Key Learnings From the Phase 2 Ladder Trial of the Port Delivery System With Ranibizumab (PDS) in Patients With Neovascular AMD

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Purpose:
The PDS is an investigational drug delivery system consisting of a permanent, refillable implant for continuous intravitreal delivery of ranibizumab. Ladder outcomes have created a wealth of information about efficacy, safety, and procedures associated with the PDS. Key learnings from Ladder, focusing on comparing the PDS 100 mg/mL arm with monthly intravitreal ranibizumab 0.5 mg injections, are provided herein.

Methods:
Ladder (NCT02510794; N=220) compared the PDS with 3 formulations (10, 40, or 100 mg/mL ranibizumab) with monthly intravitreal ranibizumab 0.5 mg injections. The primary endpoint was time to first required implant refill, assessed when the last enrolled patient completed the month 9 visit. Secondary outcomes included mean BCVA and CFT change. Serum ranibizumab concentrations were measured using a validated immunosorbent assay.

Results:
In the PDS 100 mg/mL arm, median time to first required refill was 15.8 months; 79.8% and 59.4% went ≥6 and ≥12 months, respectively, without meeting refill criteria. In patients who met refill criteria at least once, median time to first and second refills was consistent at 8.8 months. At 22 months (total mean time on study), mean CFT, and percentage of patients who maintained BCVA in the PDS 100 mg/mL (87.5%) and monthly intravitreal ranibizumab (88.9%) arms were comparable. Serum PK analysis showed that the implant continues to release ranibizumab through month ≥16 at levels comparable with monthly intravitreal ranibizumab. Optimization of the implant insertion procedure through introduction of novel clinical procedures, including pars plana laser ablation, was key in mitigating incidence of postsurgical vitreous hemorrhage from 50.0% to 3.8%. The refill-exchange procedure requires a perpendicular approach and precise targeting. Mitigations for PDS-related conjunctival events were implemented. Procedures introduced in Ladder were incorporated into virtual reality simulation-based training and subsequently implemented in the phase 3 Archway trial (NCT03677934).

Conclusions:
Ladder has enabled key learnings about the PDS. Visual and anatomic outcomes were comparable between PDS 100 mg/mL and monthly intravitreal ranibizumab treatment. The PDS procedures were generally well tolerated. Ladder data indicate that the PDS has potential to reduce treatment burden in patients with nAMD while maintaining vision results comparable to monthly ranibizumab dosing.