SAFETY AND FEASIBILITY OF A NOVEL 25-GAUGE BIODEGRADABLE IMPLANT OF DEXAMETHASONE FOR TREATMENT OF MACULAR EDEMA ASSOCIATED WITH RETINAL VEIN OCCLUSION: A PHASE I CLINICAL TRIAL

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Purpose: To evaluate the safety and feasibility of a 25-gauge biodegradable implant containing 350 μg of dexamethasone (DDS-25) for the treatment of decreased vision due to macular edema associated with central or branch retinal vein occlusion.

Methods: Prospective, nonrandomized, open-label, Phase I clinical trial, including 10 patients with decreased vision (best-corrected early treatment diabetic retinopathy study visual acuity of 20/40 or worse) due to macular edema associated with central retinal vein occlusion (n = 4) or branch retinal vein occlusion (n = 6) for more than 4 months. Comprehensive ophthalmic evaluation, including best-corrected visual acuity, spectral domain optical coherence tomography (Spectralis Heidelberg Engineering) for determination of central subfield thickness, full-field electroretinography (ISCEV standard ERG), and fluorescein angiography, was performed at baseline, and 1, 4, 12, and 24 weeks after intravitreal DDS-25 insertion.

Results: Mean best-corrected visual acuity was 0.72 ± 0.1 logMAR (20/100) at baseline and improved by 7 early treatment diabetic retinopathy study letters to 0.58 ± 0.08 logMAR (20/80 + 1) at 24 weeks (P = 0.049), with 3 central retinal vein occlusion and 3 branch retinal vein occlusion patients improving between 1 and 4 early treatment diabetic retinopathy study lines. Significant central subfield thickness reduction was observed at 24 weeks compared with baseline (P = 0.011); mean ± standard error (range) central subfield thickness (μm) was 461.2 ± 41.3 (288–701) at baseline, and 439.6 ± 40.4 (259–631), 442.5 ± 44.6 (255–632), 354.6 ± 31.2 (228–537), and 316.5 ± 26.4 (226–441) at 1, 4, 12, and 24 weeks, respectively. No significant changes in electroretinography responses or area of retinal nonperfusion were observed during 24 weeks of follow-up. There was no significant change in mean intraocular pressure at any of the study visits compared with baseline. One patient had mild anterior chamber inflammation (1–5 cells) at one week after DDS-25 insertion.

Conclusion: In this Phase I study demonstrating the feasibility of intravitreal DDS-25 insertion for the treatment of decreased vision due to macular edema associated with retinal vein occlusion, no safety concerns were observed. A larger prospective randomized study with longer follow-up is warranted to confirm these findings.

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Central (CRVO) and branch retinal vein occlusions (BRVO) are frequent retinal vascular diseases, with varying levels of severity depending mainly on the degree of macular edema and ischemia.[1–5] Macular edema (ME) is the most common cause of visual loss in both CRVO and BRVO.[6] The pathogenesis of ME secondary to retinal vein occlusion is incompletely understood, but reported contributory factors include hydrostatic effects from increased venous pressure, inflammatory cytokines (e.g., prostaglandins and interleukin-6), dysregulation of endothelial tight junction proteins, and/or upregulation of vascular permeability factors, such as vascular endothelial growth factor.[7,8]

Several therapies have been described for the treatment of ME associated with retinal vein occlusion. For decades, the standard of care for ME associated with nonischemic retinal vein occlusion was grid photocoagulation for BRVO[9] and observation for CRVO.[10] In 2009, the SCORE Study investigative group reported that in multicenter Phase III randomized controlled clinical trials, intravitreal triamcinolone acetonide was superior to observation for CRVO-associated ME, but failed to demonstrate superiority in efficacy or safety over grid photocoagulation in patients with BRVO-associated ME.[11–17] A prospective, open-label study (IBeVO study), including 7 consecutive patients (7 eyes) with ME associated with ischemic central or hemicentral RVO, showed that intravitreal injection of 2.0 mg (0.08 mL) of bevacizumab every 12 weeks was associated with short-term best-corrected visual acuity (BCVA) stabilization or improvement, and ME reduction in all patients.[18] Subsequently, intravitreal ranibizumab was approved by the United States Food and Drug Administration (FDA) for the treatment of ME associated with CRVO and BRVO based on the results of two multicenter, randomized, double-masked clinical trials: the CRUISE Study (conducted in patients with CRVO) and the BRAVO Study (conducted in patients with BRVO).[19,20] Based on the results of the Copernicus and Galileo studies, the Food and Drug Administration approved aflibercept for the treatment of ME associated with CRVO. On October 2014, the Food and Drug Administration approved aflibercept for the treatment of ME after retinal vein occlusion, which includes ME after BRVO in addition to the previously-approved indication of ME after CRVO. The expanded indication was based on the previously-approved indication for ME after CRVO and the favorable results from the VIBRANT Study, which included 181 patients with ME after BRVO.[21–24] A sustained-release intravitreal dexamethasone implant (Ozurdex; Allergan Inc, Irvine, CA) has also been approved by the Food and Drug Administration for the treatment of ME associated with CRVO and BRVO. The dexamethasone implant was designed to permit controlled delivery of drug, with a potentially lower rate of adverse events traditionally associated with intravitreal steroid administration (such as cataract and intraocular pressure elevation).[25–29]

Although antivascular endothelial growth factor therapy for RVO-associated macular edema has been demonstrated in Phase III clinical trials to be an efficacious treatment option with an acceptable safety profile, steroids may also play an important therapeutic role. For example, in the Cruise Study,[19] 15% of patients treated with ranibizumab experienced no visual gain and 12% of patients lost vision despite therapy.

Our group developed a 25-gauge biodegradable intravitreal implant of dexamethasone (DDS-25) that has been demonstrated to be safe in preclinical studies.[30–34] Herein, the authors report the safety and efficacy of the DDS-25 implant in a Phase I study of patients with ME secondary to retinal vein occlusion.

Methods

Ethics Statement

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local institutional (Comite de Ética em Pesquisa do HCFMRP-USP) and national (Conselho Nacional de Ética em Pesquisa) review boards and registered at clinicaltrials.gov (NCT01662518). All participants gave written informed consent. Patients were evaluated in the Retina and Vitreous Section of the Department of Ophthalmology, Otorhinolaryngology

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A. d. S. Cunha-Junior and R. Siqueira registered a patent on August 31, 2006 regarding the dexamethasone implant (DDS 25-gauge) in the Brazilian National Institute for Intellectual Property (INPI). Remaining authors have no any conflicting interests to disclose.

Clinical Trial registry: NCT01662518 (Clinicaltrials.gov).

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Trial Design and Procedures

In this prospective, nonrandomized, open-label, Phase I clinical trial, a single certified examiner performed Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity measurement before any other study procedures. Ophthalmic evaluation was performed by a single retinal specialist (R.B.C.), and color fundus photography, fluorescein angiography, and spectral domain optical coherence tomography (OCT; Spectralis, Heidelberg Engineering) were performed by a single certified ophthalmic technician. Insertions of the DDS-25 implant were performed by R. C. Siqueira in a minor procedure room in the clinic.

Eligibility Criteria

Inclusion criteria. 1) ETDRS BCVA in the study eye between 20 letters (approximate Snellen acuity of 20/400) and 70 letters (approximate Snellen acuity of 20/40); 2) Center-involved macular edema associated with CRVO or BRVO for more than 4 months duration and central subfield thickness (CSFT) greater than 300 μm on spectral domain OCT.

Exclusion criteria. 1) Previous intraocular surgery other than cataract extraction; 2) presence of cataract or other media opacity that would prohibit high-quality ocular imaging or that would affect electroretinography (ERG); 3) presence of other ophthalmic disease such as diabetic retinopathy, glaucoma or uveitis; 4) any type of steroid or antivascular endothelial growth factor treatment (intravitreal, oral, or intravenous) within 90 days before study enrollment; 5) systemic use of immunomodulatory agents.

Ophthalmologic Evaluation

Patients underwent a comprehensive ophthalmologic examination at baseline, including ETDRS BCVA measurement, undilated and dilated slit-lamp biomicroscopic examinations, applanation tonometry, and dilated funduscopic indirect ophthalmoscopy. Presence of cells in the anterior chamber was graded from 0 to 4, where 0 = none (no cells), 1 = mild (1–5 cells), 2 = moderate (6–15 cells), 3 = severe (16–30 cells), and 4 = very severe (>30 cells). Anterior chamber flare was also scored from 0 to 4, where 0 = none (no Tyndall effect), 1 = mild (barely discernible Tyndall effect), 2 = moderate (moderately intense Tyndall beam in anterior chamber), 3 = severe (severely intense Tyndall beam), and 4 = very severe. Intraocular pressure was measured by Goldman applanation tonometry.

Best-corrected visual acuity was measured according to the standardized ETDRS refraction protocol using a retroilluminated Lighthouse for the Blind distance visual acuity test chart (using modified ETDRS Charts 1, 2, and R).

Optical Coherence Tomography and Fluorescein Angiography

Fourier Domain OCT evaluation (Spectralis Eye-tracker Tomographer, HRA-OCT, Heidelberg, Germany) was performed in all patients, and retinal thickness measurements were acquired using a standard 20° × 15° raster scan protocol consisting of 19 horizontal sections (each computed out of 25 frames) with a distance of 240 μm between each horizontal scan, covering a square of 20° × 15° on the retina and centered on the foveal region. Follow-up mode was used to reduce test–retest variability.

Automatic delineation of the inner and outer boundaries of the neurosensory retina generated by OCT built-in software was verified for each of the scans to optimize the accuracy of OCT data. Central subfield thickness values were calculated automatically as the average thickness of a central macular region 1,000 μm in diameter centered on the patient's foveola by built-in Heidelberg software using retinal map analysis. Digital color fundus photography and fluorescein angiography were performed using a Topcon fundus camera system (TRC-50IA/IMAGEnet; Topcon, Tokyo, Japan).

Electroretinography

Electroretinography was recorded according to the International Society for Clinical Electrophysiology of Vision standard[35] using the Espion E2 (Diagnosys LLC) coupled to the ColorDome (Diagnosys LLC, Impington, Cambridge, United Kingdom) as Ganzfeld LED stimulator. The protocol included 3 stimuli under dark-adapted (30 minutes) conditions: Rod response (0.01 cd.s/m^2), followed by dark-adapted maximum response (3.0 cd.s/m^2) and a high intensity flash (10.0 cd.s/m^2). Oscillatory potentials were filtered from the second stimulus using a band-pass filter (Espion built-in) set between 75 Hz and 300 Hz.

Thereafter, eyes were light-adapted using the same Ganzfeld bowl at 30 cd/second^2 for 10 minutes before recording cone single flash (3 cd.s/m^2) and 30 Hz flicker (3 cd.s/m^2) responses.

Intravitreal Implant and Insertion Technique

The intravitreal biodegradable implant containing 350 μg of dexamethasone (DDS-25) was designed and manufactured as described elsewhere.[31–33] Briefly, the

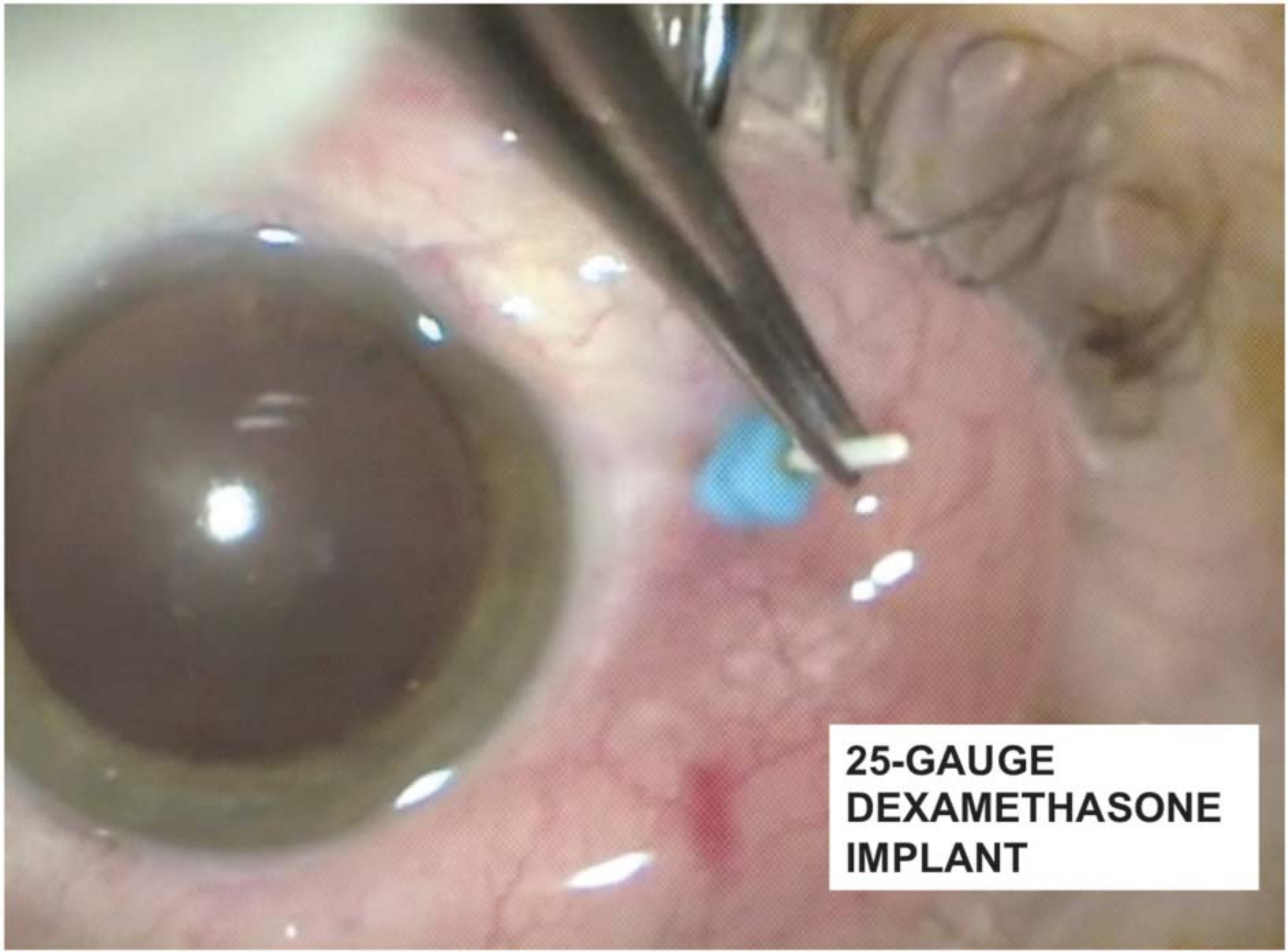

Fig. 1. Insertion of 25-gauge dexamethasone implant. The dexamethasone implant was injected into the vitreous cavity using a 25-gauge trocar/cannula (Alcon, Fort Worth, TX).

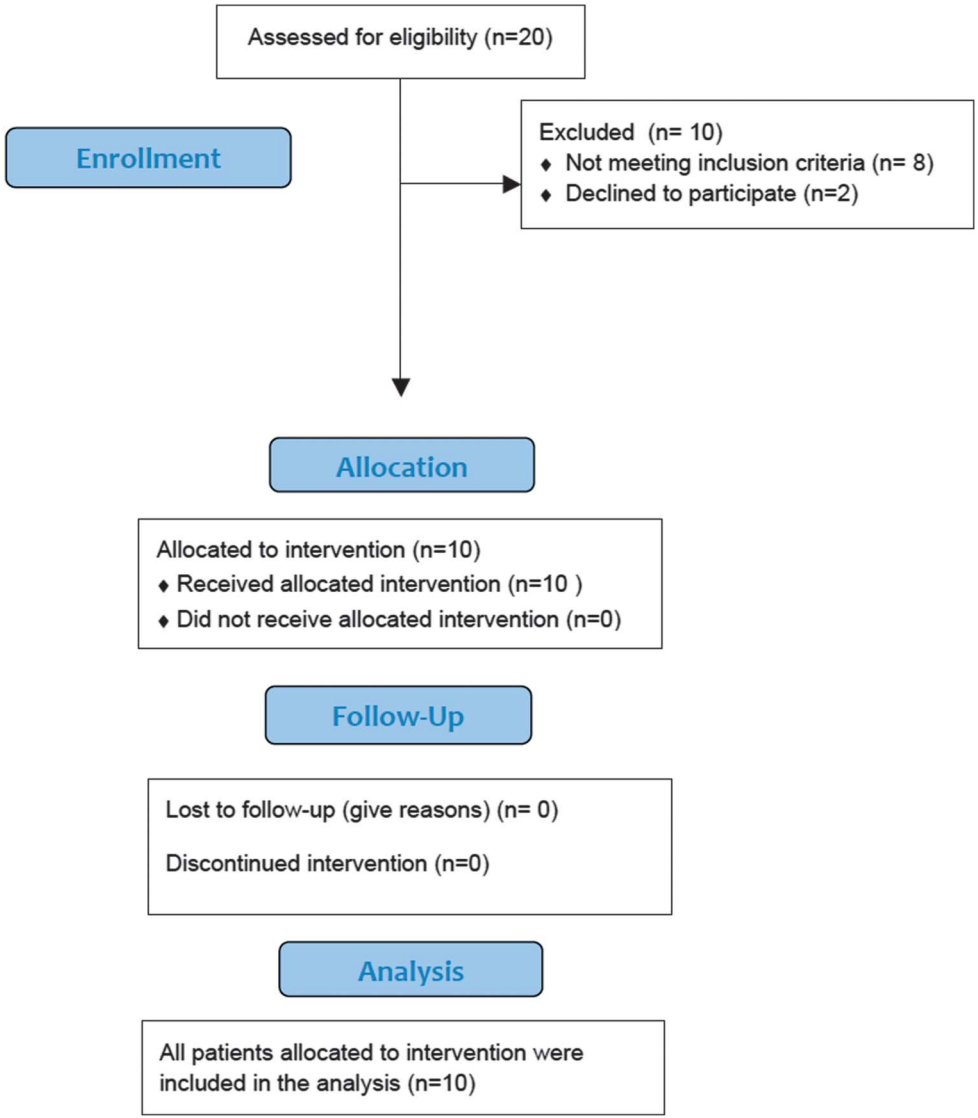

Fig. 2. Patient Flow Diagram of a Phase I nonrandomized clinical trial to evaluate the safety and feasibility of a 25-gauge biodegradable implant containing 350 μg of dexamethasone (DDS-25) for the treatment of decreased vision due to macular edema associated with central (CRVO) or branch (BRVO) retinal vein occlusion.

Table 1. Patients' Demographic Data and Baseline Characteristics

	CRVO	BRVO
Age, mean ± SD, years	60.2 ± 6.2	63.8 ± 10.8
Gender, male/female	03/01	05/01
Race, Black/Hispanic/White	01/00/03	03/00/03
Duration of symptoms, mean ± SD, months	33.0 ± 14.4	37.5 ± 27.8
Previous treatment		
Focal/grid LASER	0	3
Intravitreal TAAC	1	1
Intravitreal anti-VEGF agent	4	1
None	0	3

CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion, TAAC, triamcinolone acetonide; VEGF, vascular endothelial growth factor, SD, standard deviation.

Intraocular Pressure

Mean ± SE intraocular pressure (IOP) was 15.0 ± 0.8, 15.7 ± 1.0, 14.1 ± 0.6, 15.6 ± 0.9, and 18.2 ± 1.8 mmHg at baseline and at Weeks 1, 4, 12, and 24, respectively. There was no significant elevation in mean IOP at any of the study visits compared with baseline.

Mean ± SE IOP among the patients with BRVO was 13.5 ± 0.6, 14.6 ± 1.2, 13.6 ± 0.7, 14.8 ± 1.1, and 17.1 ± 2.9 at baseline and at Weeks 1, 4, 12, and 24, respectively. There was no significant elevation in mean IOP in patients with BRVO at any of the study visits compared with baseline.

Mean ± SE IOP among the patients with CRVO was 17.2 ± 1.1, 17.2 ± 1.6, 14.7 ± 1.2, 16.7 ± 1.8, and 19.7 ± 1.9 at baseline and at Weeks 1, 4, 12, and 24, respectively. There was no significant elevation in mean IOP in patients with CRVO at any of the study visits compared with baseline (Figure 3 and Table 2).

Three patients had IOP elevation above 21 mmHg (24, 28, 23 mmHg) at the 6-month follow-up visit. The IOP was controlled with the transient use of one IOP-lowering topical medication in all three patients.

Central Subfield Thickness

Mean ± SE CSFT (μm) was 461.2 ± 41.3 at baseline and did not change significantly at Week 1 (439.6 ± 40.4; P = 0.145) and Week 4 (442.5 ± 44.5; P = 0.049). However, mean CSFT demonstrated significant improvement at Weeks 12 (354.6 ± 31.2; P = 0.049) and 24 (316.5 ± 26.4; P = 0.011).

In patients with BRVO, mean ± SE CSFT (μm) was 405.6 ± 45.7 at baseline and did not change significantly at Week 1 (391.3 ± 48.3; P = 0.156), Week 4 (389.8 ± 46.2; P = 0.218), and Week 12 (356.6 ± 47.9; P = 0.156). Mean CSFT demonstrated significant improvement at Week 24 (328 ± 33.5; P = 0.046). In 3 BRVO patients, rescue therapy with intravitreal ranibizumab was performed because CSFT was ≥300 μm and was reduced by <10% compared with baseline CSFT at Week 12.

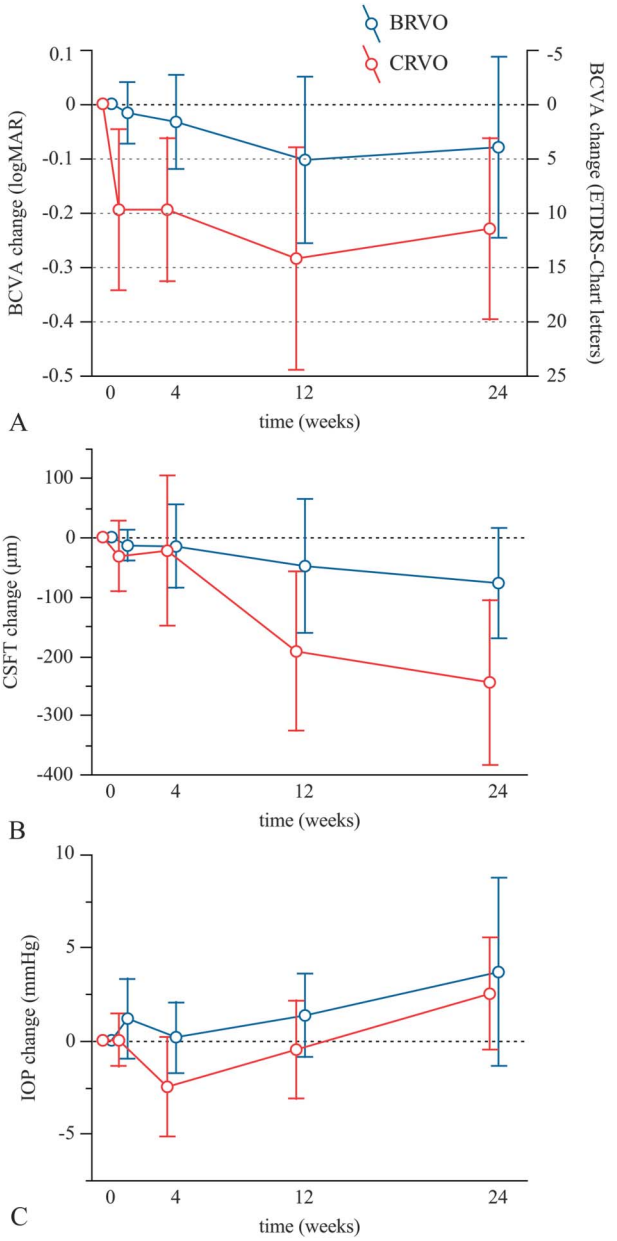

Fig. 3. Circles correspond to the means, and error bars denote the limits of the 95% confidence interval. **A**) Mean change in BCVA compared with baseline—the left y-axis shows the BCVA change in logMAR, while on the right y-axis in ETDRS-chart letters; **B**) Mean change in CSFT compared with baseline; **C**) Mean change in IOP compared with baseline. Red lines correspond to the CRVO group and blue lines correspond to the BRVO group.

In patients with CRVO, mean ± SE CSFT (μm) was 544.5 ± 60.9 at baseline and did not change significantly at Week 1 (512 ± 58.7; P = 0.177) and Week 4

Table 2. Data Summary: Mean ± SE (standard error; Lower 95% Confidence Limit; Upper 95% Confidence Limit) for Best-Corrected Visual Acuity (BCVA), Central Subfield Thickness (CSFT) and Intra-ocular Pressure (IOP)

Group	Week	BCVA Change, logMAR	CSFT Change, μm	IOP Change, mmHg
BRVO	1	–0.02 ± 0.03 (–0.07 to 0.04)	–14.33 ± 13.08 (–40.50 to 11.83)	1.17 ± 1.08 (–0.99 to 3.32)
	4	–0.03 ± 0.04 (–0.12 to 0.05)	–15.83 ± 35.05 (–85.94 to 54.27)	0.17 ± 0.95 (–1.72 to 2.06)
	12	–0.10 ± 0.08 (–0.26 to 0.05)	–49.00 ± 56.03 (–161.06 to 63.06)	1.33 ± 1.12 (–0.90 to 3.56)
	24	–0.08 ± 0.08 (–0.25 to 0.09)	–77.67 ± 46.58 (–170.82 to 15.49)	3.67 ± 2.51 (–1.36 to 8.69)
CRVO	1	–0.20 ± 0.07 (–0.34 to –0.05)	–32.50 ± 29.75 (–92.00 to 27.00)	0.00 ± 0.71 (–1.41 to 1.41)
	4	–0.20 ± 0.07 (–0.33 to –0.06)	–23.00 ± 62.92 (–148.85 to 102.85)	–2.50 ± 1.32 (–5.15 to 0.15)
	12	–0.29 ± 0.10 (–0.49 to –0.08)	–193.00 ± 66.97 (–326.93 to –59.07)	–0.50 ± 1.32 (–3.15 to 2.15)
	24	–0.23 ± 0.08 (–0.40 to –0.06)	–245.25 ± 69.72 (–384.68 to –105.82)	2.50 ± 1.50 (–0.50 to 5.50)

Data are shown as difference to baseline (change) at all study periods.
BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

(521.5 ± 78; P = 0.369). Mean CSFT demonstrated significant improvement at Week 12 (315.5 ± 39.1; P = 0.031) and Week 24 (299.2 ± 47.6; P = 0.019) (Figure 3 and Table 2).

Electroretinography

No significant changes compared with baseline were observed in any ERG parameters at 4 and 24 weeks after DDS-25 implant insertion. Figure 4 shows examples of ERG responses before and 24 weeks after DDS-25 implant insertion for one patient.

Fluorescein Angiography

No change in area of retinal nonperfusion was observed in any patient during the 24-week study period. One patient with CRVO developed retinal neovascularization and underwent panretinal photocoagulation.

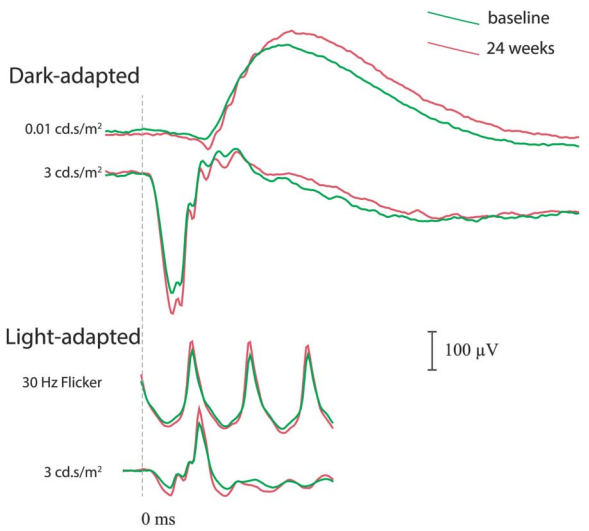

Fig. 4. Examples of ERG responses at baseline (green) and at 24 weeks after DDS-25 implant insertion in an eye with CRVO; similar traces are observed at both time points.

Discussion

Data from the current study demonstrate that a single dose of the intravitreal DDS-25 implant is safe with respect to clinical, electroretinographic, and angiographic parameters, at least in the short term. One out of ten patients presented with anterior chamber cells at one week after implantation but this was mild and transient, and no other patient exhibited any intraocular inflammation. There was no significant elevation in mean IOP compared with baseline at any of the study visits. Three patients demonstrated IOP >21 mmHg at Week 24 (23, 28, and 24 mmHg) but the IOP was controlled successfully with the transient use of one IOP-lowering topical medication in all three patients. Intraocular pressure elevation treated with IOP-lowering eyedrops has also been reported in previous studies of patients treated with dexamethasone implants.[29,30]

Electroretinography demonstrated no significant change in retinal function after dexamethasone implant insertion, indicating the lack of toxicity, at least in the short term, with respect to rod and cone driven retinal responses. Similarly, there was no change in area of peripheral retina capillary nonperfusion and area of macular capillary nonperfusion. No systemic adverse events were observed related to the injection procedure or drug delivery system.

Based on the results of the Geneva Study,[25] in which 350 μg and 700 μg dexamethasone implants were associated with similar results with respect to BCVA improvement and CSFT reduction, a 350 μg dose was selected for investigation in this first clinical study of the DDS-25 implant (the first intravitreal implant developed and tested in humans in Brazil). Another reason we selected a 350 μg dose implant for the current study was to try to minimize adverse events.

The use of commercially available 25-gauge trocar/cannulas for implant injection in the current

study was safe and feasible. The implants did not break apart when grasped with a 0.12 mm forceps and inserted gently into the vitreous cavity through the 25-gauge cannula. This may represent an advantage over the commercially available system, since the power used to push the implant into the vitreous cavity is controlled completely by the surgeon, whereas other implants are pushed automatically by means of spring-controlled devices and usually move further toward the center of the vitreous cavity and visual axis, especially in previously vitrectomized eyes.[25,26,37] In addition, the trocar cannula used in the current study is less traumatic, since it is 25 gauge (0.5 mm diameter),[38] whereas the commercially available implantation device diameter is 22 gauge (0.64 mm).[25,26] Finally, the cost of the DDS-25 implant is 4 times lower (600 reais/240 dollars versus 2.600 reais/1.040 dollars) than the cost of Ozurdex.

Mean BCVA improved significantly at Week 24 in pooled RVO patients and in CRVO patients. The lack of a demonstrated significant improvement in BCVA in BRVO patients may be due to the higher baseline BCVA in the BRVO group compared with the CRVO group. Mean CSFT improved significantly at Week 24 in all groups.

It should be noted that one intravitreal injection of ranibizumab was administered in 3 out of 6 patients with BRVO at Week 12, which might have positively influenced BCVA and CSFT outcomes in this subgroup of patients and may also explain the long lasting effects (through Week 24) observed in the current study. Notably the effects of the Ozurdex implant on BCVA and CSFT peaked at 3 months after implantation.[25,26]

Limitations of this Phase I study include the inherent challenges of interpreting data from a small sample with heterogeneous types of retinal vein occlusion and varying durations of ME. The short follow-up duration also limits the evaluation of such safety parameters as cataract progression, which was not detected in any of the nine phakic patients included in the current study.

In conclusion, this Phase I study with a short follow-up period (6 months) demonstrates the feasibility of a biodegradable implant of dexamethasone (DDS-25) as a treatment option for RVO-associated macular edema; no safety concerns were observed. Improvement in BCVA and reduction in CSFT represent preliminary evidence of efficacy. A prospective randomized study with a larger number of patients and longer follow-up is needed to confirm our preliminary findings.

Key words: retina, retinal vein occlusion, macula, edema, dexamethasone, implant, vitreous.

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