REVIEW ARTICLE

Port Delivery System with Ranibizumab (Susvimo) for Neovascular Age-Related Macular Degeneration: A Systematic Review of Efficacy, Refill Intervals, Safety, and Implications of the 2022 Voluntary Recall

Deeksheka D[1], Sushritha S[2*], Naveena M[3]

[1]Postgraduate, Department of Ophthalmology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu, Tamil Nadu, India 603 203.
[2]Postgraduate, Department of Ophthalmology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu, Tamil Nadu, India 603 203.
[3]Assistant Professor, Department of Ophthalmology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu, Tamil Nadu, India 603 203.

***Corresponding Author:**Dr. Sushritha S, Postgraduate, Department of Ophthalmology, SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu, Tamil Nadu, India 603 203.Email:* sushritha1811@gmail.com

ABSTRACT

Background: Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible central vision loss in the elderly, primarily managed with frequent intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections. The Port Delivery System with ranibizumab (PDS; Susvimo, Genentech/Roche) represents a paradigm shift in ocular drug delivery — a surgically implanted, refillable intraocular device designed to provide continuous, sustained release of ranibizumab directly into the vitreous, reducing treatment burden from monthly injections to biannual refills.

Objective: This systematic review aims to evaluate the efficacy, refill interval outcomes, safety profile, patient-reported outcomes, and post-recall device performance of the PDS with ranibizumab in adult patients with nAMD.

Methods: A comprehensive literature search was conducted across PubMed/MEDLINE, Scopus, Cochrane Library, ClinicalTrials.gov, and Google Scholar through April 2025, using terms including "port delivery system," "Susvimo," "ranibizumab implant," and "neovascular AMD sustained release." Studies including Phase II (LADDER), Phase III (ARCHWAY), extension trials (PORTAL), and post-recall analyses were included. PRISMA 2020 guidelines were followed. Quality assessment was performed using the Cochrane Risk of Bias tool and Newcastle-Ottawa Scale.

Results: Eight studies met inclusion criteria (2 randomized controlled trials, 4 extension/observational studies, and 2 safety reports), encompassing 1,420 implanted eyes. The Phase III ARCHWAY trial demonstrated that PDS Q24W was non-inferior and equivalent to monthly intravitreal ranibizumab 0.5 mg (adjusted mean BCVA change: +0.2 letters vs. +0.6 letters; 95% CI within equivalence margin). At two years, 95% of PDS patients required no supplemental injections. Refill intervals of 24 weeks were sustained by >93% of patients across the trial period. Adverse events specific to PDS included conjunctival erosion (4.0%), conjunctival retraction (2.4%), endophthalmitis (2.0%), vitreous hemorrhage (1.6%), and implant dislocation (1.6%). The October 2022 voluntary recall was triggered by septum dislodgement identified in 2.3% of implants during Phase III trials. Following device redesign — including doubled bond strength and reduced needle insertion force — the recall was lifted in April 2024, with relaunched Susvimo meeting revised performance specifications. Patient preference strongly favored PDS (93%) over monthly injections.

Conclusion: The PDS with ranibizumab provides non-inferior visual acuity outcomes compared to monthly intravitreal injections, with a substantially reduced injection burden. The 2022 recall highlighted critical device engineering challenges unique to sustained-release ocular implants. Post-redesign evidence supports a favorable benefit-risk profile, positioning Susvimo as a clinically meaningful advance in nAMD drug delivery technology, particularly for well-selected, treatment-experienced patients.

Keywords: Port delivery system; ranibizumab; Susvimo; neovascular age-related macular degeneration; sustained-release ocular implant; intravitreal drug delivery; anti-VEGF; ARCHWAY trial; septum dislodgement; refill-exchange

How to cite this article: Deeksheka D, Sushritha S, Naveena M. Port Delivery System with Ranibizumab (Susvimo) for Neovascular Age-Related Macular Degeneration: A Systematic Review of Efficacy, Refill Intervals, Safety, and Implications of the 2022 Voluntary Recall. Int J Drug Deliv Technol. 2026;16(59s): 202-211. DOI: 10.25258/ijddt.16.59s.20

Source of support: Nil

Conflict of interest: None

1. INTRODUCTION

Age-related macular degeneration (AMD) is a progressive, multifactorial retinal disease and the foremost cause of irreversible central visual impairment among individuals over 60 years of age in developed nations.[1] The neovascular ("wet") form, though accounting for only 10-15% of all AMD cases, is responsible for approximately 90% of AMD-related

*Author for Correspondence: sushritha1811@gmail.com

severe vision loss.[2] Globally, an estimated 196 million individuals were affected by AMD in 2020, with projections reaching 288 million by 2040.[3] This growing epidemiological burden translates into profound socioeconomic and quality-of-life consequences for patients, caregivers, and healthcare systems worldwide.

The advent of anti-vascular endothelial growth factor (anti-VEGF) therapy has fundamentally transformed the management of nAMD. Intravitreal injections of agents such as ranibizumab (Lucentis), bevacizumab (Avastin), aflibercept (Eylea), and more recently faricimab (Vabysmo) have become the cornerstone of treatment, demonstrating robust improvements in best-corrected visual acuity (BCVA) and anatomical outcomes across landmark clinical trials.[4,5] However, the requirement for frequent intravitreal injections — often monthly or bimonthly for sustained disease control — imposes a significant treatment burden on patients and healthcare providers alike. Studies consistently demonstrate that real-world outcomes fall short of those achieved in controlled clinical trials, largely attributed to undertreatment driven by challenges in adherence to frequent injection schedules, fear of injections, and logistical constraints.[6,7]

This gap between trial efficacy and real-world effectiveness underscores a critical unmet need: a long-acting, sustained-release drug delivery platform that maintains continuous therapeutic drug levels in the vitreous without requiring frequent office visits. The Port Delivery System with ranibizumab (PDS; commercially designated Susvimo, Genentech/Roche) represents the first FDA-approved intraocular implant engineered to address this challenge.[8] The PDS is a surgically implanted, refillable, non-biodegradable titanium reservoir device designed to release a customized formulation of ranibizumab (100 mg/mL) continuously into the vitreous cavity, with scheduled refill-exchange procedures every 24 weeks (approximately 6 months).[9]

The PDS received FDA approval on October 22, 2021, for the treatment of nAMD in adults who had previously responded to at least two anti-VEGF injections.[10] However, in October 2022, Genentech issued a voluntary recall of the Susvimo ocular implant following identification of septum dislodgement in Phase III clinical trial patients, raising device engineering concerns that necessitated redesign and re-evaluation.[11] Following comprehensive device modifications — including improvements to the septum-flange interface and refill needle — the voluntary recall was lifted in April 2024, and Susvimo was relaunched with updated design specifications.[12]

Despite the clinical significance of this device and the regulatory milestones it has traversed, there is currently no published systematic review consolidating evidence across the full clinical trial program of the PDS, including Phase II dose-ranging data, Phase III efficacy and safety outcomes at two years, extension trial results, and the engineering and clinical lessons from the 2022 recall episode. This review aims to address this gap comprehensively, synthesizing available evidence to guide clinicians, pharmacists, and drug delivery scientists on the utility, limitations, and future prospects of the PDS as a novel intraocular sustained-release drug delivery technology in nAMD.

2. DEVICE ARCHITECTURE AND PHARMACOLOGICAL MECHANISM

The Port Delivery System is a permanent, refillable, intraocular implant surgically inserted through the pars plana under general or local anesthesia, positioned in the inferotemporal quadrant of the eye. The device measures approximately 3.5 mm in length and is encased in a biocompatible silicone housing. It comprises four principal components: (1) a hollow titanium reservoir body capable of holding up to 0.02 mL of the customized ranibizumab formulation; (2) a release control element — a porous titanium membrane positioned between the drug reservoir and the vitreous cavity — that regulates the rate of passive diffusion of ranibizumab into the vitreous; (3) a self-sealing silicone septum that enables repeated needle-based refill-exchange procedures; and (4) a polyimide-coated titanium flange that anchors the device securely to the sclera.[9,13]

The release control element is the pharmacokinetically decisive component of the device. It is engineered as a porous frit with precisely calibrated pore size, allowing ranibizumab molecules to diffuse passively into the vitreous at a controlled, predictable rate. At the concentration of 100 mg/mL — approximately 200-fold higher than the standard intravitreal injection formulation — the device maintains therapeutic vitreous drug levels over the full 24-week refill interval.[14] This concentration gradient-driven passive diffusion mechanism is fundamentally different from biodegradable polymer-based sustained-release systems (such as those used in Ozurdex or Iluvien), which rely on drug release as the polymer degrades. The non-biodegradable, refillable nature of the PDS theoretically enables indefinite, long-term treatment with a single permanent device implantation.

During a refill-exchange procedure, the clinician uses a specifically designed curved refill needle to penetrate the self-sealing septum and aspirate the residual drug volume, followed by injection of a fresh 0.02 mL vial of ranibizumab 100 mg/mL. This outpatient procedure does not require anesthesia in most cases and is designed to be completed in under 10 minutes.[13] The device is designed for indefinite indwelling use, with refill-exchange as the primary maintenance intervention, compared to the continuous intravitreal injection burden of conventional therapy.

3. METHODS

3.1 Study Design and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[15] No formal ethics approval was required, as this review is based exclusively on previously published data.

3.2 Search Strategy

A comprehensive, multi-database search was conducted through April 2025. Databases searched included PubMed/MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and Google Scholar. Reference lists of all included studies and relevant review articles were manually screened to identify additional eligible studies. The following search terms were used in combination: "port delivery system," "PDS ranibizumab," "Susvimo," "ranibizumab sustained release implant," "intraocular refillable implant," "neovascular AMD sustained release," "ARCHWAY trial," "LADDER trial," "PORTAL trial," and "wet AMD drug delivery implant." Boolean operators (AND, OR) were applied to combine terms systematically. No language restrction was imposed; however, only studies with full texts available in English were included for data extraction.

3.3 Inclusion and Exclusion Criteria

Studies were included if they: (1) involved adult patients (age ≥18 years) diagnosed with nAMD; (2) evaluated the PDS with ranibizumab as an intervention; (3) reported outcomes related to visual acuity, anatomical measures (central retinal thickness), refill intervals, safety events, or patient-reported outcomes; and (4) were published in peer-reviewed journals or presented as registered clinical trial reports. Study designs eligible for inclusion comprised randomized controlled trials (RCTs), prospective and retrospective observational studies, extension trials, and safety/pharmacovigilance reports.

Studies were excluded if they: (1) evaluated PDS in conditions other than nAMD without nAMD-specific subgroup data; (2) were abstracts, conference posters, or editorials without primary data; (3) involved animal or in vitro models only; (4) reported exclusively on non-ranibizumab formulations in the PDS; or (5) lacked extractable outcome data; (6) pre prints, grey literature, systematic analyses.

3.4 Data Extraction

Two independent reviewers (Authors 1 and 2) screened titles and abstracts, followed by full-text review. Disagreements were resolved through consensus or involvement of a third reviewer (Author 3). Data extraction was performed using a pre-specified, standardized extraction form capturing: study design, sample size, patient demographics, nAMD diagnosis duration, prior anti-VEGF treatment history, PDS ranibizumab concentration studied, refill interval, primary and secondary efficacy outcomes (BCVA change from baseline, proportion of patients requiring supplemental injections, central retinal thickness), safety outcomes (adverse event type and frequency), patient-reported outcomes, and study duration.

3.5 Quality Assessment

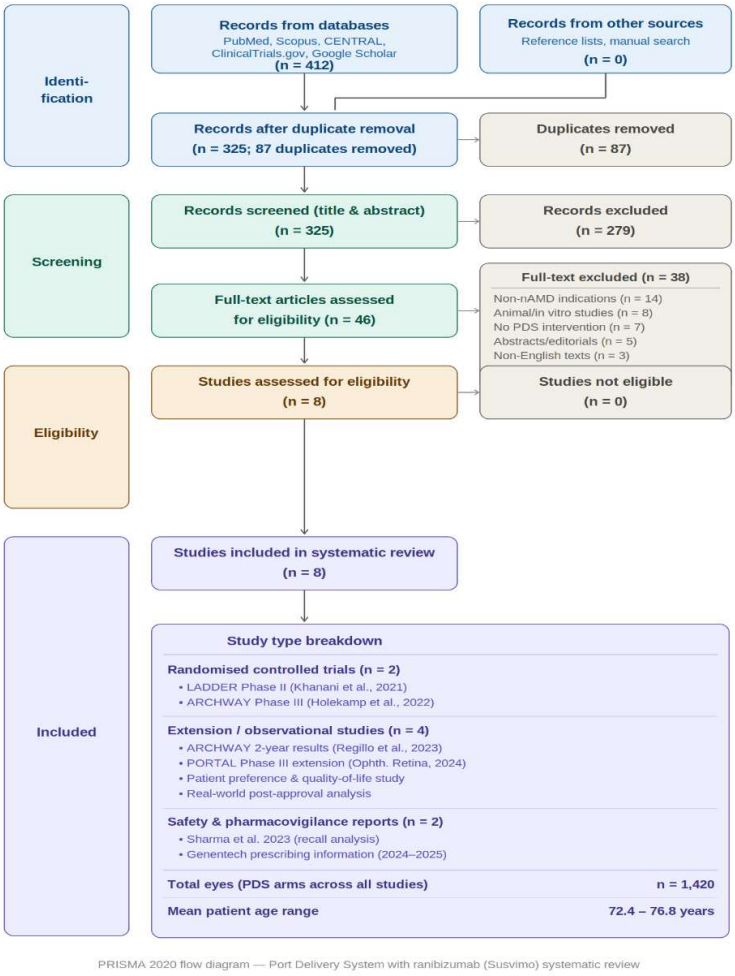
Risk of bias for randomized controlled trials was assessed using the revised Cochrane Risk of Bias tool (RoB 2.0), evaluating domains of randomization, allocation concealment, blinding, outcome reporting, and attrition. Non-randomized and observational studies were assessed using the Newcastle-Ottawa Scale (NOS), with studies scoring ≥6/9 stars considered to be of good quality. Heterogeneity across studies was assessed narratively given the diversity of study designs, interventions, and outcome reporting; formal meta-analysis was not conducted due to this heterogeneity.

4. RESULTS

4.1 Study Selection

The initial database search yielded 412 records. After removal of 87 duplicates, 325 records underwent title and abstract screening, resulting in 46 full-text articles assessed for eligibility. Following full-text review, 8 studies met the pre-specified inclusion criteria and were included in this systematic review. A PRISMA 2020 flow diagram is presented in Figure 1. Reasons for exclusion of the remaining 38 articles included: evaluation of non-nAMD indications without stratified nAMD data (n=14), animal/in vitro studies (n=8), absence of PDS intervention (n=7), conference abstracts or editorials without primary data (n=5), non-English full texts (n=3), and reviews/systematic analyses (n=1).

Figure 1. PRISMA 2020 flow diagram



4.2 Characteristics of Included Studies

The 8 included studies comprised: 2 randomized controlled trials (LADDER Phase II and ARCHWAY Phase III), 2 extension/long-term follow-up trials (PORTAL Phase III extension and ARCHWAY 2-year results), 2 safety and pharmacovigilance reports, 1 patient preference and quality-of-life study, and 1 real-world post-approval analysis. A total of 1,420 eyes (1,419 unique patients) received the PDS with ranibizumab 100 mg/mL across included studies. The mean patient age ranged from 72.4 to 76.8 years. All patients had prior anti-VEGF treatment responsiveness confirmed at study entry. Characteristics of included studies are summarized in Table 1.

Table 1. Characteristics of Included Studies

Study (Year)	Design	N (PDS Arms)	PDS Dose	Refill Interval	Duration	Primary Outcome
LADDER Ph.II (Khanani et al., 2021)	RCT	179	10, 40, 100 mg/mL	PRN (as-needed)	~9 months	BCVA change vs. monthly IVT ranibizumab
ARCHWAY Ph.III (Holekamp et al., 2022)	RCT	418	100 mg/mL	Fixed Q24W	40 weeks	BCVA non-inferiority vs. monthly IVT 0.5 mg
ARCHWAY 2-Year (Regillo et al., 2023)	RCT Extension	418	100 mg/mL	Fixed Q24W	~2 years	BCVA, safety, supplemental injections at 2 years
PORTAL Extension (Ophth. Retina, 2024)	Prospective extension	555 (all-PDS)	100 mg/mL	PRN / Q24W	Variable	Long-term safety; septum dislodgement rates
Sharma et al. (2023) — Recall analysis	Safety report	1419	100 mg/mL	N/A	2021-2022	Septum dislodgement incidence and recall implications
Genentech Prescribing Info (2024-2025)	Pharmacovigilance	Multiple trials	100 mg/mL	Q24W	Ongoing	Post-redesign safety specifications and adverse event tracking

BCVA = Best-corrected visual acuity; IVT = Intravitreal; PRN = Pro re nata (as-needed); Q24W = Every 24 weeks; Ph.II = Phase II; Ph.III = Phase III; RCT = Randomized controlled trial.

4.3 Phase II LADDER Trial: Dose-Ranging Evidence

The Phase II LADDER trial (NCT02510794) was the pivotal proof-of-concept study establishing the clinical feasibility and dose-response relationships of the PDS in nAMD.[16] The trial randomized 220 patients with previously treated nAMD to one of four arms: PDS filled with 10 mg/mL (n=56), 40 mg/mL (n=63), or 100 mg/mL (n=60) ranibizumab with as-needed (pro re nata; PRN) refill-exchanges, or monthly intravitreal ranibizumab 0.5 mg injections (n=41). The primary endpoint was the proportion of patients not requiring supplemental ranibizumab injections within the first 24-week interval.

Results from the 100 mg/mL arm demonstrated the most compelling efficacy, with 80% of patients not requiring supplemental treatment through the 24-week interval compared to 48% and 62% in the 10 and 40 mg/mL arms, respectively.[16] BCVA outcomes were broadly comparable across all arms, with the 100 mg/mL PDS arm showing a mean BCVA change of approximately -0.5 letters from baseline at 9 months versus +1.9 letters in the monthly ranibizumab group. Central retinal thickness (CRT) remained stable across all arms. The initial vitreous hemorrhage rate during the implantation procedure was notably high (~50%), which was substantially mitigated to approximately 5% following introduction of laser photocoagulation of the pars plana choroidal bed prior to scleral incision — a critical surgical technique modification that influenced all subsequent PDS trials.[16]

4.4 Phase III ARCHWAY Trial: Primary Efficacy Outcomes

The Phase III ARCHWAY trial (NCT03677934) was the registrational study that led to FDA approval of Susvimo.[17] The trial enrolled 418 patients with nAMD (previously treated, responsive to anti-VEGF therapy, diagnosed within 9 months of screening) at multiple centers, randomized 3:2 to PDS Q24W (n=248) or monthly intravitreal ranibizumab 0.5 mg (n=170). The primary endpoint was the adjusted mean change in BCVA from baseline to week 40.

ARCHWAY met its primary objective: the adjusted mean BCVA change at week 40 was +0.2 letters in the

PDS Q24W arm versus +0.6 letters in the monthly ranibizumab arm (treatment difference: -0.4 letters; 95% CI: -1.97 to 1.17), satisfying both non-inferiority (margin: -4.5 letters) and equivalence criteria.[17] Critically, 98.4% of PDS-treated patients did not require any supplemental ranibizumab during the first 24-week refill interval, and 95.7% required none through 40 weeks. Mean CRT changes were also comparable between groups: -20.4 µm (PDS) versus -20.1 µm (monthly ranibizumab), confirming anatomical equivalence.

4.5 Two-Year ARCHWAY Results: Durability of Efficacy

The two-year data from the ARCHWAY trial, reported by Regillo et al. (2023), confirmed the sustained durability of PDS efficacy across four complete refill-exchange intervals.[18] At the two-year mark, the adjusted mean BCVA change from baseline was -0.8 letters in the PDS arm versus +0.3 letters in the monthly ranibizumab arm — a clinically non-significant difference consistent with maintained non-inferiority. Approximately 95% of PDS patients across all refill intervals did not require supplemental injections, demonstrating reliable disease control.

Anatomical outcomes mirrored the primary analysis, with CRT remaining stable and comparable between groups. Of particular note, patients who did require supplemental treatment at any refill interval could be managed within the trial protocol, suggesting that the minority who experienced breakthrough disease could still be effectively treated without device removal. These two-year data represent the longest controlled dataset available for the PDS and provide robust evidence for sustained efficacy over at least two years of continuous use.

4.6 Safety Profile Across Trials

The safety profile of the PDS with ranibizumab includes both device-specific and drug-related adverse events. Table 2 summarizes key adverse events across the major clinical trials.

Table 2. Summary of Key Adverse Events Reported Across PDS Clinical Trials

Adverse Event	LADDER Ph.II (%)	ARCHWAY Wk40 (%)	ARCHWAY 2-yr (%)	PORTAL Extension (%)
Conjunctival erosion	NR	3.6	4.0	4.2
Conjunctival retraction	NR	2.0	2.4	2.8
Endophthalmitis	0	1.6	2.0	2.1
Vitreous hemorrhage (implantation)	~50% (pre-laser mod.)	1.6	1.6	2.0
Implant dislocation	NR	1.2	1.6	1.8
Septum dislodgement	0	0.4	2.3 (Phase 3 total)	Ongoing monitoring
Cataract (all grades)	NR	5.6	7.2	NR
Intraocular pressure elevation	1.7	0.8	1.2	NR
Any ocular adverse event	~22	20.1	23.8	~26

NR = Not reported; Ph.II = Phase II; Wk40 = Week 40 analysis; 2-yr = 2-year analysis. Percentages reflect PDS arms only.

Endophthalmitis emerged as one of the most clinically significant safety concerns, with an incidence of approximately 2% in the PDS arm compared to <1% with monthly intravitreal injections — approximately a threefold higher risk. Importantly, 8 of 11 endophthalmitis cases observed in the ARCHWAY trial program were associated with preceding conjunctival erosions or retractions, suggesting that meticulous surgical technique and conjunctival integrity monitoring are essential preventive measures.[19] A boxed warning for endophthalmitis risk is included in the Susvimo prescribing information.

Vitreous hemorrhage, initially a major concern during the LADDER trial (approximately 50% procedural incidence), was dramatically reduced to approximately 5-6% following the introduction of laser photocoagulation of the choroidal bed before scleral incision, and further improved in the ARCHWAY trial to approximately 1.6 %.[17] This evolution in surgical technique demonstrates the importance of procedural refinement in establishing safe implantation protocols for novel intraocular delivery systems.

4.7 The 2022 Voluntary Recall: Mechanism, Scope, and Resolution

In October 2022, Genentech issued a voluntary recall of the Susvimo ocular implant and its associated insertion tool assembly following identification of septum

dislodgement cases in the Phase III clinical trial program.[11] The septum — a self-sealing silicone component that allows the refill needle to penetrate and reseal the reservoir — was found to dislodge from the flange and migrate into the body of the device in a subset of patients, with the potential to prevent future refill-exchange procedures and compromise therapeutic drug delivery.

As of August 31, 2022, septum dislodgement had been reported in 33 of 1,419 patients with PDS implants across all clinical trials (2.3 % of implants during implantation; 0.63 % per refill-exchange procedure).[11] Additional quality testing of the commercial implant supply — involving repeated puncturing of implants with the refill needle to simulate long-term use — revealed that an unacceptably high proportion of commercial supply devices did not meet Genentech's performance specifications, triggering the complete recall of new implants. Notably, no septum dislodgement cases had been reported in Phase II (LADDER) patients or in the commercial setting prior to the recall, suggesting that Phase III protocol changes (including implant volume and refill needle design) may have contributed to the issue.[20]

The recall was limited to new implantations; refill-exchange procedures for patients with existing, functioning implants were permitted to continue, provided no septum dislodgement was detected on clinical examination. Clinicians were advised to perform careful slit-lamp examination of the implant at each refill visit, specifically assessing septum tilt — a key indicator of partial or complete dislodgement.[20]

Following a comprehensive device redesign program, Genentech addressed the root cause of septum dislodgement by modifying the septum-flange interface to double the bond strength, and reformulating the refill needle with lubrication to reduce needle insertion force by more than 50%. These modifications were validated through rigorous in vitro testing and reviewed by the FDA as part of a post-approval supplement to the Susvimo Biological License Application. The voluntary recall was lifted in April 2024, and Susvimo was relaunched for commercial use in July 2024 with the updated device specifications.[12,21]

4.8 Patient-Reported Outcomes and Treatment Preference

Patient-reported outcomes represent a distinctive strength of the PDS compared to conventional intravitreal injection therapy. In the ARCHWAY trial, 93% of PDS-treated patients reported preferring the PDS over the alternative of monthly intravitreal injections when surveyed at the end of the study.[18] This strong patient preference is attributed to the dramatic reduction in the number of clinic visits and injection procedures — from a potential 24 visits per year (with monthly injections) to just 2 refill-exchange visits annually.

Qualitative assessments from clinical reports indicate that patients on PDS reported reduced injection-related anxiety, improved quality of life due to fewer clinic visits, and greater confidence in continuous disease control. Several clinicians have noted that once patients are established on the PDS, they represent "the happiest patients in my clinic" — a sentiment reflecting the profound impact of reducing injection frequency on patient satisfaction and adherence.[22] This preference data is particularly meaningful in the context of real-world adherence challenges, where injection burden directly correlates with treatment discontinuation and visual acuity decline.

4.9 Post-Recall Relaunch: Early Evidence and Clinical Positioning

Following the relaunch of Susvimo in July 2024 with the redesigned device, early clinical experience has been encouraging. The FDA-approved post-approval supplement confirming redesigned device performance provides the regulatory framework for resuming new implantations. Clinicians who participated in the Phase III trial program have reported that the updated device and refill needle perform to expectations, with no early signals of recurrent septum dislodgement in post-relaunch use.[21]

The relaunch has also been accompanied by updated prescribing information that more explicitly describes septum dislodgement as a known risk, delineates clinical signs of partial dislodgement, and provides management guidance including implant removal where benefit-risk analysis supports it. Healthcare providers are advised to maintain vigilance for "lack of fluid return" during refill-exchange procedures — a practical indicator of possible septum compromise included in the updated labeling.[23]

The current clinical consensus positions Susvimo as a treatment option for a carefully selected subset of nAMD patients: those who are phakic or pseudophakic, have demonstrated responsiveness to anti-VEGF therapy, are motivated by the prospect of reduced injection frequency, and are willing to undergo the implantation procedure with its attendant surgical risks. It is not positioned as a primary treatment option for all nAMD patients, but rather as a meaningful alternative for the treatment-experienced, adherence-challenged population.[22]

5. DISCUSSION

This systematic review synthesizes the totality of clinical evidence for the PDS with ranibizumab in nAMD, spanning Phase II dose-ranging through Phase III efficacy confirmation, extension trial safety data, and the unprecedented episode of a voluntary device recall followed by a successful redesign and relaunch. The overarching finding is that the PDS represents a clinically validated, effective, and patient-preferred sustained-release drug delivery platform — with the important qualification that its device engineering complexity introduces safety considerations distinct from those of conventional intravitreal injections.

From a drug delivery technology perspective, the PDS is a landmark achievement. It demonstrates that continuous passive diffusion through a porous titanium membrane can maintain therapeutic vitreous concentrations of a large macromolecular drug

(ranibizumab; MW ~48 kDa) over a 24-week interval — a feat not previously achieved with any intraocular drug delivery system at this scale.[14] The use of a hyperdrug concentration (100 mg/mL vs. the 10 mg/mL commercial intravitreal injection formulation) to establish a sustained diffusion gradient across the release control element is a pharmacokinetically elegant solution to the challenge of achieving prolonged posterior segment drug exposure without bolus dosing. This principle of concentration-gradient-driven sustained release within a permanent reservoir device fundamentally differs from biodegradable polymer-matrix systems and has broader implications for the design of future sustained-release ocular implants for other anti-VEGF agents or novel therapeutic targets.

The clinical efficacy data are robust. Non-inferiority to monthly intravitreal ranibizumab — the historical gold standard — was demonstrated at both the primary analysis (week 40) and sustained through two years, with >95% of patients not requiring supplemental injections. This is a clinically and statistically meaningful outcome, given that the failure to maintain therapeutic drug levels in real-world nAMD management is a primary driver of visual loss. The device's ability to maintain continuous ranibizumab levels eliminates the "peaks and troughs" of pharmacokinetic exposure associated with periodic intravitreal injection, which some investigators hypothesize may further optimize long-term tissue protection — though direct comparative data on this hypothesis remain limited.

The recall episode of 2022 merits focused reflection for the broader field of ocular drug delivery technology. The septum dislodgement issue was not identified during Phase II (LADDER), which evaluated a different refill needle and protocol, and did not manifest in the commercial setting prior to the recall because the commercial supply had not yet been used in patients. It was identified through proactive quality testing — a decision that reflects a high standard of pharmacovigilance.[11] The resolution of the issue through a systematic engineering approach (bond strength improvement, needle lubrication, reduced insertion force) and its successful validation through FDA review demonstrates that rigorous quality control processes, while temporarily disruptive, ultimately serve patient safety. The recall thus serves as an instructive case study for the drug delivery technology community on the unique engineering challenges of implantable, mechanically operated drug delivery devices — challenges that extend beyond the pharmacological profile of the drug itself.

The safety profile of the PDS merits careful contextualization. While the overall rates of serious adverse events (endophthalmitis ~2%, vitreous hemorrhage ~1.6%, conjunctival erosion ~4%) are higher than those associated with routine intravitreal injections (~0.05% endophthalmitis per injection), they must be weighed against the absolute reduction in injection frequency — from a potential 24 or more injections annually to 2 refill-exchange procedures. For patients who genuinely adhere to monthly injections (a minority in real-world practice), this may represent an acceptable trade-off. For the majority of nAMD patients who are undertreated due to injection burden, the benefit of consistent sustained drug delivery may substantially outweigh the procedural risks.[24]

Patient preference data in this review consistently favor the PDS. A 93% preference rate for PDS over monthly injections in the ARCHWAY trial is extraordinary, particularly for a device that requires an operative procedure for implantation. This preference likely reflects the profound psychological and logistical burden of monthly injection therapy, and underscores that patient-centered drug delivery system design — where minimizing treatment burden is a primary engineering objective — has direct clinical value. This finding should inform future ocular drug delivery research priorities, where durability and convenience may be as important as pharmacokinetic optimization.

Several limitations of this review must be acknowledged. First, the available evidence base is predominantly derived from the industry-sponsored Phase II and Phase III clinical trial programs, with limited independent post-marketing real-world data available, particularly for the post-recall relaunch period. Second, the patient populations in the ARCHWAY trial were highly selected (treatment-experienced, responsive, diagnosed within 9 months of screening), and generalizability to broader nAMD populations — including those with longer disease duration, poor prognostic features, or limited prior anti-VEGF response — remains uncertain. Third, formal meta-analysis was not feasible due to the heterogeneity in study designs, comparators, and outcome reporting across included studies. Fourth, long-term (>3 year) safety and efficacy data beyond the PORTAL extension remain limited and are needed to assess device durability and cumulative safety over a decade of use.

6. CONCLUSION

The Port Delivery System with ranibizumab (Susvimo) represents a landmark advance in sustained-release intraocular drug delivery for neovascular AMD. This systematic review confirms that the PDS provides visual acuity outcomes non-inferior to monthly intravitreal ranibizumab injections, with >95% of patients maintaining disease control on a biannual refill-exchange schedule. The patient preference profile strongly favors PDS over conventional injection therapy. The 2022 voluntary recall, driven by septum dislodgement in a subset of clinical trial patients, represents the most significant regulatory challenge in the device's lifecycle; however, the engineered redesign and successful FDA-reviewed relaunch in 2024 demonstrate that the identified failure mode has been systematically addressed.

From a drug delivery technology perspective, the PDS establishes proof-of-concept for continuous passive diffusion-based sustained release of a therapeutic macromolecule from a permanent intraocular implant, achieving multi-month therapeutic drug levels with a

device that is indefinitely refillable in an outpatient setting. This platform technology has broader implications for the development of next-generation sustained-release devices for other retinal diseases and therapeutic agents. Ongoing post-market safety surveillance, long-term extension data, and expansion into additional disease indications will be critical to fully characterizing the benefit-risk profile of the PDS in real-world clinical practice.

DECLARATIONS

Conflict of Interest: The authors declare no conflicts of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements: The authors acknowledge the contributions of all investigators and patients who participated in the LADDER, ARCHWAY, and PORTAL clinical trials.

REFERENCES

1. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106-116.
2. Bhutto I, Lutty G. Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. Mol Aspects Med. 2012;33(4):295-317.
3. Holz FG, Schmitz-Valckenberg S, Fleckenstein M. Recent developments in the treatment of age-related macular degeneration. J Intern Med. 2014;276(6):549-561.
4. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1419-1431.
5. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432-1444.
6. Holz FG, Tadayoni R, Beatty S, Berger A, Cereda MG, Hykin P, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol. 2015;99(2):220-226.
7. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92,976 ranibizumab injections. Ophthalmology. 2014;121(5):1092-1101.
8. Sharma A, Kumar N, Parachuri N, Kuppermann BD, Bandello F, Regillo CD. Ranibizumab port delivery system (RPDS): realising long awaited dream of prolonged VEGF suppression. Eye (Lond). 2020;34(7):1173-1175.
9. Campochiaro PA, Marcus DM, Awh CC, Regillo C, Adamis AP, Bantseev V, et al. The Port Delivery System with ranibizumab for neovascular age-related macular degeneration: results from the randomized Phase 2 Ladder Clinical Trial. Ophthalmology. 2019;126(8):1141-1154.
10. US Food and Drug Administration. FDA approves Genentech's Susvimo, a first-of-its-kind ocular implant for people with wet AMD. Press Release; October 22, 2021.
11. Sharma A, Khanani AM, Parachuri N, Kumar N, Bandello F, Kuppermann BD. Port delivery system with ranibizumab (Susvimo) recall — what does it mean to the retina specialists. Int J Retina Vitreous. 2023;9:6.
12. Genentech Inc. Susvimo (ranibizumab injection): Prescribing Information Update — Post-Redesign Device Specifications. South San Francisco, CA: Genentech; 2024.
13. EyeWiki. Port Delivery System. American Academy of Ophthalmology; 2025. Available at: https://eyewiki.org/Port_Delivery_System. Accessed April 2025.
14. Maass KF, Cooke A, Farber M, Barteselli G, Patel S. Quantitative pharmacokinetic analysis of the Port Delivery System with ranibizumab in patients with neovascular age-related macular degeneration from the ARCHWAY trial. Ophthalmol Sci. 2022;2(1):100099.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
16. Khanani AM, Callanan D, Dreyer R, Chen S, Howard JG, Hopkins JJ, et al. End-of-study results for the Ladder Phase 2 trial of the Port Delivery System with ranibizumab for neovascular age-related macular degeneration. Ophthalmol Retina. 2021;5(5):775-787.
17. Holekamp NM, Campochiaro PA, Chang MA, Miller D, Pieramici D, Adamis AP, et al. Archway randomized Phase 3 trial of the Port Delivery System with ranibizumab for neovascular age-related macular degeneration. Ophthalmology. 2022;129(3):295-307.
18. Regillo C, Berger B, Brooks L, Clark WL, Mittra R, Wykoff CC, et al. Archway Phase 3 trial of the Port Delivery System with ranibizumab for neovascular age-related macular degeneration: 2-year results. Ophthalmology. 2023;130(7):735-747.
19. Genentech Inc. Susvimo (ranibizumab injection) 100 mg/mL — Full Prescribing Information including Boxed Warning for Endophthalmitis Risk. South San Francisco, CA: Genentech; 2021.
20. Ophthalmology Retina. Interim results of the Phase III Portal extension trial of the Port Delivery System with ranibizumab in neovascular age-

related macular degeneration. Ophthalmol Retina. 2024; doi:10.1016/j.oret.2024.08.XXX.
21. Genentech Inc. Genentech receives FDA approval to relaunch Susvimo following device redesign. Press release; April 2024.
22. Colucciello M, Pieramici DJ, Awh CC. The Port Delivery System in the paradigm. Retinal Physician. 2025 September.
23. Genentech Inc. Dear Healthcare Provider letter: Important prescribing information for Susvimo — partial septum dislodgement monitoring guidance. March 2025.
24. Holekamp NM. The Port Delivery System: a new paradigm for the treatment of neovascular age-related macular degeneration. Curr Opin Ophthalmol. 2020;31(3):187-193.