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REVIEW

Systematic Literature Reviews Comparing the Long-Term Safety Outcomes for the Port Delivery System with Ranibizumab (PDS) Versus Other Ocular Implants

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ABSTRACT

Objectives: To determine whether the types and rates of post-surgical complications associated with the Port Delivery System with ranibizumab (PDS) are comparable with those reported for other ocular implants that cross the sclera.
Methods: Systematic literature reviews were conducted to determine the long-term (≥ 18-month) safety of ocular implants that cross the sclera in clinical trials and real-world studies. Complication types and rates were compared with those reported for the PDS in phase III clinical trials (Archway, Pagoda, and Pavilion).
Results: Sixteen clinical trials (24 publications) and 43 real-world studies were identified reporting 30 complications in eyes with 15 implant types and 8 ocular diseases. Implants were associated with an acceptable, well-characterized safety profile, with most complications resolving spontaneously or with treatment. Device-related complications were reported in 0.7% (0.0–5.0%) of study eyes in clinical trials and 1.3% (0.0–14.5%) of eyes in real-world studies. Rates of conjunctival complications were 2.1% (0.0–22.8%) and 2.2% (0.9–4.6%), respectively. The overall types and rates of adverse events of special interest reported for the PDS in phase III trials (cataract, conjunctival bleb, vitreous hemorrhage, conjunctival erosion, conjunctival retraction, endophthalmitis, implant dislocation, retinal detachment, and hyphema) were within the ranges reported for other ocular implants.
Conclusions: The rates of complications reported in phase III clinical trials for the PDS were within the ranges reported for other ocular implants that cross the sclera. This suggests that the long-term safety of the PDS is consistent with other ocular devices established in ophthalmology clinical practice.

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Keywords: Age-related macular degeneration; Diabetic retinopathy; Diabetic macular edema; Ocular implants; Port Delivery System with ranibizumab (PDS); Retinal diseases

Key Summary Points

Systematic literature reviews (SLRs) were conducted to capture the evidence for the long-term safety of ocular implants that cross the sclera in clinical trials and real-world studies.

The types and rates of adverse events of special interest associated with the Port Delivery System with ranibizumab (PDS) in phase III clinical trials were compared with those reported for ocular implants in the SLRs.

Rates of complications reported in phase III clinical trials for the PDS were within the range reported for more established ocular implants.

These results will help build confidence in the long-term safety of ocular implants, including the PDS.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and diabetic retinopathy (DR) are leading causes of vision loss worldwide [1–3]. Standard of care for these conditions includes regular (up to monthly) intravitreal injections with anti-vascular endothelial growth factor (VEGF), including ranibizumab, aflibercept, and brolucizumab [4]. Although effective, the vision benefits of anti-VEGF injections are less marked in real-world practice than in clinical trials, probably because of missed or delayed injections attributed to the high treatment burden [5–7]. The Port Delivery System with ranibizumab 100 mg/ml (PDS) (Genentech, Inc., South San Francisco, CA, USA) is a surgically placed, refillable ocular implant that continuously delivers a customized formulation of ranibizumab into the vitreous, thereby reducing treatment burden compared with monthly injections [8, 9]. The PDS with fixed refill-exchanges every 24 weeks (Q24W) is approved by the US Food and Drug Administration for use in adults with nAMD responsive to anti-VEGF injections [10].

The safety and efficacy of the PDS Q24W have been previously reported up to 96 weeks in 248 eyes with nAMD in the phase III Archway trial [11, 12]. The phase III Pagoda trial subsequently assessed the safety and efficacy of the PDS Q24W up to 64 weeks in 381 eyes with DME [13], while the phase III Pavilion trial evaluated the PDS with refill-exchanges every 36 weeks up to 52 weeks in 106 eyes with DR [14]. Results from all three trials show that the PDS effectively maintained long-term vision and anatomic outcomes across indications, with comparable results to monthly or as-needed ranibizumab injections. Adverse events of special interest (AESIs) (post-surgical complications common to all three trials) include cataract, conjunctival bleb, vitreous hemorrhage, conjunctival erosion, conjunctival retraction, endophthalmitis, implant dislocation, retinal detachment, and hyphema (Table 1). The objective of this systematic literature review (SLR) is to assess the long-term post-surgical safety of ocular implants that cross the sclera in adults with (but not restricted to) nAMD, DME, or DR. Results will be used to determine whether the types and rates of AESIs associated with the PDS in phase III trials are comparable to those reported for other implants.

METHODS

Two SLRs (one for clinical trials and the other for real-world studies) were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. Both were conducted by Envision Value & Access, funded by Genentech, Inc. (a member of the Roche Group), and are

Table 1 Summary of AESIs in eyes treated with the PDS in phase III clinical trials and in eyes treated with any ocular implant that crosses the sclera in clinical trials and real-world studies

Trial	Archway ($n = 248$)	Pagoda ($n = 320$)	Pavilion ($n = 105$)	Clinical trials SLR[a]	Real-world SLR[b]
Population	**nAMD**	**DME**	**DR**	**Any retinal disease**	**Any retinal disease**
Follow-up	**96 weeks**	**64 weeks**	**52 weeks**	**≥ 72 weeks**	
Implant	**PDS 100 mg/ml Q24W**	**PDS 100 mg/ml Q24W**	**PDS 100 mg/ml Q36W**	**Any ocular implant that crosses the sclera**	
% of eyes with AESIs				**% or median (range) % of eyes with AESIs**	
Cataract[c]	8.9	10.9	6.7	NR	NR
Unwanted conjunctival bleb[d]	6.9	7.8	1.9	2.1 (0.0–22.8)	0.9
Conjunctival erosion	4.0	1.9	1.0	2.2	3.5 (2.4–4.6)
Conjunctival retraction	2.4	1.3	1.9	0.6	NR
Implant dislocation[e]	1.6	0.3	0.0	NA (0.0–0.3)	1.1 (0.1–4.1)
Endophthalmitis	1.6	0.0	0.0	0.6 (0.0–2.7)	0.0 (0.0–2.1)
Hyphema	0.4	1.9	1.9	3.0 (0.0–8.6)	4.5 (0.0–30.4)
Retinal detachment	0.8	0.0	1.0	1.0 (0.0–1.9)	1.5 (0.0–20.5)
Vitreous hemorrhage	6.0	9.7	5.7	2.7 (1.3–13.1)	1.1 (0.0–50)

Results are presented as absolute or median (range) percentage of study eyes

AESI adverse event of special interest, *DME* diabetic macula edema, *DR* diabetic retinopathy, *MedDRA* Medical Dictionary for Regulatory Activities, *nAMD* neovascular age-related macular degeneration, *NR* not reported, *PDS* Port Delivery System with ranibizumab, *Q24W* refill-exchange every 24 weeks, *Q36W* refill-exchange every 36 weeks, *SLR* systematic literature review

[a]Includes PDS-related AESIs reported by the phase II Ladder trial but not the phase III Archway, Pagoda, or Pavilion trials

[b]Does not include any real-world studies for the PDS

[c]All cataracts were reported by the Archway, Pagoda, and Pavilion trials, whereas only traumatic cataracts were reported in the SLRs

[d]Unwanted conjunctival bleb includes any bleb in eyes without glaucoma and uncomfortable, encapsulated, and encysted bleb in eyes with glaucoma. It excludes planned, uncomplicated bleb resulting from glaucoma-filtering surgeries

[e]"Implant dislocation" is reported in MedDRA as "device dislocation." Note: care should be taken when comparing data across clinical trials because of differences in trial design, in particular patient populations, doses, re-treatment intervals, and trial duration

registered on the PROSPERO international prospective register of systematic reviews (CRD5202234129 and CRD42022343129). This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Sources

Searches were run using Embase and Medline via Ovid and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (CDSR) via the Cochrane Library (https://www.cochranelibrary.com/).

Study Screening and Selection

Study inclusion criteria were defined according to the Population, Intervention, Comparator, Outcome, and Study type (PICOS) framework using the criteria outlined online in Table S1. Eligible studies met the following criteria: (1) included ≥ 50 study eyes in adults (age ≥ 18 years) receiving any ocular implant that crosses the sclera; (2) evaluated safety outcomes in patients with ≥ 18 months of follow-up (thereby capturing long-term complications such as conjunctival erosion and device exposure), and (3) were published in English. One SLR included phase II–IV clinical trials published before May 2022, and the other included real-world studies published between 2012 and June 2022. Duplicate results were deleted from each SLR, and one researcher conducted a pre-screen with another checking excluded records. Abstracts were screened by two independent researchers per SLR (level 1 [L1] screening), and both researchers screened full-text L1 papers at level 2. Disagreements were resolved by a third researcher.

Data Extraction and Quality Assessment

Data were extracted into pre-specified Microsoft Excel grids. The quality of randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias 2 tool (RoB2) [16]; non-RCT studies and real-world studies were assessed using the Newcastle-Ottawa scale (NOS) [17].

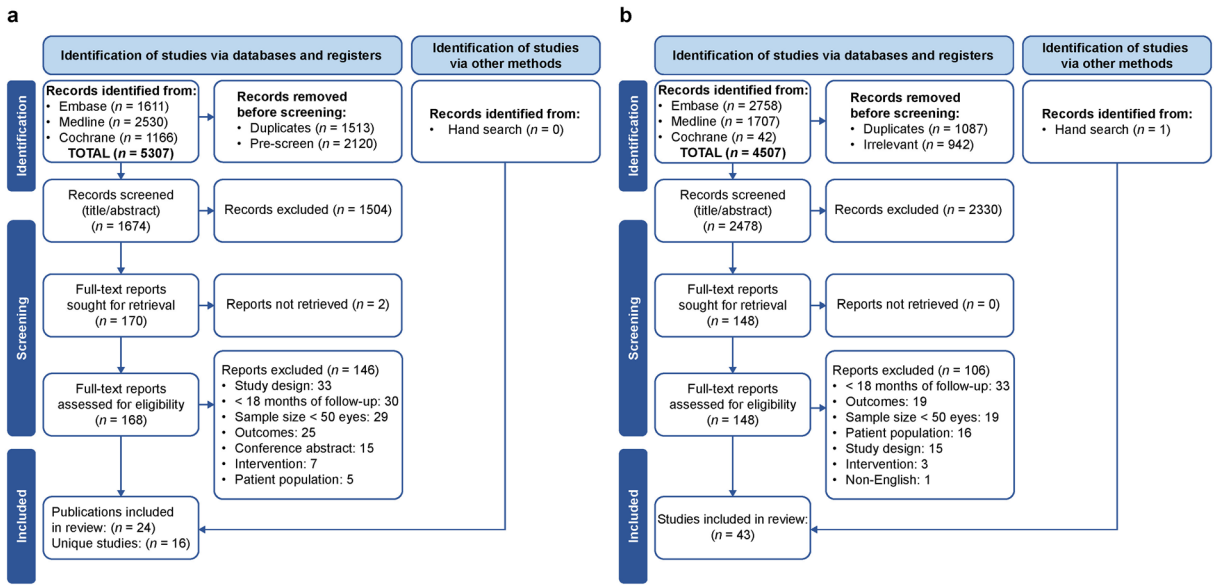

Fig. 1 Search strategy and selection of **a** clinical trials and **b** real-world studies presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

RESULTS

The clinical trial SLR identified 5307 relevant publications, 5283 of which were excluded before or at screening (Fig. 1A). Twenty-four publications, representing 16 studies (13 RCTs and three non-RCTs) published between 2004 and 2021, were included in the report. Phase III clinical trials for the PDS (Archway [11, 12], Pagoda [13], and Pavilion [14]) were published after 2001 and were not included in the SLR. The review of real-world studies identified 4507 records, 4465 of which were excluded before or at screening (Fig. 1B). One eligible study [18] was identified through hand searches. Forty-three studies (four prospective and 39 retrospective) published between 2005 and 2022 were included in the report.

Study Characteristics

Clinical Trials

For the 16 clinical trials, median number of study eyes per treatment arm was 72 (range 25 [19] to 351 [20]), mean (standard deviation) patient age was 59.4 (1.5) [21] to 78.5 (8.5) [22] years, and the proportion of male patients was 27.0% [23] to 60.7% [20]. Trial duration typically ranged from 2 to 5 years [8, 9, 19, 21, 24–34], with one study [35] reporting follow-up to 10 years. Trials included eyes with nAMD (one RCT) [8, 9, 20], DME (one RCT) [20], and glaucoma (11 RCTs and three non-RCTs) [19, 21–40]. No trials were identified that included eyes with DR. Eight different implants were investigated, including Ahmed (five RCTs) [19, 21, 26–30, 36], Baerveldt (five RCTs) [26–34, 37], Ex-Press (three RCTs) [24, 25, 38], XEN (one non-RCT) [22, 23, 39], glaucoma collagen implants (two non-RCTs) [35, 40], and the PDS [8, 9], Ozurdex [20], and Molteno [21] (one RCT each). Seven publications reported data from Europe [22, 23, 35, 39, 40], six from the US [8, 9, 20, 26, 27, 36], eight from multiple countries [25, 28–33, 37], and one each from Canada [38], Iran [21], and India [19].

Real-World Studies

Sample sizes for the 43 real-world studies (39 retrospective [41–78] and four prospective [18, 79–81]) ranged from 26 [45] to 2661 [65] eyes, mean patient age (reported in 41 publications) was 27.6 [48] to 79.4 [66] years, and the proportion of male patients varied from 26.7% [76] to 51.3% [81]. Mean follow-up (where reported) was between 17.3 months [78] and 8.5 years [57], with one study reporting data to 10 years [59]. Thirty-five studies included eyes with glaucoma [41–55, 58–61, 63–67, 72–80], two each included macular edema [62, 81], rhegmatogenous retinal detachment [57, 69], and uveitis [56, 68], and one each included DME [18], inadequate capsular support [70], and aphakia [71]. No studies were identified that included eyes with nAMD or DR. Nineteen studies reported complications for Ahmed implants [41, 43–46, 48–50, 54, 61, 65, 67, 68, 72–74, 78, 79, 82]; eight for Baerveldt [51, 55, 63–65, 67, 68, 80]; five for XEN [58, 60, 75–77]; three each for Ex-Press [52, 53, 66, 73], Ozurdex [56, 62, 81], and scleral fixation of intraocular lens (SFIOL) implants [42, 70, 71]; two each for Aurolab aqueous drainage implants [47, 49] and scleral buckle [57, 69], one each for Iluvien [18] and other implants [42, 59, 65, 66]; and none for the PDS. Sixteen studies were conducted in Asia [41–55], ten in Europe [56–63, 79, 80], and seven in the US [18, 64–69], four in the Middle East [70–73], two in Canada [74, 75], three in multinational countries [76, 77, 81], and one in Brazil [78].

Quality Assessment

All but one of the 13 RCTs failed to mask patients and/or assessors to treatment allocation or did not specify whether allocation was masked (Table S2A), raising concerns about bias. This is common for surgical trials where masking is not possible because of readily apparent differences between devices. NOS scores indicate a high risk of bias for all three non-RCTs (Table S2B) and 24/43 real-world studies (Table S2C), medium risk for 18/43 real-world studies, and low risk for 1/43 real-world studies.

Table 2 Frequency and range of complications reported by 16 clinical trials (24 publications, 28 treatment arms) and 43 real-world studies (43 publications)

Complication	Clinical trials				Real-world studies			
	Studies (publications), *n*	Treatment arms, *n*	Range, %	Median, %	Studies, *n*	Treatment arms, *n*	Range, %	Median, %
Shallow anterior chamber	10 (15)	13	0.0–17.0	2.2	11	16	0.0–23.1	5.5
Choroidal effusion/detachment	8 (14)	12	0.0–16.0	6.4	13	18	0.0–27.3	4.1
Hyphema/persistent hyphema	**8 (14)**	**11**	**0.0–8.6**	**3.0**	**16**	**21**	**0.0–30.4**	**4.5**
Unwanted conjunctival bleb[a]	**7 (15)**	**10**	**0.0–22.8**	**2.1**	**1**	**1**	**0.9**	**0.9**
Endophthalmitis	**7 (15)**	**13**	**0.0–2.7**	**0.6**	**22**	**26**	**0.0–2.1**	**0.0**
Hypotony	7 (14)	13	0.0–23.3	1.0	19	25	0.0–22.7	2.6
Retinal detachment	**6 (12)**	**9**	**0.0–1.9**	**1.0**	**12**	**13**	**0.0–20.5**	**1.5**
Macular edema	5 (8)	8	0.0–7.2	2.7	11	14	0.0–5.6	3.3
Iritis	4 (9)	6	2.0–12.0	5.8	0	–	–	–
Tube erosion	4 (9)	6	0.0–5.0	2.4	12	19	0.0–14.5	2.0
Bleb leak	4 (7)	4	0.0–8.6	0.5	3	4	0.5–2.4	1.6
Diplopia	3 (6)	4	2.0–12.7	8.9	3	5	0.0–3.8	0.3
Vitreous hemorrhage	**3 (5)**	**5**	**1.3–13.1**	**2.7**	**14**	**17**	**0.0–50.0**	**1.1**
Suprachoroidal hemorrhage	2 (5)	4	0.0–3.0	1.0	9	12	0.0–2.8	1.3
Conjunctival retraction	**1 (2)**	**1**	**0.6**[b]	**–**	**0**	**–**	**–**	**–**
Conjunctival erosion	**1 (2)**	**1**	**2.2**[b]	**–**	**2**	**2**	**2.4–4.6**	**3.5**
Wound dehiscence	1 (1)	2	4.3[c]	–	2	2	0.9–3.9	2.4
Retinal tear	1 (1)	2	0.9–1.4	–	1	1	0.0	0.0
Implant dislocation	**1 (1)**	**2**	**0.0–0.3**	**–**	**5**	**5**	**0.1–4.1**	**1.1**
Tube retraction	1 (1)	1	1.0[b]	–	3	4	0.5–2.6	1.5
Plate exposure	1 (1)	1	1.0[b]	–	4	4	0.9–1.9	1.4
Conjunctival dehiscence	0 (0)	–	–	–	0	–	–	–
Traumatic cataract	**0 (0)**	**–**	**–**	**–**	**0**	**–**	**–**	**–**
Vitritis	0 (0)	–	–	–	0	–	–	–
Retinal vasculitis	0 (0)	–	–	–	0	–	–	–
Exposed implant	0 (0)	–	–	–	1	1	1.8	1.8

Table 2 continued

Complication	Clinical trials				Real-world studies			
	Studies (publications), *n*	Treatment arms, *n*	Range, %	Median, %	Studies, *n*	Treatment arms, *n*	Range, %	Median, %
Shunt erosion	0 (0)	–	–	–	0	–	–	–
Intraocular inflammation	0 (0)	–	–	–	0	–	–	–
Device-related complications[d]	6 (11)	9	0.0–5.0	0.7	18	26	0.0–14.5	1.3
Conjunctival complications[e]	7 (15)	10	0.0–22.8	2.1	3	3	0.9–4.6	2.2
Total	**16 (24)**	**28**	–	–	**43**	**52**	–	–

For studies with multiple time points, data for the most recent time point were used for calculation in number of arms, range, and median. AESIs are shown in bold text

AESI adverse event of special interest

[a]The term "unwanted bleb" includes any conjunctival bleb in eyes without glaucoma and encysted, encapsulated, or uncomfortable bleb in eyes with glaucoma. It excludes planned, uncomplicated bleb resulting from glaucoma-filtering surgeries

[b]Data from one arm only

[c]Same value in both arms

[d]Device-related complications include tube erosion, implant dislocation, tube retraction, exposed implant, and plate exposure

[e]Conjunctival complications include conjunctival retraction, conjunctival erosion, unwanted conjunctival bleb, and conjunctival dehiscence

Post-Surgical Complications

Clinical Trials

Thirty complications were investigated across 16 clinical trials (28 treatment arms) (Table 2). The most frequently assessed complications were shallow anterior chamber (10 studies), choroidal effusion/detachment and hyphema/persistent hyphema (eight studies each), and endophthalmitis and hypotony (seven studies each). Median complication rate was highest for diplopia (8.9%, range 2.0–12.7%) (three studies), followed by choroidal effusion/detachment (6.4%, 0.0–16%) (eight studies), and iritis (5.8%, 2.0–12.0%) (four studies). Median rates of device-related complications (tube erosion, implant dislocation, tube retraction, exposed implant, and plate exposure) and conjunctival complications (conjunctival retraction, erosion, unwanted bleb, and dehiscence) were 0.7% (range 0.0–5.0%) (six studies) [20, 26–34, 37] and 2.1% (0.0–22.8%) (seven studies) [8, 9, 22, 23, 26–33, 35, 37, 39], respectively. Device deficiency (implant failure) was reported by seven trials [21–23, 26–33, 35, 38, 39], all of which were conducted in eyes with glaucoma (Table S3A). Median rate of device deficiency was 27.2% (range 3.8–45.0%), with definitions varying across studies. Two clinical trials assessed device explantation [26–30]. One reported the post-failure replacement of an Ahmed implant with Baerveldt in eyes with glaucoma [26, 27] and another reported the use of a secondary implant to regulate intraocular pressure (IOP) in two eyes with glaucoma [34].

Real-World Studies

Thirty complications were reported across 43 real-world studies (52 arms). Endophthalmitis

was the most frequently assessed complication (22 studies), followed by hypotony (19), hyphema (16), vitreous hemorrhage (14), choroidal effusion/detachment (13), and tube erosion and retinal detachment (12 studies each) (Table 2). Median complication rates were highest for hyphema (4.5%, range 0.0–30.4%), followed by choroidal effusion/detachment (4.1%, 0.0–27.3%), hypotony (2.6%, 0.0–22.7%), tube erosion (2.0%, 0.0–14.5%), vitreous hemorrhage (1.1%, 0.0–50.0%), and endophthalmitis (0.0%, 0.0–2.1%). Median rates of device-related complications and conjunctival complications were 1.3% (range 0.0–14.5%) (18 studies) [43, 45, 48–50, 54, 55, 57, 60, 61, 67, 72, 73, 77, 79, 81, 83] and 2.2% (0.9–4.6%) (three studies) [58, 61, 63, 74], respectively. Median rate of device deficiency (reported by 14 studies in eyes with glaucoma [47, 48, 50, 52–54, 58, 64, 66, 67, 72, 74, 76, 82]) was 19.9% (1.0–61.6%) (Table S3B). Six studies [50, 54, 58, 64, 72, 74] reported device explantation, with three providing no reason and one each reporting removal due to extrusion [64], conjunctival erosion [58], and plate exposure [50]. All cases of explantation occurred in eyes with glaucoma and Ahmed, Baeveldt, or XEN implants. Two studies reported the use of a secondary implant to regulate IOP in an eye with glaucoma [74, 82].

Post-Surgical AESIs

Clinical Trials

The most frequently assessed AESIs in clinical trials were hyphema (eight studies), unwanted conjunctival bleb, and endophthalmitis (seven studies each), retinal detachment (six), and vitreous hemorrhage (three), followed by conjunctival retraction, conjunctival erosion, and implant dislocation (one study each). Median rates of AESIs were highest for hyphema (3.0%, range 0.0–8.6%), vitreous hemorrhage (2.7%, 1.3–13.1%), conjunctival erosion (2.2%, range not applicable), and conjunctival bleb (2.1%, 0.0–22.8%) (Table 3).

Real-World Studies

The most frequently assessed AESI in real-world studies was endophthalmitis (22 studies), followed by hyphema (16), vitreous hemorrhage (14), retinal detachment (12), implant dislocation (five), conjunctival erosion (two), and unwanted conjunctival bleb (one). Median rates of AESIs were highest for hyphema (4.5%, range 0.0–30.4%), conjunctival erosion (3.5%, 2.4–4.6%), retinal detachment (1.5%, 0.0–20.5%), implant dislocation (1.1%, 0.1–4.1%), and vitreous hemorrhage (1.1%, 0.0–50.0%) (Table 4).

Traumatic Cataract

Traumatic cataract was not reported by any of the studies in the SLRs.

Unwanted Conjunctival Bleb

Unwanted conjunctival bleb (any conjunctival bleb in eyes without glaucoma and encysted, encapsulated, or uncomfortable bleb in eyes with glaucoma) was reported in seven clinical trials (five RCT and two non-RCT), with mean follow-up ranging from 22 to 101.5 months [8, 9, 22, 26–33, 35, 37]. Mean number of study eyes per treatment group was 114 (range 44–179). One trial reported bleb in one eye (0.6%) with nAMD and the PDS at 22 months [8, 9] and six reported unwanted (encysted, encapsulated, or uncomfortable) bleb in eyes with glaucoma and collagen, XEN, Ahmed, or Baerveldt implants (median 2.1% [range 0.0–22.8%] at 2 years to 101.5 months [22, 26–33, 35, 37]) (Table 3). One retrospective real-world study reported encapsulated bleb in one eye (0.9%) with glaucoma and Ahmed after 3.8 years [61] (Table 4).

Vitreous Hemorrhage

Vitreous hemorrhage was assessed by three RCTs, one each in eyes with nAMD, DME, and glaucoma (Table 3). Study duration ranged from 2 to 5 years and median number of eyes per treatment arm was 143 (range 110–347). Median rate of vitreous hemorrhage was 2.7% (range 1.3–13.1%), with the highest rate in eyes with

Table 3 Summary of AESIs reported in clinical trials by condition and implant type

Disease	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
nAMD	Khanani (2021) [9]; Campochiaro 2019) [8]	PDS	179	Mean [range]: 22 [10.8–7.6] months	NR	1 (0.6)	2 (1.3)	4 (2.2)	1 (0.6)	2 (1.1)	NR	Rheg.: 3 (1.7) Tract.: 1 (0.6)	2 (1.1)
DME	Boyer (2014) [20]	Ozurdex 0.7 mg	351	3 years	NR	NR	NR (6.9)	NR	NR	2 (0.6)	1 (0.3)	2 (0.6) SAE: 1 (0.3)	NR
		Ozurdex 0.35 mg	347	3 years	NR	NR	NR (13.1)	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	NR
Glaucoma	Bissig (2008 [35]	Collagen implant (deep sclerectomy)	105	Mean (SD) [range]: 101.5 (43.1) [3–144] months Median: 120 months	NR	Encysted 24 (22.8)	NR	NR	NR	NR	NR	NR	9 (8.6)
	Gillmann (2020) [23]	Bilateral XEN stent (affected eyes)	37	2 years	NR	NR	NR	NR	NR	0 (0.0)	NR	NR	NR
		Bilateral XEN stent (fellow eyes)	37		NR	NR	NR	NR	NR	1 (2.7)	NR	NR	NR
	Mansouri (2019) [39]	XEN w/ and wo phacoemulsification	149	2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR (6.7)
	Gillmann (2019) [22]	XEN w/ cataract surgery	57	2 years	NR	Uncomfortable 0 (0.0)	NR	NR	NR	1 (2.0)	NR	NR	NR
		XEN wo cataract surgery	53	2 years	NR	1 (2.3)	NR	NR	NR	0 (0.0)	NR	NR	NR
	Shaarawy (2004) [40]	Collagen implant (deep sclerectomy)	105	Mean (SD): 64 (26.6) months	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 3 continued

Disease	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
	Budenz (2016) [26]; Barton (2014) [27]	Ahmed	143	3 years	NR	Encysted 1 (0.9)	3 (2.7)	NR	NR	0 (0.0)	NR	2 (1.6)	2 (1.5)
				5 years		1 (0.9)	3 (2.7)			0 (0.0)		2 (1.6)	2 (1.5)
		Baerveldt 101–350	133	3 years	NR	Encysted 0 (0.0)	3 (2.5)	NR	NR	1 (0.8)	NR	2 (1.7)	2 (1.6)
				5 years		0 (0.0)	3 (2.5)			2 (2.2)		2 (1.7)	2 (1.6)
	Christakis (2011) [28]; (2013) [29]; (2016) [30]	Ahmed	124	3 years	NR	Encaps 14 (11.0)	NR	NR	NR	2 (2.0)	NR	1 (1.0)	5 (3.0)
				5 years		14 (11.0)				1 (1.0)		1 (1.0)	4 (3.0)
		Baerveldt 350	114	3 years	NR	Encaps 3 (3.0)	NR	NR	NR	0 (0.0)	NR	3 (3.0)	6 (5.0)
				5 years		4 (4.0)				0 (0.0)		0 (0.0)	6 (5.0)
	Gedde (2009) [31]; (2012) [33]; (2012) [32]	Baerveldt 350	107	3 years	NR	Encaps 2 (2.0)	NR	NR	NR	(1.0)	NR	1 (1.0)	NR
				5 years		2 (2.0)				1 (1.0)		1 (1.0)	
	Gedde (2020) [37]	Baerveldt 350	125	3 years	NR	Encaps 14 (11.0) Conjunctival cyst 1 (1.0)	NR	NR	NR	NR	NR	NR	NR
	Islamaj (2020) [34]	Baerveldt 350	59	1–5 years	NR	NR	NR	NR	NR	NR	NR	NR	NR
				5 years									
	Law (2016) [36]	Ahmed	52	Mean (SD): 21.9 (10.7) months	NR	NR	NR	NR	NR	NR	NR	1 (1.9)	NR
	Parihar (2017) [19]	Ahmed	25	2 years	NR	NR	0 (0.0)	NR	NR	NR	NR	NR	2 (8.0)
		Ahmed (pars plana clip modified)	25	2 years	NR	NR	2 (8.0)	NR	NR	NR	NR	NR	0 (0.0)

Table 3 continued

Disease	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
	Fraczkiewicz-Skok (2019) [24]	Ex-Press	42	Mean (SD): 24 (3.0) months	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Ex-Press (deep sclerectomy w/ phaco-emulsification)	72	Mean (SD): 24 (7.0) months	NR	NR	NR	NR	NR	NR	NR	NR	1 (1.7)
	Gonzalez-Rodriguez (2016) [38]	Ex-Press	32[a]	3 years	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Nassiri (2010) [21]	Ahmed	46	2 years	NR	NR	NR	NR	NR	NR	NR	NR	> 1 mm: 3 (6.5)
		Molteno (single-plate)	46		NR	NR	NR	NR	NR	NR	NR	NR	> 1 mm: 2 (4.3)
	Netland (2014) [25]	Ex-Press	59	2 years	NR	NR	NR	NR	0 (0.0)	NR	NR	NR	NR
Total number of studies (RCT, non-RCT)					0 (NA)	7 (5, 2)	3 (3, 0)	1 (1, 0)	1 (1, 0)	7 (6, 1)	1 (1, 0)	6 (6 0)	8 (6, 2)
Follow-up, range					NA	22–101.5 months	22 months–5 years	10.8–37.6 months	10.8–37.6 months	2–5 years	3 years (NA)	3–5 years	22–101.5 months
Study eyes per treatment arm, *n* (range)					NA	114 (44–179)	143 (110–347)	179 (NA)	179 (NA)	114 (37–347)	343–347	119 (52–347)	114 (46–179)
Studies per implant type, *n*					NA								
Ahmed						1	1	0	0	2	0	3	3
Baerveldt						2	1	0	0	3	0	3	2
Collagen						1	0	0	0	0	0	0	1
Ozurdex						0	1	0	0	1	1	1	0
PDS						1	1	1	1	1	0	1	1
XEN						1	0	0	0	1	0	0	1
Molteno						0	0	0	0	0	0	0	1
Studies per condition, *n*					NA								

Table 3 continued

Disease	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)									
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
nAMD						1	1	1	1	1	0	1	1
DME						0	1	0	0	1	1	1	0
Glaucoma						6	1	0	0	5	0	1	7
AESIs, median (range) %					NA	2.1 (0.0–22.8)	2.7 (1.3–13.1)	NA	NA	0.6 (0.0–2.7)	NA (0.0–0.3)	1.0 (0.0–1.9)	3.0 (0.0–8.6)

AESI adverse event of special interest, *DME* diabetic macular edema, *Encaps.* encapsulated, *NA* not applicable, *nAMD* neovascular age-related macular degeneration, *NR* not reported, *PDS* Port Delivery System with ranibizumab, *RCT* randomized controlled trial, *Rheg.* rhegmatogenous, *SAE* serious adverse event, *SD* standard deviation, *Tract.* tractional, *w/* with, *wo* without

[a]The term "unwanted bleb" includes any conjunctival bleb in eyes without glaucoma and encysted, encapsulated, or uncomfortable bleb in eyes with glaucoma. It excludes planned, uncomplicated bleb resulting from glaucomafiltering surgeries

DME and Ozurdex 0.35 mg (13.1% at 3 years) [20] and the lowest rate in eyes with nAMD and the PDS (1.3% [two eyes] at 22 months) [8, 9].

Fourteen real-world studies (two prospective and 12 retrospective) assessed vitreous hemorrhage, with one study each including eyes with uveitis, macular edema, rhegmatogenous retinal detachment, DME, and inadequate capsular support and nine including eyes with glaucoma (Table 4). Studies ranged from 23.4 months to 13 years in duration and included a median 146 (range 50–803) eyes per treatment group. Median rate of vitreous hemorrhage in real-world studies was 1.1% (range 0.0–50.0%), with the highest rates in eyes with glaucoma and Ahmed (50.0% [73 eyes] at 43.6 months) [82] or Aurolab implants (14.0% [12 eyes] at 30.6 months) [47] and the lowest rates in eyes with DME and Iluvien implants (0.5% [one eye] at 27.6 months) [18] and in eyes with glaucoma and Ahmed (0.0% at 3 years) [49], XEN (0.0% [zero eyes] at 30.5 months) [75], or RPICIOL (0.0% [zero eyes] at 27.3 months) [42].

Conjunctival Erosion

Conjunctival erosion was assessed by one RCT [8, 9] and two retrospective real-world studies [58, 74]. The RCT followed 179 eyes with nAMD and the PDS for 22 months and reported conjunctival erosion in four eyes (2.2%) (Table 3). The real-world studies followed eyes with glaucoma for 2 years and reported a median rate of 3.5% (range 2.4–4.6%) (2.4% [two of 84 eyes] for Ahmed implants [74] and 4.6% [seven of 151 eyes] for XEN implants [58]) (Table 4).

Conjunctival Retraction

Conjunctival retraction was assessed by one RCT [8, 9] and no real-world studies. The RCT reported events in one of 179 eyes with nAMD and the PDS (0.6%) at 22 months (Table 3).

Endophthalmitis

Endophthalmitis was assessed by seven clinical trials (one RCT and six non-RCTs), one of which was conducted in eyes with nAMD, one in eyes with DME and five in eyes with glaucoma

Table 4 Summary of AESIs reported in real-world studies by condition and implant type

Condition	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
Aphakia	Kandemir Besek (2020) [71]	SFIOL	136	Mean (SD): 50.8 (27) months	NR	NR	NR	NR	NR	NR	IOL dislocation: 3 (2.2)	2 (1.5)	NR
DME	Singer (2022) [18]	Iluvien	202	Mean (SD): 27.6 (11.0) months	NR	NR	1 (0.5)	NR	NR	0 (0.0)	NR	1 (0.5)	NR
Inadequate capsular support	Bulut (2022) [70]	SFIOL	131	Mean (SD): 24.3 (11.4) months	NR	NR	5 (3.8)	NR	NR	0 (0.0)	NR	6 (4.6)	2 (1.5)
Macular edema	Pommier (2016) [62]	Ozurdex	94	Mean [range]: 26.3 [5–41] months	NR	NR	NR	NR	NR	0 (0.0)	NR	0 (0.0)	NR
	Tufail (2018) [81]	Ozurdex	803	2 years	NR	NR	29 (3.3)	NR	NR	1 (0.1)	1 (0.1)	4 (0.5)	NR
Rheg. retinal detachment	Xu (2021) [69]	Scleral buckle	60	Mean (SD): 22.9 (15.6) months	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Quijano (2016) [57]	Scleral buckle	88	Mean (SD) [range]: 8.5 (2.6) [5–13] years	NR	NR	1 (1.1)	NR	NR	NR	Explant extrusion: 1 (1.1)	NR	NR
Uveitis	Alba-Linero (2020) [56]	Ozurdex	79	60 months	NR	NR	1 (0.7)	NR	NR	0 (0.0)	NR	0 (0.0)	NR
Glaucoma	Bao (2018) [41]	Ahmed	67	Mean (SD) [range]: 53.3 (8.5) [48–60] months	NR	NR	NR	NR	NR	NR	NR	12 months: 2 (NR)	NR
	Choo (2018) [54]	Ahmed	76	3 years Mean (SD): 33.2 (6.9) months	NR	NR	NR	NR	NR	NR	NR	NR	2 (2.6)
	Gdih (2017) [74]	Ahmed	84	2 years	NR	NR	NR	2 (2.4)	NR	NR	NR	NR	15 (18.0)
	Jo (2018) [82]	Ahmed	146	Mean (SD): 43.6 (23.1) months	NR	NR	73 (50.0)	NR	NR	NR	NR	30 (20.5)	NR

Table 4 continued

Condition	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
	Kang (2022) [43]	Ahmed	135	Mean (SD): 40.6 (25.2) months	NR	NR	NR	NR	NR	0 (0.0)	NR	NR	41 (30.4)
	Kapelushnik (2021) [72]	Ahmed	95	10 years Mean (SD) [range]: 687 (673) [90–3085] days	NR	NR	NR	NR	NR	2 (2.1)	NR	NR	NR
	Kaushik (2022) [48]	Ahmed	52	Mean (SD): 29.5 (3.4) months	NR	NR	NR	NR	NR	NR	NR	NR	6 (15.8)
	Lee (2017) [44]	Ahmed	302	Median (SD) [Range]: 62.3 (37.2) [6–190] months	NR	NR	NR	NR	NR	3 (1.0)	NR	NR	15 (5.0)
	Lee (2020) [45]	Ahmed (aqueous suppressants)	40	Mean (SD): 32.4 (8.3) months	NR	NR	NR	NR	NR	NR	NR	NR	2 (5.0)
		Ahmed (prostaglandin analogues)	26	Mean (SD): 31.4 (8.9) months	NR	NR	NR	NR	NR	NR	NR	NR	5 (19.2)
	Marta (2022) [61]	Ahmed	114	Mean (SD) [range]: 3.8 (2.1) [1.00–8.28] years	NR	Encaps.: 1 (0.9)	NR	NR	NR	NR	NR	NR	NR
	Pandav (2020) [49]	Ahmed	189	3 years Mean (SD): 27.4 (18.8) months	NR	NR	Vitreous block: 0 (0.0)	NR	NR	NR	NR	NR	NR
	Park (2022) [46]	Ahmed	248	Mean (SD): 97.4 (53.5) months	NR	NR	5 (2.0)	NR	NR	3 (1.2)	NR	3 (1.2)	NR
	Rabkin-Mainer (2018) [73]	Ahmed	43	Median: 36 months	NR	NR	NR	NR	NR	0 (0.0)	NR	NR	NR
		Ex-Press	49	Median: 36 months	NR	NR	NR	NR	NR	1 (2.0)	NR	NR	NR

Table 4 continued

Condition	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
	Resende (2016) [67]	Ahmed	37	Mean (SD): 2.3 (1.6) years	NR	NR	NR	NR	NR	NR	NR	NR	2 (5.4)
	Rotsos (2018) [79]	Ahmed	342	Mean [range]: 63.2 [18–120] months	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Schimiti (2016) [78]	Ahmed	61	24 months Mean (SD) [range]: 17.28 (6.24) [3–24] months	NR	NR	NR	NR	NR	NR (1.6)	NR	NR	NR
	Allan (2015) [64]	Baerveldt 250	36	Mean (SD): 40.24 (21.17) Median [range]: 45 [2–78]	NR	NR	NR	NR	NR	0 (0.0)	NR	NR	NR
		Baerveldt 350	50	Mean (SD): 31.44 (22.52) Median [range]: 27 [3–75]	NR	NR	1 (1.9)	NR	NR	0 (0.0)	NR	NR	NR
	Hau (2021) [80]	Baerveldt	72	5 years	NR	NR	NR	NR	NR	NR	NR	NR	1 (NA)
	Kitnarong (2020) [55]	Baerveldt 101–350	102	Mean [range]: 59.9 [1–144.7] months	NR	NR	NR	NR	NR	2 (1.9)	NR	NR	3 (2.9)
	Resende (2016) [67]	Baerveldt 250 or 350	38	Mean (SD): 2.4 (1.7) years	NR	NR	NR	NR	NR	NR	NR	NR	4 (10.5)
	Tojo (2021) [51]	Baerveldt	107	Mean (SD): 29.0 (15.0) months	NR	NR	9 (8.4)	NR	NR	0 (0.0)	NR	Rheg. detachment: 2 (1.9)	5 (4.7)
	van Hoefen Wijsard (2018) [63]	Baerveldt 101–350 w/ donor sclera	163	Median [range]: 31 [13–36] months	NR	NR	NR	NR	NR	0 (0.0)	NR	NR	NR
	Craven (2022) [66]	Ex-Press	223	5 years	NR	NR	NR	NR	NR	NR	NR	NR	NR
		Tube shunt	551	5 years	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 4 continued

Condition	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
	Tojo (2019) [52]	Ex-Press	191	Mean (SD): 28.1 (15.3) months	NR	NR	NR	NR	NR	1 (0.6)	NR	NR	6 (3.8)
	Tojo (2020) [53]	Ex-Press	129	> 2 years	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Gabbay (2019) [58]	XEN	151	2 years	NR	NR	NR	7 (4.6)	NR	0 (0.0)	NR	NR	NR (3.0)
	Lewczuk (2021) [60]	XEN	72	Mean (SD): 26.9 (15.3) months Median [range]: 26.1 [6–50] months	NR	NR	NR	NR	NR	NR	Implant extrusion: 3 (4.1)	NR	NR
	Rauchegger (2021) [76]	XEN	79	2 years	NR	NR	NR	NR	NR	NR	NR	NR	5 (3.9)
	Reitsamer (2022) [77]	XEN	212	3 years	NR	NR	2 (0.9)	NR	NR	1 (0.5)	Surgical repositioning: 3 (1.4) Implant migration: 2 (0.9)	NR	4 (1.9)
	Szigiato (2022) [75]	XEN ab interno gelatin microstent	83	Mean (SD): 30.5 (10.2) months	NR	NR	0 (0.0)	NR	NR	0 (0.0)	NR	NR	0 (0.0)
	Gnanavelu (2021) [47]	Aurolab	85	Mean (SD): 30.6 (5.3) months	NR	NR	12 (14.0)	NR	NR	2 (2.0)	NR	2 (2.0)	2 (2.0)
	Pandav (2020) [49]	Aurolab	206	3 years Mean (SD): 24.6 (18.1) months	NR	NR	Vitreous block: 1 (0.5)	NR	NR	NR	NR	NR	NR
	Figus (2022) [59]	Gold micro shunt	55	10 years	NR	NR	NR	NR	NR	1 (1.8)	NR	NR	NR

Table 4 continued

Condition	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
	Banitt (2015) [65]	Molteno/Ahmed/Baerveldt/Krupin/Schocket	2661	10 years	NR	NR	NR	NR	NR	10 (0.8)	NR	42 (2.7)	NR
	Kang (2021) [42]	RPICIOL	158	Mean (SD): 27.3 (17.5) months	NR	NR	0 (0.0)	NR	NR	NR	NR	0 (0.0)	NR
		SFIOL	237	Mean (SD): 33 (19.6) months	NR	NR	3 (1.3)	NR	NR	NR	NR	6 (2.5)	NR
Total number of studies (prospective, retrospective)					0 (NA)	1 (0, 1)	14 (2, 12)	2 (0, 2)	0 (NA)	22 (2, 20)	5 (1, 4)	12 (2, 10)	16 (1, 15)
Follow-up, range					NA	NR	24.3 months–13 years	2 years	NA	2–10 years	2–13 years	24–97.4 months	2–5 years
Study eyes per treatment arm, *n* (range)					NA	114	146 (50–803)	84–151	NA	95 (18–2661)	136 (72–803)	141 (67–2661)	87 (52–302)
Studies per implant type, *n*					NA				NA				
Ahmed						1	3	1		5	0	3	7
Aurolab						0	2	0		1	0	1	1
Baerveldt						0	2	0		5	0	1	4
Collagen						0	0	0		0	0	0	0
Ex-Press						0	0	0		2	0	0	1
Gold micro shunt						0	0	0		1	0	0	0
Iluvien						0	1	0		1	0	1	0
Molteno						0	0	0		0	0	0	0
Multiple[b]						0	0	0		1	0	1	0
Ozurdex						0	2	0		3	1	3	0
RPICIOL						0	1	0		0	0	1	0
Scleral buckle						0	1	0		0	1	0	0
SFIOL						0	2	0		1	1	3	1
XEN						0	2	1		3	2	0	3

Table 4 continued

Condition	Study	Implant	Study eyes, *n*	Follow-up	AESIs, *n* (%)								
					Traumatic cataract	Unwanted conjunctival bleb[a]	Vitreous hemorrhage	Conjunctival erosion	Conjunctival retraction	Endophthalmitis	Implant dislocation	Retinal detachment	Hyphema
Studies per condition, *n*					NA				NA				
Aphakia						0	0	0		0	1	1	0
DME						0	1	0		1	0	1	0
Glaucoma						1	9	2		16	2	7	15
Inadequate capsular support						0	1	0		1	0	1	1
Macular edema						0	1	0		2	1	2	0
Retinal detachment (rheg.)						0	1	0		0	1	0	0
Uveitis						0	1	0		2	0	0	0
AESIs, median (range) %					NA	0.9 (NA)	1.1 (0.0–50.0)	3.5 (2.4–4.6)	NA	0.0 (0.0–2.1)	1.1 (0.1–4.1)	1.5 (0.0–20.5)	4.5 (0.0–30.4)

AESI adverse event of special interest, *DME* diabetic macular edema, *Encaps*. encapsulated, *IOL* intraocular lens, *NA* not applicable, *NR* not reported, *PDS* Port Delivery System with ranibizumab, *RCT* randomized controlled trial, *Rheg*. rhegmatogenous, *SD* standard deviation, *SFIOL* scleral fixation of intraocular lens, *w/* with, *wo* without

[a]The term "unwanted bleb" includes any conjunctival bleb in eyes without glaucoma and encysted, encapsulated, or uncomfortable bleb in eyes with glaucoma. It excludes planned, uncomplicated bleb resulting from glaucoma-filtering surgeries

[b]Multiple implants include Molteno, Ahmed, Baerveldt, Krupin, and/or Schocket implants

(Table 3). Study duration ranged from 2 to 5 years and median number of eyes per treatment arm was 114 (range 37–347). Median rate of endophthalmitis in clinical trials was 0.6% (range 0.0–2.7%), with the highest rates reported in eyes with glaucoma and bilateral XEN stents (2.7% [one eye] at 2 years) [23], glaucoma and Ahmed or Baerveldt implants (0.0–2.0% and 0.0–2.2% at 2–5 years) [26–33], primary open-angle glaucoma and XEN implants (2.0% [one eye] at 2 years) [22], and nAMD with the PDS (1.1% [two eyes] at 22 months) [8, 9].

Twenty-two real-world studies (two prospective and 20 retrospective) assessed endophthalmitis; 16 included eyes with glaucoma, two each included eyes with uveitis or macular edema, and one each included eyes with inadequate capsular support or DME (Table 4). Study duration ranged from 2 to 10 years, mean number of eyes per treatment arm was 95 (range 18–2661), and median rate of endophthalmitis was 0.0% (0.0–2.1%). No cases of endophthalmitis were reported up to 2 years post implant in eyes with DME and Iluvien implants [18], inadequate capsular support and SFIOL [70], or uveitis and Ozurdex implants [56], and only one case (0.0–0.1%) was reported in eyes with macular edema and Ozurdex [62, 81]. Rates in eyes with glaucoma ranged from 0.0–2.1% at 10 years for Ahmed [43, 44, 46, 72, 73, 78], 0.0–1.9% at 5 years for Baerveldt [51, 55, 63, 64], 2.0% (two eyes) at 10 years for Aurolab drainage implants [47], 2.0% (one eye) at 36 months for Ex-Press [73], and 1.8% (one eye) at 10 years for Gold microshunts [59]. Rates in eyes with glaucoma and other implants remained ≤ 0.6% at all times [52, 58, 65, 75, 77].

Implant Dislocation

Implant dislocation (0.3% [one eye]) was reported by one RCT conducted in 698 eyes with DME and DEX 0.7 mg implants followed for a mean 3 years (Table 3) [20]. Additional cases were assessed in five real-world studies (one prospective and four retrospective) following 136 (72–803) eyes per treatment arm for 2–13 years (Table 4). One study each included eyes with aphakia, rhegmatogenous retinal detachment, and macular edema, and two included eyes with glaucoma. Median rate of implant dislocation in real-world studies was 1.1% (range 0.1–4.1%), with the highest rates reported in eyes with glaucoma and XEN implants (up to 4.1% at ~ 2 years) [60] and lower rates reported in eyes with retinal detachment and scleral buckle (1.1% [one eye] at 8.5 years) [57] or macular edema and Ozurdex (0.1% [one eye] at 2 years) [81].

Retinal Detachment

Retinal detachment was assessed by six RCTs, four of which were conducted in eyes with glaucoma and one each in eyes with nAMD and DME (Table 3). Study duration was 3–5 years and median number of eyes per treatment arm was 119 (range 52–347). Median rate of retinal detachment in clinical trials was 1.0% (range 0.0–1.9%), with rates of 0.6% (two eyes) and 0.3% (one eye) reported at 3 years in eyes with DME and DEX 0.7 or 0.35 mg, respectively [20], and slightly higher rates in eyes with glaucoma and Ahmed or Baerveldt implants (1.0–1.6% and 0.0–3.0%, respectively, at 3 and 5 years [26–33]). Rates of rhegmatogenous detachment and tractional detachment in eyes with nAMD and the PDS were 1.7% (three eyes) and 0.6% (one eye), respectively, at 22 months [8, 9].

Twelve real-world studies (two prospective and 10 retrospective) assessed retinal detachment (Table 4). Studies were 24–97.4 months in duration and included a median 141 (67–2661) eyes per treatment arm. Seven studies included eyes with glaucoma, two with macular edema, and one each with DME, aphakia, or inadequate capsular support. Median rate of retinal detachment in real-world studies was 1.5% (range 0.0–20.5%), with the highest rate in eyes with glaucoma and Ahmed implants (20.5% [30 eyes] at 43.6 months) [82] and the lowest rate in eyes with DME and Iluvien (0.5% [one eye] at 27.6 months) [18], macular edema and Ozurdex (0.0–0.5% at ~ 2 years) [62, 81], uveitis and Ozurdex (0.0% [zero eyes] at 60 months) [56], and glaucoma treated with RPICIOL (0.0% [zero eyes] at 27.3 months) [42].

Hyphema

Hyphema was assessed by eight clinical trials (six RCTs and two non-RCTS), one in eyes with nAMD and seven in eyes with glaucoma (Table 3). Mean study duration was 22–101.5 months and median number of eyes per treatment arm was 114 (range 46–179). Median rate of hyphema in clinical trials was 3.0% (range 0.0–8.6%). The highest rates were in eyes with glaucoma and collagen implants (8.6% [nine eyes] at 101.5 months) [35] or conventional Ahmed implants (8.0% [two eyes] at 2 years) [19], and the lowest rates were in eyes with glaucoma and pars plana clip modified Ahmed implants (0.0% [zero eyes] at 2 years) [19] and in eyes with nAMD and the PDS (1.1% [two eyes] at 22 months) [8, 9].

Sixteen real-world studies (one prospective and 15 retrospective) assessed hyphema, 15 of which were in eyes with glaucoma and one in eyes with inadequate capsular support (Table 4). Follow-up was 2–5 years, and median number of eyes per treatment arm was 87 (52–302). Median rate of hyphema in real-world studies was 4.5% (range 0.0–30.4%). The highest rates were in eyes with glaucoma and Ahmed (2.6–30.4% at ~ 2–4 years) [43, 45, 48, 54, 67, 74] or Baerveldt implants (2.9–10.5% at 2–5 years) [51, 55, 67], and the lowest rates were in eyes with inadequate capsular support and SFIOL (1.5% [two eyes] at ~ 2 years) [70] and in eyes with glaucoma and XEN implants (0.0–3.9% at 2–3 years) [58, 75–77].

Other Post-Surgical Complications

Although suprachoroidal hemorrhage was not reported during the phase III PDS trials [11–14], it is a serious and significant post-surgical complication identified by two RCTs [26–30] and nine retrospective real-world studies [42, 46, 51, 54, 60, 64, 65, 67, 72] (Table 2), all of which were conducted in eyes with glaucoma. Clinical trial duration ranged from 3–5 years, the number of eyes per treatment arm was 114–143, and the median rate of events was 1.0% (range 0.0–3.0% at 3–5 years). All cases occurred in eyes with Baerveldt-350 or Ahmed implants.

Four of the nine real-world studies reporting suprachoroidal hemorrhage were in eyes with Ahmed implants [46, 54, 67, 72], three with Baerveldt [51, 64, 67], and one each with XEN [60], RPICIOL or SFIOL [42], and multiple implant types [65]. Mean follow-up was approximately 2–10 years, the median number of eyes per treatment arm was 83 (36–2661), and the median rate of suprachoroidal hemorrhage was 1.3% (0.0–2.8%). Rates were similar for eyes with XEN (2.8% at ~ 2 years), Ahmed (0.0–2.7% at ~ 2–3 years and 1.0–1.2% at 8–10 years), and Baerveldt implants (0.0–2.6% at ~ 2–3 years) and were slightly lower in eyes with RPICIOL or SFIOL (0.4–1.3% at 2–3 years).

DISCUSSION

The aim of this study is to investigate the long-term safety of implants that cross the sclera, thereby enabling us to determine whether the types and rates of complications reported for the PDS are comparable to those reported for other ocular implants. Sixteen clinical trials (24 publications) and 43 real-world studies were identified reporting 30 complications in eyes with 15 implant types across eight ocular diseases. Median rates of device-related complications (0.7% [range 0.0–5.0%] at 3–5 years in clinical trials and 1.3% [0.0–14.5%] at 24 months to 13 years in real-world studies) and conjunctival complications (2.1% [0.0–22.8%] at 22–101.5 months and 2.2% [0.9–4.6%] at 2–3.81 years, respectively) were similar across study types, with most complications resolving spontaneously or with treatment. As expected, some complications (e.g., excessive or inadequate IOP control, uncomfortable bleb, shallow anterior chamber, and suprachoroidal hemorrhage) were primarily observed in eyes with glaucoma drainage devices. Median rates of device deficiency (implant failure) were 27.2% (range 3.8–45.0%) in clinical trials and 19.9% (1.0–61.6%) in real-world studies, with 10 and 24 eyes, respectively, requiring explantation. All cases of device deficiency/explantation were in eyes with glaucoma and either Ahmed, Baeveldt, or XEN implants, with none occurring

in eyes with the PDS (Table S3). Most cases of device deficiency/explantation were related to inadequate IOP control rather than to secondary complications with the surgical device.

The rates of AESIs for the PDS in the phase III Archway, Pagoda, and Pavilion trials [11–14] were within the ranges observed for implants in the SLRs (Table 1). All AESIs were well understood, resolved using standard procedures, and, in most cases, did not prevent patients from achieving optimal outcomes [84]. This suggests that the potential real-world benefits of the PDS (greater efficacy, longer durability, and reduced treatment burden) are unlikely to be significantly affected by any additional burden of managing the low rate of AEs associated with the device.

Cataract formation and/or progression was reported in 6.7–10.9% of study eyes in the phase III PDS trials [11–14], with most cases considered unrelated to surgery [11]. Consistent with this observation, traumatic cataract was not reported for ocular implants in the SLRs. Rates of unwanted conjunctival bleb in the phase III PDS trials [11–14] (1.9–7.8%) were lower than those reported for glaucoma-related implants in clinical trials (0.0–22.8%) and higher than those reported in real-world studies (0.9%). The discrepancy between clinical trials (six studies) and real-world studies (one study) might be due to the paucity of real-world evidence. Since the PDS is not indicated for people with glaucoma drainage devices, none of the studies included eyes implanted with both device types. Rates of conjunctival erosion, retraction, and implant dislocation were slightly higher for the PDS in phase III trials (1.0–4.0%, 1.3–1.9%, and 0.3–1.9%, respectively) than for implants in the SLRs (2.2%, 0.6%, and 0.0–0.3%). This seems counterintuitive because, at the time of writing, the durations of the Pavilion [14] and Pagoda [13] trials (52 and 64 weeks, respectively) were shorter than in the studies in the SLRs (≥ 18 months). However, 29/103 (28%) AESIs reported for the PDS in the Archway trial occurred within 37 days of surgery, with most (67/103; 65%) occurring within 40 weeks [12]. This suggests that many AESIs in the Pavilion and Pagoda trials will have been captured during the reported timeframe. Furthermore, rates of conjunctival erosion might have been underreported for glaucoma drainage devices because erosion is sometimes associated with underlying implant exposure [85], and yet these complications were reported separately. Finally, real-world experience of PDS implantation and refill-exchange is currently limited compared with other implants, and surgical techniques will potentially improve as surgeons become more familiar with the procedures. Longer-term (up to 5 years) safety data for the PDS in eyes with nAMD will be provided by the ongoing Portal trial [86, 87].

Although device deficiency/explantation was not reported for the PDS in the SLRs, incidences of septum dislodgement (a type of device deficiency) have been reported in the phase III PDS clinical trials. Roche/Genentech voluntarily recalled the PDS implant between October 2022 and April 2024 to conduct a thorough root cause analysis and subsequently made component-level changes and manufacturing process improvements to the implant and refill needle to mitigate the risk of septum dislodgement moving forwards. New implantations have resumed in the PDS clinical trials, and commercial PDS will soon be reintroduced to clinical practice in the USA.

Key strengths of the SLRs include their use of a standardized, methodical, thorough, and transparent approach to identify and appraise relevant studies. As for any SLR, limitations include the possible omission of studies that were either missed, not published in English, or published after the searches were conducted. In addition, (1) most studies were conducted in eyes with glaucoma (49/59), with only two studies each in eyes with DME, macular edema, rhegmatogenous retinal detachment, and uveitis, one in eyes with nAMD, and none in eyes with DR. This limits our ability to draw comparisons across indications. (2) Most studies included eyes with Ahmed or Baerveldt implants (33), with seven reporting complications for Ex-Press implants, eight for XEN, four for Ozurdex, and up to two each for other implants. Of these, only six studies directly compared complications across implants. (3) Comparisons across studies were further limited by inconsistencies in the types and

definitions of complications assessed and differences in study duration. (4) Studies with follow-up of < 18 months were excluded, thereby limiting our ability to compare results with those from the Pavilion [14] and Pagoda [13] trials, both of which reported < 18 months of follow-up at the time of writing. (5) The number of studies reporting conjunctival complications (seven clinical trials and three real-world studies), device-related complications (six and 18 studies, respectively), and implant replacement (one clinical trial) was low. (6) Study quality was variable, with concerns raised for bias in all but one RCT and a medium or high risk of bias in 42 real-world studies and all three non-RCTs.

CONCLUSION

Ocular implants offer definite advantages for patients with ocular diseases when non-surgical treatments are insufficient. However, it is important to balance their potential advantages (greater efficacy, longer durability, and reduced treatment burden) with the potential risks. This review provides valuable insight into the types and rates of long-term complications associated with ocular implants that cross the sclera. Implants were associated with a well-characterized safety profile, with median device-related complications reported in 0.7% (range 0.0–5.0%) of eyes in clinical trials and 1.3% (0.0–14.5%) in real-world studies. The rates of AESIs reported in the phase III PDS trials [11–14] were typically within the ranges reported for more established ocular devices in the SLRs. Further studies with longer follow-up, larger sample sizes, and a greater range of pre-specified, consistently defined complications will help contextualize and build confidence regarding the long-term safety of ocular implants, including the PDS.

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Declarations

Conflict of Interest. Nancy M Holekamp reports employment by F. Hoffmann-La Roche Ltd. (visiting professor); consulting fees from Apellis, Bayer, Biogen, Boehringer Ingelheim, Cardinal, Clearside, EyePoint, Genentech, Inc., Gyroscope, Medpace, Medscape, Notal Vision, Novartis, Regeneron, Roche, Stealth, and Vial; speaker's bureaus for Apellis, Bausch + Lomb, Genentech, Inc., and Regeneron; contracted research for Gemini, Genentech, Inc., Gyroscope, and Notal Vision; data monitoring and safety committees for Editas, Ocuphire, and Roche; and stock or stock options in Apellis, Nacuity, and Notal Vision. Manejeh Yaqub reports employment by Genentech, Inc.; stock/stock options in F. Hoffmann-La Roche Ltd.; and non-financial involvement with the Kashmiri Group of North America. Shrirang V Ranade and Ronald A Cantrell report employment by Genentech, Inc.; and stock/stock options in F. Hoffmann-La Roche Ltd. Sheena Singh reports

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