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SURGICAL VIDEO ANALYSIS IN THE PORT DELIVERY PLATFORM WITH RANIBIZUMAB (PDS) CLINICAL TRIALS: LESSONS LEARNED

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The Port Delivery Platform is a drug delivery system that continuously delivers customized medicines to the eye, with the Port Delivery Platform with ranibizumab (PDS) as the first combination which can be refilled every 6 or 9 months. The PDS includes a refillable ocular implant surgically placed at the pars plana for continuous intravitreal release of a customized ranibizumab formulation. The PDS is the first and only continuous delivery treatment that has shown positive phase 3 data in neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and diabetic retinopathy (DR) and is approved in the US for nAMD and DME. The PDS implant insertion procedure has 7 critical steps: case preparation and peritomy, implant preparation, scleral dissection, laser ablation of the pars plana, pars plana incision, implant insertion, and conjunctiva and Tenon's capsule closure. Meticulous adherence to all surgical steps as outlined in the Instructions for Use (IFU) is critical to maximize optimal surgical outcomes. In addition, surgical procedures have evolved during the PDS clinical development program to optimize safety outcomes, with key updates in insertion and refill-exchange procedure IFUs implemented from June 2020. During the PDS development program, which spans 10 years of surgical experience, timely video review of PDS procedures (eg, implantation, refill-exchange) were performed to assess program-level insights throughout the PDS clinical trials. Here, we provide examples of how video review has been utilized to help improve the safety profile of the PDS during the clinical development program.

PDS clinical trials include the Ladder (NCT02510794), Archway (NCT03677934), and Portal (NCT03683251) trials in nAMD; the Pagoda (NCT04108156) trial in DME; and the Pavilion (NCT04503551) trial in DR. A total of 1514 PDS implant insertion videos and 9366 refill-exchange procedure videos were collected to January 2025 (95.7% of all procedures have video records). In 2020, implant dislocations, where the implant was not at the expected location at the scleral incision implantation site, were detected as a safety signal. They were noted in 6 cases in approximately 450 patients who had been implanted in Ladder, Archway, or Portal at the time. Surgical videos for these patients were reviewed, and it was noted that 5 of 6 had a long scleral incision (> 3.7 mm; IFU specified 3.5–3.7 mm before June 2020), 5 of 6 had wound discoloration at the edge of the implant flange, and the time of dislocation was most often after a refill-exchange attempt. After noting the characteristics associated with implant dislocation (ie, long scleral incision > 3.7 mm, presence of wound discoloration), a systematic review of all available surgical videos and implant photos was initiated to characterize associated risk factors and identify additional patients at risk. The review was conducted by staff ophthalmologists at Roche/Genentech, Inc. (n = 12) who independently reviewed all available implant insertion procedure videos and corresponding longitudinal implant photos for patients in Ladder, Archway, and Portal (n = 450). Similarly, for the refill-exchange procedure, video review noted critical aspects of the procedure, including a strict perpendicular approach, visualization and precise targeting into the septum center, and avoidance of twisting and maneuvering during the procedure.

Results from this prospective review of videos have driven key updates to the PDS surgical techniques over time, including updates that were implemented in June 2020, where a precise scleral incision length of 3.5 mm was specified and guidance on careful application of the laser to the pars plana while avoiding misdirection toward the adjacent sclera and remeasuring after laser to confirm that incision is not > 3.5 mm using measurement gauge were added. In addition, for patients with final incisions > 3.5 mm, mandatory suture placement was added to reduce the scleral incision down to 3.5 mm. Following these updates, a notable trend towards a reduction in implant dislocations has been observed in a retrospective analysis, which included patients enrolled in Ladder, Archway, Portal, Pagoda, and Pavilion who were implanted with the PDS before vs after June 2020 across indications (2.2% [10/457] vs 0.5% [4/804], respectively). Updates to the refill-exchange procedure led to the development of Environment, Visualization, and Perpendicularity (E.V.P) refill-exchange education. After E.V.P training, 99 videos from Pagoda, Pavilion, and Portal of 20 surgeons who had completed training were reviewed; 88% of refill-exchanges were successful with the first needle insertion attempt and 94% of attempts did not involve twisting.

The use of a systematic prospective video review process has facilitated key surgical learnings in PDS phase 3 clinical trials, reducing the risk of adverse events like implant dislocations. Systematic and ongoing video reviews are now performed in the Port Delivery Platform development program to proactively identify opportunities for continuous improvement, where warranted.