Port Delivery System With Ranibizumab Implant Insertion Procedure Optimization and Use of Virtual Reality Simulators in PDS Trials

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Disclosures

- Financial disclosures
  - DMM: Stock Ownership – Vortex Surgical; Consultant/ Advisory Committee – Genentech, Inc., Novartis, Regeneron; Research Support – Genentech, Inc., Regeneron, Novartis, AGTC, Iveric, Allergan, Lowry Foundation, Chengdu Kanghong Biotech, Neurotech
  - SG, GB: Employee: Genentech, Inc.

- Study disclosures
  - 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 Betsy C. Taylor, PhD, CMPP, of Envision Pharma Group

Challenges Unique to Clinical Trials That Involve a Surgical Procedure

- Requires standardization of surgical approach
  - Inconsistent and/or improper surgical technique may impact trial results and patient outcomes
- Robust training on surgical steps needed before patient enrollment
  - Expedite the learning curve to ensure appropriate technique and consistency
- Requires monitoring and review of procedures
  - Determine if procedures are being followed and identify modifiable reasons for complications

Key Takeaways About PDS Procedures

Optimized PDS Implant Insertion

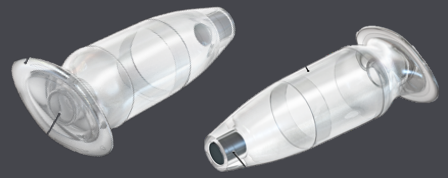
- Prophylactic laser ablation of the pars plana before incision was key to mitigation of postoperative vitreous hemorrhage in the Ladder phase 2 trial

Procedural Consistency

- Adherence to the standardized steps and best practices of the PDS implant insertion procedure reduces variability and maximizes successful outcomes

Virtual Reality for PDS Training

- Potential to enhance surgical readiness and optimize patient outcomes through practice in PDS procedure–specific simulators

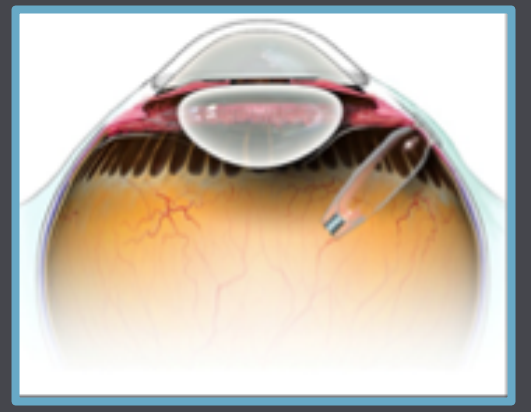


PDS implant

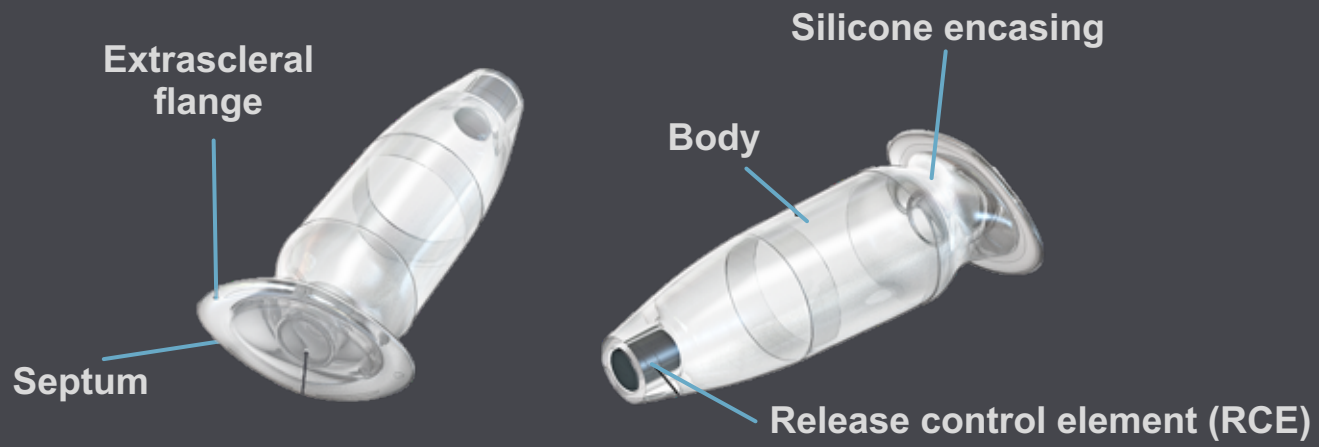
Ladder: NCT02510794.
PDS, Port Delivery System with ranibizumab.

The Port Delivery System With Ranibizumab (PDS)

- Continuous drug delivery system
  - Permanent, refillable intraocular implant
  - Customized formulation of ranibizumab
  - Implant surgically placed at the pars plana
  - Refills performed in office



OR-based insertion procedure



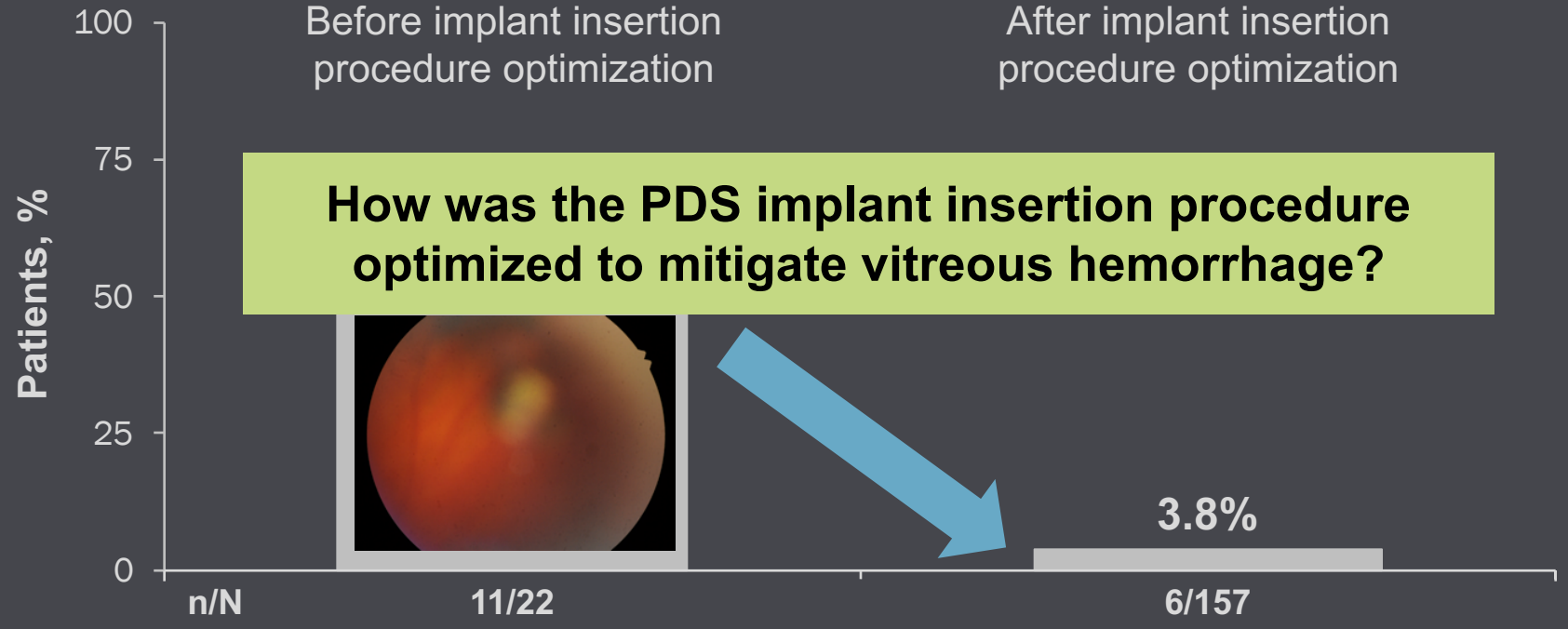
OR, operating room; PDS, Port Delivery System with ranibizumab.

Ladder Post-operative Vitreous Hemorrhage Successfully Mitigated After Implant Insertion Procedure Optimization

Pre-optimization implant insertion procedure included

- Conjunctival peritomy
- Full thickness sclero-pars plana stab incision
- Device insertion
- Closure

Post-operative Vitreous Hemorrhage Rates,* Pooled PDS Treatment Arms



* Ladder post-operative vitreous hemorrhage results from end of study analysis. Results are for events that occurred up to day 37 post implant insertion.
PDS, Port Delivery System with ranibizumab.

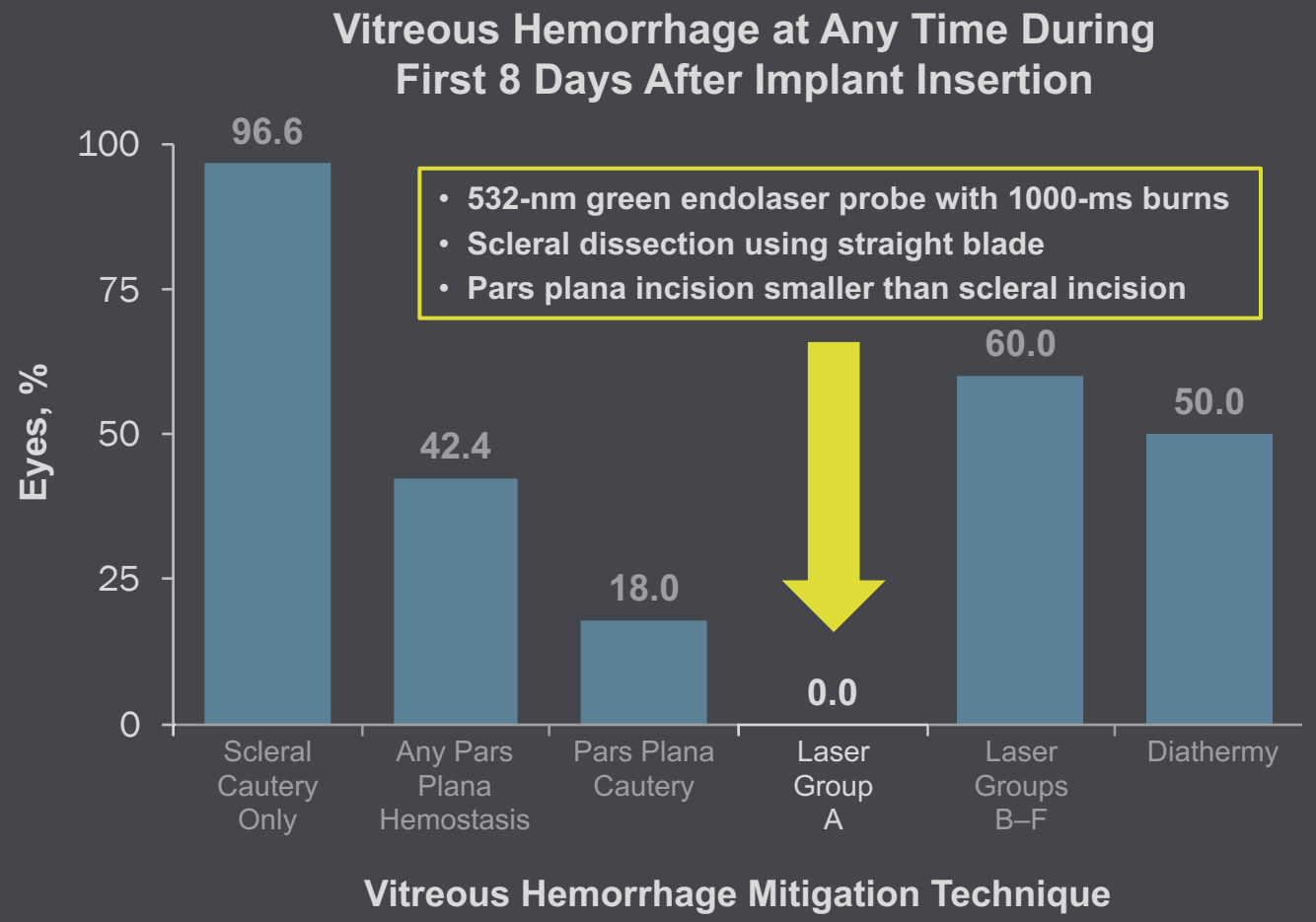
Root Cause Analysis for Vitreous Hemorrhage Key Findings of the Minipig Surgical Study

Purpose:

- To investigate the source of vitreous hemorrhage following the PDS implant insertion procedure
- To evaluate surgical procedure modifications to mitigate vitreous hemorrhage following PDS implant insertion

Findings:

- Pars plana was the main source of bleeding
- Most effective method for vitreous hemorrhage mitigation was laser ablation of the pars plana



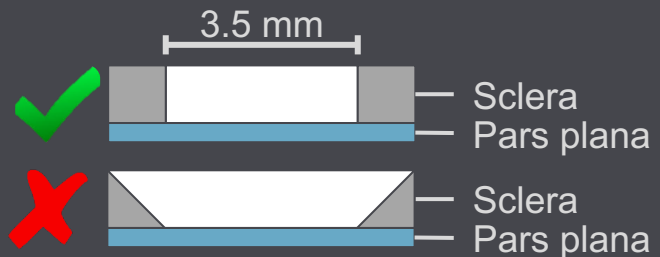
Study conduct adhered to the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the Office of Laboratory Animal Welfare, and all relevant local, state, and federal laws.

Laser group A: 1000-ms duration laser spots, full-field ablation, pars plana incision shorter than scleral dissection, straight blade used for scleral dissection. Laser groups B–F: ≤ 1000-ms duration laser spots and/or less than full-field ablation and/or pars plana incision shorter than scleral dissection, and/or crescent blade used for scleral dissection. Techniques assessed for vitreous hemorrhage mitigation. Techniques assessed for vitreous hemorrhage mitigation (n = 90 eyes from 45 Yucatan minipigs): Prophylactic pars plana hemostasis, scleral incision length, scleral cauterization, surgical blade type and size, viscoelastic usage. Bantseev V et al. *Retina* [published online August 19, 2019]. doi: 10.1097/IAE.0000000000002614.

Minipig Surgical Study: Additional Insights

Edge-to-edge laser ablation of pars plana within scleral incision critical for mitigation of vitreous hemorrhage

- Use of straight-edged knife to create squared-off corners
- Pars plana incision length less than or equal to ablated pars plana
- Steady in-and-out motion of slit knife while avoiding side-to-side movements



Optimized PDS Implant Insertion Procedure

Placeholder for Video: Miller_Video_Slide 9_Optimized Implant Insertion Procedure

Campochiaro PA et al. *Ophthalmology*. 2019;126(8):1141-1154.
PDS, Port Delivery System with ranibizumab.

Training Surgeons on the Use of a Novel Intraocular Device

Training Methodologies

- Didactics
- Mentorship
- Videos
- Animal labs
- Autopsy eyes
- Artificial eyes
- Virtual reality

Virtual Reality Simulators for PDS Implant Insertion and Implant Refill-Exchange Procedures

Overview

- Computer-simulated environments that allow users to practice the novel PDS procedures in a risk-free environment

Advantages

- Skill development through repetition of specific procedural steps
- Instantaneous feedback through use of guidance elements
- Allows users to experience different scenarios and varying degrees of difficulty
- Quantitative assessment of accuracy and consistency

PDS, Port Delivery System with ranibizumab.

Virtual Reality Simulators for PDS Implant Insertion and Implant Refill-Exchange Procedures

OR-based implant insertion procedure

Office-based refill-exchange procedure

Both the implant insertion and refill-exchange systems are controlled through customized force feedback devices that emulate the look and the feel of the instruments used during the real procedures, while providing visual feedback to the user

PDS, Port Delivery System with ranibizumab.

Virtual Reality Simulator for PDS Implant Insertion Procedure

Placeholder for Video: Miller_Video_Slide 12_VR Simulator for PDS Implant Insertion Procedure

PDS, Port Delivery System with ranibizumab.

PDS Implant Refill-Exchange Procedure

Placeholder for Video: Miller_Video_Slide 13_PDS Implant Refill-Exchange Procedure

PDS, Port Delivery System with ranibizumab.

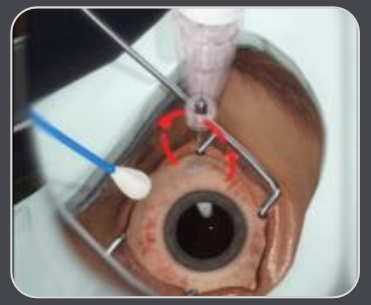
Key Learnings to Maximize Optimal Outcomes With PDS Procedures

Optimized implant insertion procedure successfully mitigated postoperative vitreous hemorrhage

- Lamellar scleral dissection to gain access to pars plana
- Edge-to-edge laser ablation of pars plana to attain hemostasis

Adherence to specified methodology is key for maximizing optimal outcomes with PDS procedures

- Standardized surgical training and ongoing procedural evaluations are important for enhancing surgeon proficiency



Virtual reality training in PDS phase 3 trials

- **Archway** (nAMD): fully enrolled, all surgeons trained
- **Portal** (nAMD extension study): ongoing, all surgeons trained
- **Pagoda** (DME): enrollment ongoing, training underway

Archway: NCT03677934; Pagoda: NCT04108156; Portal: NCT03683251.
DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab.