A trend for improvement in endophthalmitis incidence and patient outcomes was observed in patients implanted after June 2020

The Impact of Improvements to Surgical Procedure on the Incidence of Endophthalmitis and Associated Outcomes of Patients in the PDS Clinical Development Programme

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Study and Product Disclosures
- The Port Delivery Platform with ranibizumab (PDS) has been approved by the US Food and Drug Administration for the treatment of nAMD, DMO and DR 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 an up to 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
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Abbreviations
- AAO, American Academy of Ophthalmology; AE, adverse event; CCOD, clinical cut-off date; COVID-19, coronavirus disease 2019; DMO, diabetic macular oedema; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; FDA, US Food and Drug Administration; LTE, long-term extension; max, maximum; nAMD, neovascular age-related macular degeneration; OL, open label; PDS, Port Delivery Platform with ranibizumab; Ph, phase; SOC, standard of care.

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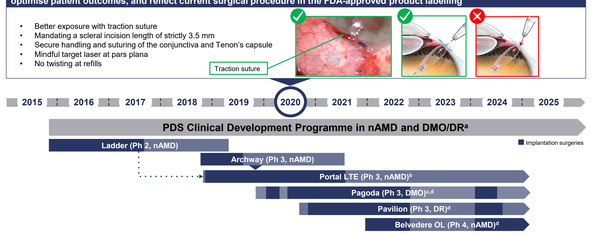
Introduction

- The Port Delivery Platform with ranibizumab (PDS) continuously delivers ranibizumab to the eye, requiring 1–2 refill-exchanges/year
- PDS is US Food and Drug Administration approved for neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DMO) and diabetic retinopathy (DR)
- In the comparator period of the PDS clinical trials, the incidence of endophthalmitis was:
  - 1.7% PDS vs 0.5% intravitreal (IVT) injections (nAMD)
  - 0% PDS vs 0.3% IVT injections (DMO)
  - 0 cases in DR
- This retrospective analysis examined the impact of programme updates since June 2020 on endophthalmitis incidence and associated patient outcomes

Key updates to the PDS implant insertion and refill-exchange procedures were implemented from June 2020, with the aim to optimise patient outcomes, and reflect current surgical procedure in the FDA-approved product labelling

- Better exposure with traction suture
- Mandating a scleral incision length of strictly 3.5 mm
- Secure handling and suturing of the conjunctiva and Tenon's capsule
- Mindful target laser at pars plana
- No twisting at refills



Methods

- Post hoc analysis of patients with nAMD, DMO and DR treated with the PDS in the clinical trial programme[a]
- Follow-up times through clinical cut-off date (CCOD):
  - nAMD: 31 January 2024 (Ladder, Archway, Portal[b]); 20 December 2024 (Belvedere[d])
  - DMO and DR: 15 March 2024 (Pagoda[c] and Pavilion[c,d])
- Analysis was based on timing of PDS implantation and pooled for patients with nAMD, DMO and DR
  - Before June 2020: PDS implantation occurred before Instructions for Use (IFU) version 8
  - After June 2020: PDS implantation occurred after IFU version 8

Analysis groups	Before June 2020 PDS patients implanted from 18 May 2016 to 3 June 2020	After June 2020 PDS patients implanted from 4 June 2020 to CCOD

Ladder clinical trial [NCT02510794]; Archway clinical trial [NCT03677934]; Portal clinical trial [NCT03683251]; Pagoda clinical trial [NCT04108156]; Pavilion clinical trial [NCT04503551]; Belvedere clinical trial [NCT04853251]. [a] Only PDS clinical trials included in the current analysis are noted. [b] Portal also enrols eligible patients from the Velodrome clinical trial [NCT04657289], but no patients from Velodrome were included in the current analysis. [c] There was a sponsor-issued pause due to the COVID-19 pandemic. [d] The PDS implant was voluntarily recalled by Roche/Genentech, Inc. from October 2022 and lifted in February 2024, causing a pause in PDS implants in ongoing clinical trials. The analysis only included the first implant for a patient (exposure or events after explant or re-implant are not included). Patients are classified as before/after 3 June 2020, according to implant insertion date; any subsequent endophthalmitis event is counted for that patient.

Results

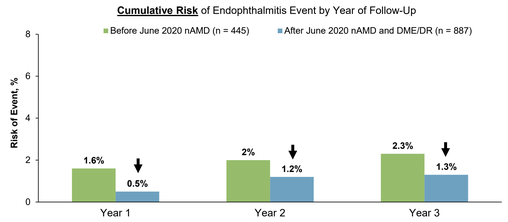
1. Endophthalmitis Incidence Shows a Trend for Improvement After June 2020[a]

PDS Implants From 18 May 2016 to 2024 CCODs	
Patients implanted, n	1344
Number of patients with endophthalmitis[b]	**22**
Mean duration of follow-up	3.21 years (max 7.38)
Overall incidence	**1.6%**

	Before June 2020	After June 2020
Patients implanted, n	457	887
Number of patients with endophthalmitis	**12**	**10**
Mean duration of follow-up	4.68 years (max 7.38)	2.45 years (max 3.77)
Incidence	**2.6%**	**1.1%**

[a] There was a numerical reduction in the percentage of patients with endophthalmitis events after June 2020 vs before June 2020. [b] There were 22 patients with 26 endophthalmitis events (2 patients before June 2020 had 2 events each of endophthalmitis and 2 patients after June 2020 had 2 events each of endophthalmitis).

2. Risk of Endophthalmitis Event Decreases After June 2020[a]



Risk of with endophthalmitis event estimated with time-to-event Kaplan-Meier curve. [a] There was a numerical reduction in the percentage of patients at risk for endophthalmitis events after June 2020 vs before June 2020.

3. Improved Outcomes in Patients Implanted After June 2020

	Before June 2020[a]	After June 2020[b]	Change
Number of Endophthalmitis Cases	**12/457 (2.6%)**	**10/887 (1.1%)**	
Vision at last follow-up			
Lost < 5 ETDRS letters or maintained ≥ 20/40 Snellen	7/12	7/10	↑
Lost ≥ 15 ETDRS letters	5/12	1/10	↓
Continued refills	3/12	8/10	↑
Implant removed	8/12	0/10	↓

[a] Three cases in the before June 2020 group were culture positive (1 case each of *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Staphylococcus aureus*).
[b] Three cases in the after June 2020 group were culture positive (1 case each of *Staphylococcus epidermidis*, *Propionibacterium acnes* and rare gram-positive cocci).

4. How Does Incidence of Endophthalmitis With Updated (Current) PDS Surgery Compare With That With SOC Injection Treatments?

AAO's 2025 Intravitreal Injection Policy Statement, which cites 2 meta-analyses (McCannel[2] and Fileta et al[3]), reports an incidence of endophthalmitis of ~0.05% per intravitreal injection[a]

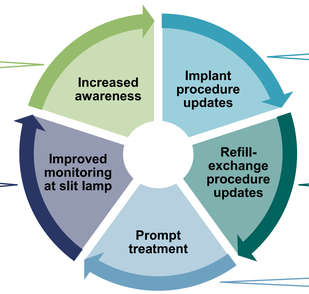
Observed data: Incidence of endophthalmitis in PDS trials after June 2020 N = 887	Projection: Incidence of endophthalmitis assuming an incidence of ~0.05% per injection over 2.45 years		
10 Cases Over 2.45 Years of Follow-Up	**Number of Injections per Year**	**Potential Injections Over 2.45 Years in 887 Patients**	**Potential Endophthalmitis Incidence[b]**
1.1%	**6**	**13,039**	**0.8%**
	9	**19,558**	**1.2%**

[a] Per AAO's 2025 Intravitreal Injection Policy: event rate per injection incidence of endophthalmitis is 1 in 1831 injections (0.054%). [b] Assuming 1 event per patient.

5. Factors Potentially Contributing to Improved Patient Outcomes in Patients With Endophthalmitis Over Time

FDA Boxed Warning in US prescribing information[1]

Education about **conjunctival AEs**, leading to earlier reporting of **conjunctival AEs**[4]



- **Better exposure** with traction suture
- Atraumatic **conjunctival handling (non-toothed forceps)**
- **Precise scleral incision length** of 3.5 mm
- **Mindful and targeted** pars plana laser
- **Complete reapposition** of both conjunctiva and Tenon's to the limbus

- **No twisting** of refill needle[5]
- **Environment, Visualisation** and **Perpendicularity (E.V.P.)** training

Prompt treatment of all endophthalmitis events with **tap and inject, implant flush** with vancomycin and **conjunctival revision** and/or **vitrectomy** as needed[a]

[a] Complete guidance as stated was implemented during the Archway trial.

Conclusion

Key surgical updates, increased awareness and improved monitoring in the PDS clinical trials may have contributed to reduced endophthalmitis incidence, and additionally, early treatment may have improved patient outcomes

- **Key Learnings: Strict adherence** to specified **surgical procedures**, **regular monitoring** at slit lamp and **prompt treatment of conjunctival adverse events** are key for mitigating the risk of endophthalmitis, while early diagnosis and prompt treatment of endophthalmitis are important for maximising patient outcomes
- **Endophthalmitis incidence:** The **overall incidence** of **endophthalmitis** in the PDS programme from 2016 to 2024 (all indications pooled) **shows a trend for improvement**
- **Outcomes in endophthalmitis cases:** Data suggest that following an event of endophthalmitis, with **prompt treatment**, **most patients** achieve **good vision outcomes** and **continue to benefit from PDS treatment**