizumab concentration inside the implant
  - These release rates ensure that the ranibizumab concentration in the vitreous is maintained within therapeutic levels
  - After 6 months, residual ranibizumab solution in the implant can be reproducibly exchanged (> 95%) with fresh ranibizumab
  - Refilled implant drug-release kinetics were comparable with that of the implant after initial fill
  - These in vitro results support the fixed 24-week refill-exchange intervals in the Archway trial
- Archway phase 3 trial results support the efficacy of the PDS
  - PDS Q24W was shown to deliver vision and anatomic outcomes comparable with monthly ranibizumab averaged over weeks 44/48

1. The Port Delivery System With Ranibizumab

The PDS implant is intentionally designed to be:

- Permanent, biocompatible and durable
- Transparent to facilitate visualisation of ranibizumab solution within the reservoir (implant contains 20 µL)
- Refillable via the self-sealing septum
- Non-interfering with the patient's field of vision
- Covered by eyelid; not visible in primary gaze

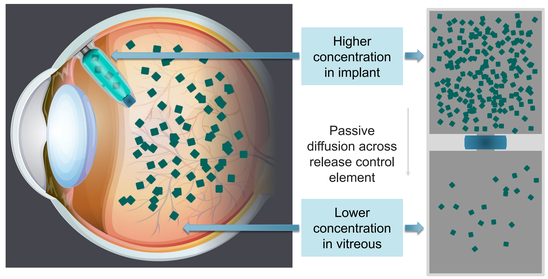


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The PDS includes a customised formulation of ranibizumab, an ocular implant and 4 ancillary devices

PDS, Port Delivery System with ranibizumab.

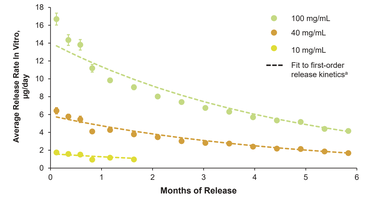
2. PDS Mechanism of Continuous Delivery: Passive Diffusion

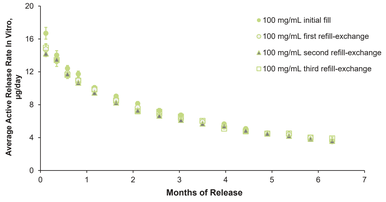


- Continuous delivery mediated by passive diffusion along a concentration gradient
- Rate of diffusion is concentration dependent and decreases over time

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

3. Drug Release From the PDS Is Dependent on the Starting Concentration of Ranibizumab and Is Consistent Across Multiple Refill-Exchange Intervals

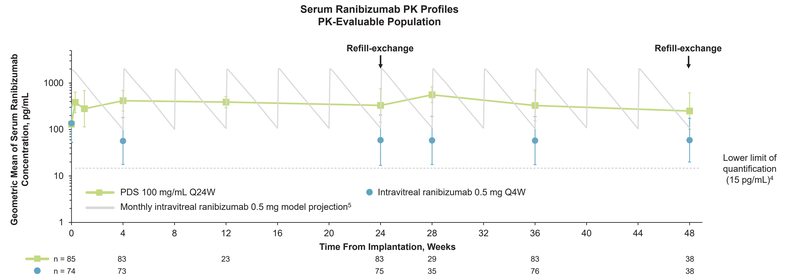




These release rates ensure that the ranibizumab concentration in the vitreous is maintained within therapeutic levels across 24-week refill-exchange intervals, as used in the phase 3 Archway trial

[a] Theoretical drug-release curves, calculated based on first-order drug-release kinetics.
PDS, Port Delivery System with ranibizumab.

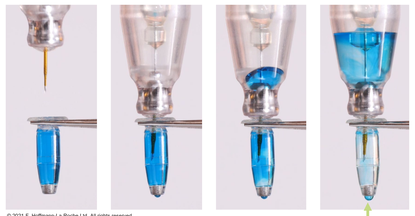
4. Mean Ranibizumab Concentrations Were Steady and Continuous Over the Refill Interval With PDS 100 mg/mL Q24W in the Phase 3 Archway Trial



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

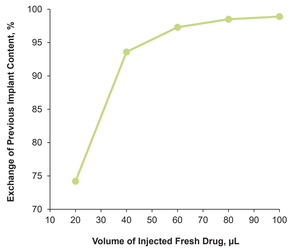
5. Each Refill-Exchange Replaces > 95% of Implant Content With Fresh Drug

Previous contents, represented by the coloured liquid, are exchanged for the fresh, colourless solution in a single stroke

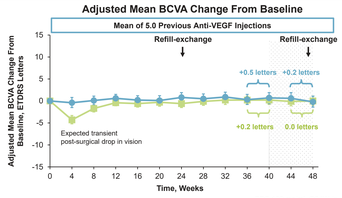


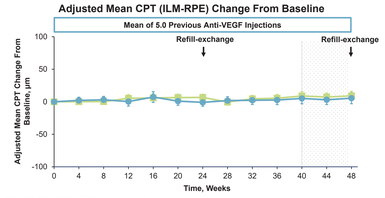
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No significant bolus occurs during the procedure



6. Continuous Ranibizumab Release Resulted in Consistent Clinical Outcomes Across Treatment Cycles in the Phase 3 Archway Trial: PDS Q24W Maintained Vision and Anatomic Outcomes Comparable With Monthly Ranibizumab Through Week 48





- Primary endpoint: PDS Q24W was non-inferior and equivalent for BCVA change at the average of weeks 36/40[3]
- BCVA change at the average of weeks 44/48 remained non-inferior[a] through 2 refill-exchange intervals
- CPT outcomes were comparable across arms

Archway, NCT03677934. [a] Equivalence not assessed per protocol. CPT defined as retinal thickness in the centre of the fovea measured between the ILM and the inner third of the RPE layer. Adjusted means were estimated using a mixed-effect model for repeated measures with 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).
BCVA, best-corrected visual acuity; CPT, centre point thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

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References

1. Susvimo [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2022.
2. Khanani AM et al. *Expert Opin Drug Deliv.* 2021;18(11):1571-1576.
3. Hoekstra N et al; Archway Investigators. *Ophthalmology.* 2022;129(3):295-307.
4. Lowe J et al. *J Immunol Methods.* 2018;461:44-52.
5. Xu L et al. *Invest Ophthalmol Vis Sci.* 2013;54(3):1616-1624.

Financial Disclosures

- MRW: Consultant, Financial Support: Genentech, Inc.; Research: Genentech, Inc., Kodiak Sciences, Noriase, Regeneron
- TT, JH, JR, GB, SR: Employee: 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 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 Dionne Turnbull, PhD, of Envision Pharma Group