

PHASE 2 RANDOMIZED STUDY (ORION-1) OF A NOVEL, BIODEGRADABLE DEXAMETHASONE IMPLANT (AR-1105) FOR THE TREATMENT OF MACULAR EDEMA DUE TO CENTRAL OR BRANCH RETINAL VEIN OCCLUSION

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Purpose: AR-1105 is a novel biodegradable sustained-release dexamethasone implant designed to deliver 6-month durability. This Phase 2 study evaluated two AR-1105 formulations with different release profiles in patients with macular edema due to retinal vein occlusion.

Methods: Patients received a single intravitreal injection with 340 μ g dexamethasone. In the initial phase, five patients received clinical formulation (CF) 1. In the randomized phase, 44 patients were randomized 1:1 to CF1 or CF2. The follow-up was 6 months. Patients had vision loss due to macular edema diagnosed ≥ 9 (central retinal vein occlusion) or ≥ 12 months (branch retinal vein occlusion) before screening, and could be treatment-naïve or -experienced (if received prior steroids, must have demonstrated response).

Results: Both formulations improved vision and reduced retinal thickening from baseline across all visits. At Month 6, mean changes in best-corrected visual acuity were +4.3 and +8.0 letters, and mean changes in central subfield thickness were $-93 \mu\text{m}$ and $-211 \mu\text{m}$ in CF1 and CF2 randomized patients, respectively. Most common adverse events were reduced visual acuity, worsening macular edema, conjunctival hemorrhage, and increased intraocular pressure. No patients required surgery or laser for intraocular pressure control.

Conclusion: Both formulations were well tolerated and demonstrated clinically meaningful and sustained improvements in vision and retinal thickening in patients with retinal vein occlusion with longstanding edema.

RETINA 43:25–33, 2023

Retinal vein occlusion (RVO), an obstruction of the retinal venous system by thrombus formation, is a common sight-threatening vascular disorder of the retina with an estimated prevalence of approximately 16 million people worldwide.^{1,2} Retinal vein occlusion may involve the central RVO (CRVO), hemicentral RVO, or branch RVO (BRVO) retinal vein, and is often due to compression by adjacent atherosclerotic retinal arteries or vasculitis.¹ One of the main complications resulting from RVO is macular edema,¹ which affects about 3 million patients with RVO and is the primary cause of visual acuity deterioration in these patients.^{3,4} This reduction in vision may be reversible

in the short term, but chronic macular edema can cause irreversible damage to the retina and permanent vision loss.³ The goal of treatment of macular edema due to RVO, therefore, is to reduce the amount of fluid leakage and decrease the edema, thus leading to improved visual acuity.

Intravitreal corticosteroids are an effective option to improve visual and anatomical outcomes. Corticosteroids not only decrease vascular permeability, but also reduce macular edema through inhibition of multiple inflammatory mediators and stabilization of the blood–retina barrier.^{5,6} Intravitreal dexamethasone and triamcinolone have demonstrated reduction

of macular edema and improvement in visual acuity.^{6–11} However, ocular treatment with corticosteroids, including dexamethasone, have been associated with risk of increased intraocular pressure (IOP) and development of cataract.^{6,12,13} Although pivotal studies of a sustained-release formulation of dexamethasone (700 μg) intravitreal implant involved treatment every 6 months, in clinical practice, reinjection is typically required more frequently to manage symptoms of RVO.^{6,11,12} A new formulation that allows a slower release of dexamethasone at a lower dose⁹ may reduce the treatment burden with less drug exposure.

AR-1105 is a novel dexamethasone intravitreal implant formulated using Particle Replication In Non-wetting Templates (PRINT[®]) micromolding technology. Particle Replication In Nonwetting Templates uses a low-surface energy micropatterned elastomeric template to produce precisely engineered micron-sized implants for drug delivery applications. AR-1105 is formulated with dexamethasone mixed with a bioerodible poly D, L-lactic-co-glycolic acid polymer blend designed to release dexamethasone more gradually and at a lower total dose (340 μg) than the currently available dexamethasone therapy.^{14,15} In preclinical studies, AR-1105 was shown to provide extended release of dexamethasone in vitro and in animal studies and was well tolerated.¹⁴ Here, we report results from a Phase 2, multicenter, 6-month, open-label study that evaluated

safety and efficacy of two formulations of AR-1105 with the same dose but different release kinetics in patients with macular edema due to BRVO or CRVO.

Methods

Study Design and Oversight

This multicenter, open-label, Phase 2 study was conducted in two phases between February 20, 2019, and July 9, 2020, in 20 centers in the United States. Because this study represented the first-in-human experience with AR-1105, the study was conducted in two phases. The initial phase was conducted to assess possible treatment-related adverse events (AEs). A maximum of five patients were treated with AR-1105 clinical formulation 1 (AR-1105 CF1). The randomized phase of the study was initiated after a minimum of 2-week follow-up of the initial cohort in which there were no clinically meaningful ocular AEs related or possibly related to treatment with AR-1105.

In the randomized phase, patients were randomly assigned in a 1:1 ratio using an interactive response technology system to either AR-1105 CF1 or AR-1105 clinical formulation 2 (AR-1105 CF2). All patients were followed for 6 months. Rescue therapy was offered to any patient in both treatment phases who, in the opinion of the investigator, required additional therapy for their RVO due to lack of efficacy. Minimum criteria for considering rescue were an increase in central subfield thickness (CST) of $\geq 50 \mu\text{m}$ and decrease in best-corrected visual acuity (BCVA) of ≥ 7 letters after Month 3 compared with baseline. After the Month 6 visit, patients who presented with visible residual implant (i.e., if the implant was not completely dissolved) were followed, as a safety measurement, until: 1) they required retreatment; 2) 1 month after the implant was no longer visible; or 3) Month 9, whichever occurred first (see **Figure, Supplemental Digital Content 1**, <http://links.lww.com/IAE/B815>).

The protocol was developed by the sponsor, Aerie Pharmaceuticals, with study details available at clinicaltrials.gov (NCT03739593). The trial was approved by institutional review boards at each site. The study was conducted in accordance with Good Clinical Practice guidelines of the International Council for Harmonization and the provisions of the Declaration of Helsinki. All patients provided written informed consent.

Eligibility Criteria

Eligible patients were aged ≥ 18 years with vision loss due to clinically detectable macular edema associated with either CRVO or BRVO and diagnosis of

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Supported by Aerie Pharmaceuticals.

Paper presented at American Society of Retina Specialists Annual Meeting, San Antonio, TX, October 8 to 12, 2021.

M. A. Singer reports consulting fees: Aerie, Allegro, Allergan, Alimera, Genentech, Kodiak, Novartis, Regeneron, Santen, and Eyepoint; speakers bureau: Allergan, Apellis, Genentech, Mallinckrodt, Novartis, Regeneron, and Spark; contracted research: Aerie, Allegro, Allergan, DRCR, Genentech, Icon, Ionis, Kalvista, Kodiak, Novartis, Opthea, Optos, Regeneron, Santen, Senju, and Sydnexis. D. S. Boyer reports consulting: Aerie, Allergan, Genentech, Regeneron, Bayer, Novartis, Eyepoint, and Ripple. S. Williams, K. Kerr, T. Pegoraro, L. Trevino, and C. C. Kocpozynski report being employed by and owning stock and stock options in Aerie Pharmaceuticals. H. McKee and D. A. Hollander were employed by Aerie Pharmaceuticals during conduct of the study.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.retinajournal.com).

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CRVO ≥ 9 months or BRVO ≥ 12 months before screening. Patients could have been treatment-naïve, or received prior steroid therapy more than 6 months before screening or prior anti-vascular endothelial growth factor treatment more than 2 months before screening. If previously treated with a steroid, patients must have demonstrated response to treatment. BCVA as measured by the early treatment of diabetic retinopathy study methodology was required to be between 25 and 70 letters in the study eye (20/320 and 20/40 Snellen equivalent). Retinal CST as measured by spectral domain ocular coherence tomography was required to be $>290 \mu\text{m}$ (females) and $>305 \mu\text{m}$ (males) in the study eye if using a Cirrus instrument (Zeiss, Oberkochen, Germany), or $>305 \mu\text{m}$ (females) and $>320 \mu\text{m}$ (males) if using a Spectralis instrument (Heidelberg Engineering, Heidelberg, Germany). Patients with ocular hypertension in the study eye at qualification or history of corticosteroid-induced IOP increase of $>10 \text{ mmHg}$ in either eye were excluded (additional exclusion criteria in **Supplemental Digital Content 2**, <http://links.lww.com/IAE/B817>).

Study Treatments

Two formulations of AR-1105 with different steroid-release profiles, CF1 and CF2, were evaluated in the study. Each implant was formulated as a solid, biodegradable, rectangular prism-shaped implant with rounded ends, and dimensions of approximately $265 \times 265 \times 4,500 \mu\text{m}$ via PRINT[®] molding technology. Implant manufacturing process via PRINT[®] involves the fabrication of highly reproducible particle templates for particle dimensions in the submicron and micron size ranges (see **Figure, Supplemental Digital Content 3**, <http://links.lww.com/IAE/B816>).^{14,15} AR-1105 was designed to undergo slow erosion of the biodegradable matrix of different poly D, L-lactic-co-glycolic acid polymers to deliver 6-month duration of therapy. In both formulations, dexamethasone was combined with a mixture of three poly D, L-lactic-co-glycolic acid polymers, two of which were the same between the two formulations. The third poly D, L-lactic-co-glycolic acid differed in each formulation by its molecular weight, and the ratio of the three polymers was also different in the two formulations. In preclinical studies, both AR-1105 formulations provided a longer duration of sustained release of dexamethasone than current dexamethasone implant Ozurdex[®], and CF2 maintained therapeutic level of retinal dexamethasone concentrations for longer than CF1.

To deliver each formulation, two implants ($170 \mu\text{g}$ dexamethasone each) were administered simulta-

neously by the applicator in a single intravitreal injection to provide a total dose of $340 \mu\text{g}$ dexamethasone. The applicator, consisting of a handle and a 25-gauge needle hub, was assembled before dosing and both implants were loaded into the lumen of the needle. All patients received a single AR-1105 treatment delivered to the study eye during the Day 1 visit (see **Figure, Supplemental Digital Content 1**, <http://links.lww.com/IAE/B815>).

Study Objectives and Assessments

The primary objective was to evaluate the safety and tolerability of two formulations of AR-1105. Key safety measures included AEs, IOP by Goldmann applanation tonometry, slit-lamp biomicroscopy, and dilated indirect ophthalmoscopy. Adverse events were recorded from the Day 1 visit until 30 days after the patient's last study visit and coded using the Medical Dictionary for Regulatory Activities version 21.1.

The secondary objectives were to evaluate the effects of AR-1105 on visual acuity and retinal thickness. The efficacy end points included percentage of patients with ≥ 15 -letter improvement (≥ 3 lines) compared with baseline BCVA, using the early treatment of diabetic retinopathy study method; change from baseline BCVA; change from baseline in CST as assessed by spectral domain ocular coherence tomography; and percentage of patients requiring rescue therapy overall and by visit. Spectral domain ocular coherence tomography imaging was conducted using either a Zeiss Cirrus or Heidelberg Spectralis instrument. Images were graded and retinal measures were recorded by an independent reading center.

Statistical Analyses

Sample size was determined empirically. This study was not powered to detect a prestated efficacy signal, but rather was intended to be used to inform the design and power for future studies. With a planned sample size of 20 evaluable patients per treatment group in the randomized phase, the study was calculated to have 95% confidence of ruling out AEs with true incidence rates of 13.9% or higher within each treatment group.

Safety and efficacy were evaluated in all patients who received study treatment. Safety data were summarized descriptively. For efficacy data, missing values and data collected after rescue before Month 6 were imputed as failures (i.e., not meeting the criterion) for categorical variables or as last observation carried forward for continuous variables. The percentage of study eyes gaining at least 15 letters in BCVA from baseline was summarized for each study visit using discrete summary statistics. Treatment group comparisons for study eye

were completed using Fisher exact test. Change from baseline in BCVA scores was summarized for each visit using continuous summary statistics. Treatment group comparisons for study eye were completed using a linear model with change from baseline BCVA letters for study eye as the response, baseline BCVA letters as a covariate, and treatment group as a main effect. Patients who received rescue medication before the summarized visit had the measure replaced with the last observation before receiving rescue medication. Change from baseline in CST scores were summarized for each visit using continuous summary statistics and treatment group comparisons were completed similar to those for change from baseline BCVA. The percentage of patients achieving resolution of macular edema, defined as CST $\leq 300 \mu\text{m}$, was summarized for each visit, with treatment group comparisons performed using Fisher exact test. The number and percentage of patients requiring rescue therapy overall and at each study visit were summarized by treatment group. All data analyses were performed using SAS Version 9.4 or higher.

Results

Patients

A total of 49 patients were enrolled, with five in the initial cohort and 22 each in the two randomized treatment groups. Two patients in the initial cohort completed the study. A similar number of patients in each randomized group completed the study: 16/22 (72.7%) in the CF1 group and 14/22 (63.6%) in the

CF2 group (Figure 1). Among all enrolled patients, 13/49 (26.5%) patients discontinued the study due to lack of efficacy; 1/49 (2.0%) patient in the CF1 initial cohort discontinued the study due to AEs of iris neovascularization and reduced visual acuity, both of which were considered moderate in severity and not related to the study medication or study procedure.

At baseline, patients in the CF1 and CF2 randomized groups had a history of RVO for a mean of 31.6 and 34.7 months, respectively. More patients in the CF2 group had CRVO compared with the CF1 randomized group: 14/22 (63.6%) versus 9/22 (40.9%), respectively. The large majority of patients in the randomized groups were treatment-experienced. Patients in the CF2 group had significantly worse visual acuity (BCVA, 49.0 letters vs. 58.4 letters) and numerically greater retinal thickening (CST, 606 μm vs. 524 μm) than those in the CF1 randomized group (Table 1).

Safety

Overall, 32/49 patients (65.3%) across all groups reported at least one treatment-emergent AE (TEAE), with the majority mild or moderate in severity. Most patients had ocular TEAEs (51.0%). The incidence of ocular and nonocular TEAEs was similar between CF1 and CF2 randomized groups (Table 2).

The most common ocular TEAEs with an incidence >10% across all groups were reduced visual acuity (20.4%), worsening macular edema (16.3%), conjunctival hemorrhage (10.2%), and increased IOP (10.2%). A total of 10 patients (20.4%) across all groups

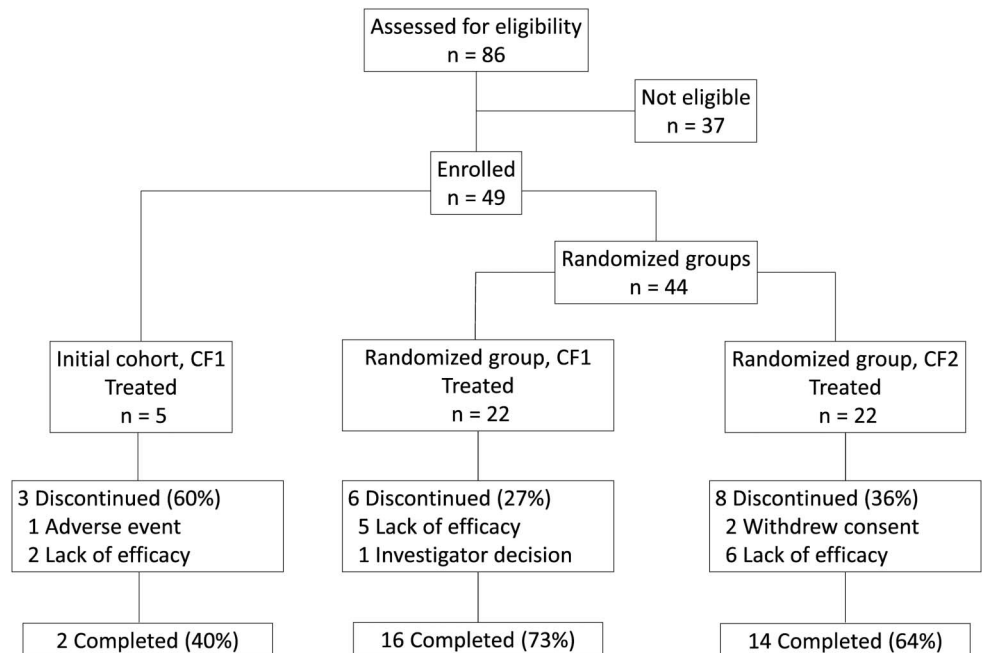


Fig. 1. Patient disposition.

Table 1. Patient Demographics and Baseline Clinical Characteristics

	Initial Cohort, CF1 (n = 5)	Randomized Group, CF1 (n = 22)	Randomized Group, CF2 (n = 22)
Age, (year)			
Mean (SD)	69.0 (11.8)	65.5 (13.8)	70.9 (9.8)
Range	57–87	27–88	47–88
Sex			
Male, n (%)	5 (100.0)	13 (59.1)	9 (40.9)
Race			
American Indian or Alaska Native, n (%)	0	1 (4.5)	0
Asian, n (%)	0	0	2 (9.1)
Black or African American, n (%)	0	2 (9.1)	1 (4.5)
White, n (%)	5 (100.0)	19 (86.4)	19 (86.4)
Ethnicity			
Hispanic or Latino, n (%)	1 (20.0)	5 (22.7)	5 (22.7)
Not Hispanic or Latino, n (%)	4 (80.0)	17 (77.3)	17 (77.3)
Lens status			
Phakic, n (%)	3 (60.0)	12 (54.5)	13 (59.1)
Glaucoma history			
Ocular hypertension, borderline glaucoma, or normal tension glaucoma, n (%)	0	2 (9.1)	2 (9.1)
Glaucoma*, n (%)	0	1 (4.5)	0
RVO diagnosis			
BRVO, n (%)	2 (40.0)	13 (59.1)	8 (36.4)
CRVO, n (%)	3 (60.0)	9 (40.9)	14 (63.6)
Duration RVO disease, (months)			
Mean (SD)	20.0 (4.3)	31.6 (24.1)	34.7 (30.8)
Range	13.5–24.2	10.9–107.1	10.0–117.8
RVO prior treatment history			
Naive to prior treatment for RVO, n (%)	1 (20.0)	3 (13.6)	2 (9.1)
Prior intravitreal anti-VEGF, n (%)	4 (80.0)	19 (86.4)	20 (90.9)
Prior intravitreal corticosteroid, n (%)	2 (40.0)	5 (22.7)	4 (18.2)
Prior retinal focal laser, n (%)	0	1 (4.5)	2 (9.1)
No. of prior anti-VEGF injections, mean (SD)	6.2 (3.6)	7.1 (6.6)	4.9 (3.6)
BCVA (ETDRS letters)			
BCVA, mean (SD)	55.2 (12.4)	58.4 (10.7) [†]	49.0 (13.6)
Range	40–70	32–70	25–67
Retinal CST, (μm)			
CST, mean (SD)	702 (196)	524 (148)	606 (214)
Range	429–862	308–990	292–998

*History of glaucoma was recorded as a protocol deviation.

[†] $P < 0.05$ for randomized to CF1 versus randomized to CF2 by two-sample t-test.

VEGF, vascular endothelial growth factor

recorded IOP increase ≥ 10 mmHg or IOP ≥ 30 mmHg at any visit. The number of patients with IOP increase ≥ 10 mmHg was similar in CF1-treated (6/27; 22%) and CF2-treated (4/22; 18%) patients (Table 3). One patient (4%) in the CF1 randomized group and 4 (18%) in the CF2 group had IOP ≥ 30 mmHg at any visit; all these patients were inclusive in those who recorded IOP increase ≥ 10 mmHg. Seven (14.3%) patients (CF1 groups, n = 2; CF2 group, n = 5) recorded an AE of IOP increase or ocular hypertension; all were treated with topical or oral IOP-lowering medications. No patients required surgical or laser intervention to lower IOP (Table 3). At Month 6, more patients in the CF2 group had visible implants, compared with CF1 randomized group (42.9% vs. 12.5%,

respectively). There was no relationship between implant visibility and safety signals.

Nine serious TEAEs (SAEs) were reported in 8 (16.3%) patients (CF1 initial cohort, n = 2; CF1 randomized group, n = 2; CF2 group, n = 4). Seven of the nine SAEs were ocular: five events of reduced visual acuity or visual impairment (CF1 initial cohort, n = 1; CF1 randomized group, n = 2; CF2 group, n = 2), one event of iris neovascularization (CF1 initial cohort), and one event of cataract (CF2 group). One SAE of vision loss >15 letters (CF1 initial cohort) was considered to be possibly related to the study medication and one SAE of worsening of cataract (CF2 group) was considered by the investigators to be possibly related to the injection procedure. Two nonocular SAEs of pneumonia and

Table 2. Adverse Events

n (%)	Initial Cohort and Randomized Group, CF1 (n = 27)	Randomized Group, CF2 (n = 22)
Summary of TEAEs		
TEAEs	41	41
Patients with any TEAE	18 (66.7)	14 (63.6)
Ocular TEAEs	31	26
Patients with ocular TEAE	14 (51.9)	11 (50.0)
Patients with ocular TEAEs in the study eye	14 (51.9)	11 (50.0)
Nonocular TEAEs	10	15
Patients with nonocular TEAE	8 (29.6)	6 (27.3)
Ocular TEAEs		
Visual acuity reduced	5 (18.5)	5 (22.7)
Macular edema worsening	6 (22.2)	2 (9.1)
Conjunctival hemorrhage	4 (14.8)	1 (4.5)
IOP increased	2 (7.4)	3 (13.6)*
Ocular hypertension	0	3 (13.6)*
Vitreous hemorrhage	0	3 (13.6)
Iris neovascularization	1 (3.7)	1 (4.5)
Vitreous floater	0	2 (9.1)
Cataract	0	1 (4.5)
Cataract nuclear	1 (3.7)†	0
Cataract subcapsular	1 (3.7)†	0
Ocular discomfort	1 (3.7)	0
Retinal disorder	0	1 (4.5)
Retinal hemorrhage	0	1 (4.5)
Vision blurred	1 (3.7)	0
Visual impairment	1 (3.7)	0

*One patient listed for both IOP increase and ocular hypertension.

†One patient listed for both nuclear and subcapsular cataract.

angina pectoralis were reported in the same patient (CF2 group); neither was considered treatment-related. All SAEs resolved by study close. There were no deaths reported during the study.

Efficacy

Visual acuity. Across all monthly follow-up visits, 18.2%–27.3% of patients in each randomized treat-

ment group gained ≥ 15 letters after a single administration, with a sustained pattern for CF2 group (Figure 2). At Month 6, ≥ 15 -letter gain from baseline in BCVA of the study eye was achieved in 4/22 (18.2% [95% confidence interval, 5.2%, 40.3%]) and 6/22 (27.3% [10.7%, 50.2%]) patients in the CF1 randomized and CF2 groups, respectively (Figure 2).

Improvements from baseline BCVA to Month 6 were observed with both formulations (Figure 3A).

Table 3. IOP Metrics

n (%)	Initial Cohort and Randomized Group, CF1 (n = 27)	Randomized Group, CF2 (n = 22)
AE of IOP increase	2 (7.4)	3 (13.6)
AE of ocular hypertension	0	3 (13.6)
Patients with IOP increase ≥ 10 mmHg	6 (22.2)	4 (18.2)
Patients with IOP ≥ 30 mmHg*	1 (3.7)	4 (18.2)
No. of IOP-lowering medications needed to treat AE of IOP increase or ocular hypertension, (range)	1–5	0–3
Patients requiring surgical/laser intervention for IOP	0	0

*Patients recording IOP ≥ 30 mmHg were inclusive in those with IOP increase ≥ 10 mmHg.

CF1-treated patients had a peak improvement of +9.7 letters at Month 2, with the treatment effect starting to wane at Month 5. CF2-treated patients achieved an increase in BCVA by Day 8 and a peak of +8.4 letters at Month 3, which was maintained at approximately +8.0-letter gain through Month 6 (Figure 3A).

Differences between groups in percentage of patients with ≥ 15 -letter gain or mean change in BCVA from baseline to Month 6 did not achieve statistical significance at any time point. The study was not sufficiently powered for between-group efficacy comparisons.

Retinal Thickness. Both formulations of AR-1105 reduced CST in the study eye from baseline to Month 6 (Figure 3B). CF1-treated patients showed greater numerical reductions in CST at Month 1, but not at later visits when compared with CF2-treated patients. Durable effects were observed in CF2-treated patients, with reductions in CST persisting through Month 6. At Month 6, mean changes from baseline were $-93 \mu\text{m}$ in the CF1 randomized group compared with $-211 \mu\text{m}$ in the CF2 group (Figure 3B).

Resolution of macular edema (CST $\leq 300 \mu\text{m}$) was achieved in approximately 50% of the patients in the CF1 randomized group from Months 1 to 5, with the effect beginning to wane at Month 6 (22.7% [95% confidence interval, 7.8%, 45.4%]; Figure 4). In the CF2 group, resolution of macular edema was maintained in approximately half of the treated patients from Month 2 (45.5% [24.4%, 67.8%]) to Month 6 (54.5% [32.2%, 75.6%]; Figure 4).

Need for Rescue Therapy. The total number and proportion of patients requiring rescue therapy was similar in those treated with CF1 or CF2: 8/27 (29.6%) patients treated with CF1 in the initial cohort and randomized group and 6/22 patients (27.3%) treated with CF2 (Table 4). Ten patients were followed beyond Month 6; eight of

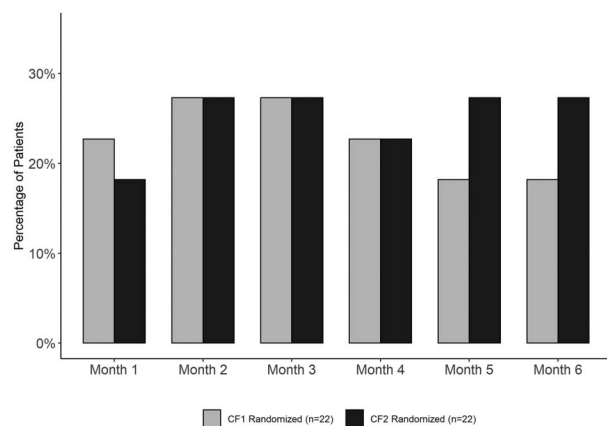


Fig. 2. Proportion of study eyes with ≥ 15 -letter gain from baseline in BCVA. Missing values and data collected after rescue were imputed as last observation carried forward.

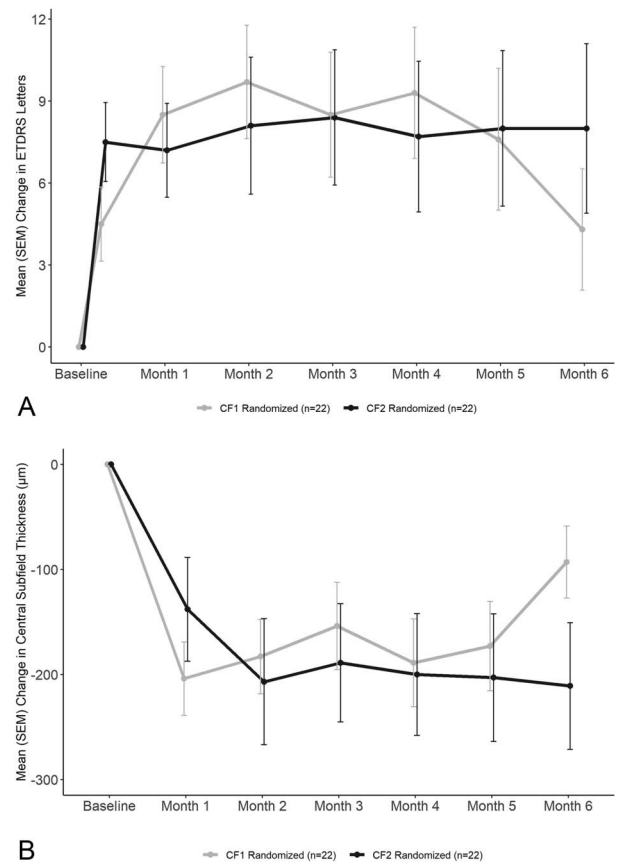


Fig. 3. **A.** Mean change from baseline BCVA in ETDRS letter score in the study eye. **B.** Mean change from baseline in CST in the study eye. In both A and B, the missing values and data collected after rescue were imputed as last observation carried forward.

these patients (two treated with CF1 and six treated with CF2) never received rescue therapy during the entire study.

Overall, the maximum recorded rescue-free duration was 8.0 months in the CF1 and 8.9 months in the CF2 groups. The need for rescue was similar in patients with BRVO and CRVO: six patients with BRVO and eight patients with CRVO received rescue therapy.

Discussion

This Phase 2 study demonstrated that both formulations of AR-1105, a novel biodegradable dexamethasone implant, were well tolerated and provided durable improvements in vision and reduction in retinal thickening in a difficult-to-treat population who had longstanding edema and a large proportion of patients with CRVO.

AR-1105 exhibited an AE profile generally consistent with corticosteroid treatment and intravitreal injections. There were no unexpected safety findings. The incidences of IOP increase $\geq 10 \text{ mmHg}$ (22% in

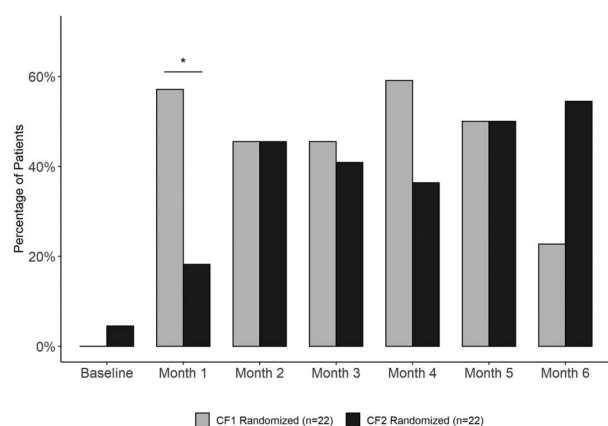


Fig. 4. Percentage of patients with resolution of macular edema (CST $\leq 300 \mu\text{m}$) in the study eye. * $P < 0.05$ for CF1 versus CF2. Missing values and data collected after rescue were imputed as last observation carried forward.

CF1-treated and 18% in CF2-treated patients) or IOP ≥ 30 mmHg (4% in CF1-treated and 18% in CF2-treated patients) in this small study were comparable with those reported in a previous large Phase 2 study (N = 1,267) of 700 and 350 μg dexamethasone implants (Ozurdex) that showed IOP increase ≥ 10 mmHg or IOP ≥ 25 mmHg peaked at $\sim 16\%$ for both doses.⁹ In this study of AR-1105, elevations in IOP were managed with topical or oral medications; no patient required surgical or laser interventions. In the previous study of 700 and 350 μg Ozurdex, most eyes with IOP increases were successfully managed with topical medications; five eyes (three in the 700 μg group, two in the 350 μg group) required a procedure to reduce IOP.⁹ This study was not long enough to assess the risk of cataract.

Patients enrolled in the current study had a long history of RVO (~ 32 months across all groups), which is known to impact potential improvements in vision acuity.^{9,16} A large proportion of patients had CRVO, a more severe clinical condition compared with BRVO,¹⁷ particularly in the CF2 group (63.6%). By comparison, 66% of patients enrolled in the Phase 2 study of Ozurdex

had BRVO and only 34% had CRVO.⁹ In addition, patients randomized to CF2 had significantly worse vision and numerically greater retinal thickness than those randomized to CF1. Despite the long-standing edema, both formulations of AR-1105 achieved clinically meaningful improvement in vision and reduction in retinal thickening in patients with CRVO or BRVO. CF2 demonstrated longer durability of treatment effect than CF1, consistent with the drug-release parameters established for each formulation. CF2 has been shown to maintain a longer duration of sustained release of dexamethasone than CF1 in preclinical studies. The 6-month duration of efficacy of CF2 suggests that potentially longer intervals between injections may be possible compared with available dexamethasone implants, which, along with a lower total dose of 340 μg dexamethasone—approximately half the amount provided by marketed dexamethasone implants (700 μg), may further reduce the treatment burden and lower drug exposure in patients with macular edema due to RVO. Further investigation is warranted to determine the optimum retreatment interval and the response to repeated injections of AR-1105.

This study demonstrated the utility and versatility of the PRINT[®] sustained-release technology platform. Implant bioerosion (assessed clinically by implant visibility) was consistent with expectations. At Month 6, more CF2-treated patients tended to have visible implants compared with CF1-treated patients, suggesting slower implant bioerosion with CF2 formulation.

Potential limitations of this study include small number of patients, a relatively short follow-up time, and the lack of placebo control group. This study was designed to determine which formulation of AR-1105 will be selected for further clinical development. It was unnecessary and would have been unethical to include an untreated or placebo-controlled group for a disease that has multiple marketed treatment options available. The results of the study have shown that safety and efficacy of AR-1105 were consistent with those of marketed dexamethasone implants, despite the

Table 4. Number of Patients Who Received Rescue Therapy By Visit

	Initial Cohort, CF1 (n = 5)	Randomized Group, CF1 (n = 22)	Randomized Group, CF2 (n = 22)
Month 1	0	0	1
Month 2	2	1	1
Month 3	0	1	4
Month 4	0	0	0
Month 5	0	4	0
Month 6	0	0	0
>6 months*	0	0	0
Total	2/5	6/22	6/22

*Ten patients were followed after Month 6. Eight of these patients (two treated with CF1 and six treated with CF2) never received rescue therapy at any time during the study.

differences in study sample size and patient population,^{9–11} and the CF2 formulation will be further evaluated in larger clinical studies with a standard-of-care control group and a longer follow-up.

In conclusion, the results of this study demonstrate that both formulations of AR-1105 were well tolerated and demonstrated clinically meaningful and sustained improvements in vision and reduction in retinal thickening despite difficult-to-treat BRVO or CRVO with longstanding edema. CF2 was associated with a 6-month durability of treatment effect, supporting potentially longer intervals between repeated injections and further reduced treatment burden than current intravitreal corticosteroids. The CF2 formulation is planned for further evaluation in an upcoming Phase 3 program in retinal disease.

Key words: branch retinal vein occlusion, central retinal vein occlusion, dexamethasone implant, intravitreal corticosteroid, macular edema, retinal vein occlusion.

Acknowledgments

Medical writing services provided by BioScience Communications, New York, NY, were funded by Aerie Pharmaceuticals, Inc., Durham, NC, in accordance with Good Publication Practice (GPP3) guidelines.

References

- Royal College of Ophthalmologists Clinical Guidelines. Retinal vein occlusion (RVO) guidelines; 2015. Available at: <https://www.rcophth.ac.uk/wp-content/uploads/2015/07/Retinal-Vein-Occlusion-RVO-Guidelines-July-2015.pdf>. Accessed September 27, 2021.
- Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology* 2010;117:313–319.
- Sacconi R, Giuffrè C, Corbelli E, et al. Emerging therapies in the management of macular edema: a review. *F1000Res* 2019; 8:F1000 Faculty Rev-1413.
- Hayreh SS. Ocular vascular occlusive disorders: natural history of visual outcome. *Prog Retin Eye Res* 2014;41:1–25.
- Zas M. When to use steroids for retinal vein occlusion; early, late or never? *Retina Today* 2017;46–50.
- OZURDEX®. Highlights of Prescribing Information. Madison, NJ: Allergan USA, Inc.;2018.
- Ip MS, Scott MM, Altaweel BA, et al. Treatment of central retinal vein occlusion with intravitreal triamcinolone acetonide. *Invest Ophthalmol Vis Sci* 2003;44:3217.
- Cekic O, Chang S, Tseng JJ, et al. Intravitreal triamcinolone injection for treatment of macular edema secondary to branch retinal vein occlusion. *Retina* 2005;25:851–855.
- Haller JA, Bandello F, Belfort R Jr, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology* 2010;117:1134–1146.
- Joshi L, Yaganti S, Gemenetzi M, et al. Dexamethasone implants in retinal vein occlusion: 12-month clinical effectiveness using repeat injections as-needed. *Br J Ophthalmol* 2013;97:1040–1044.
- Bandello F, Parravano M, Cavallero E, et al. Prospective evaluation of morphological and functional changes after repeated intravitreal dexamethasone implant (OZURDEX®) for retinal vein occlusion. *Ophthalmic Res* 2015;53:207–216.
- Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, et al. Guidelines for the management of retinal vein occlusion by the European Society of Retina Specialists (EURETINA). *Ophthalmologica* 2019;242:123–162.
- Lucentis®. Highlights of Prescribing Information. South San Francisco, CA: Genentech, Inc.; 2006.
- Tully J, Williams S, Melton D, et al. AR-1105 dexamethasone extended release and pharmacokinetics in the non-human primate. *Invest Ophthalmol Vis Sci* 2018;59:5673.
- Sandahl M, Melton D, Tully J, et al. Evaluation of reproducibility and uniformity of PRINT implant manufacturing. AR-VO 2018 annual meeting abstract. Available at: <https://iovs.arvojournals.org/article.aspx?articleid=2692992>. Accessed on December 9, 2021.
- Chatziralli I, Theodossiadis G, Chatzirallis A, et al. Ranibizumab for retinal vein occlusion: predictive factors and long-term outcomes in real-life data. *Retina* 2018;38:559–568.
- Laouri M, Chen E, Looman M, Gallagher M. The burden of disease of retinal vein occlusion: review of the literature. *Eye (Lond)* 2011;25:981–988.