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A 12-month, multicenter, parallel group comparison of dexamethasone intravitreal implant versus ranibizumab in branch retinal vein occlusion

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Abstract

Purpose: Dexamethasone intravitreal implant and intravitreal ranibizumab are indicated for the treatment of macular edema secondary to retinal vein occlusion. This non-inferiority study compared dexamethasone with ranibizumab in patients with branch retinal vein occlusion.

Methods: In this randomized, 12-month head-to-head comparison, subjects with branch retinal vein occlusion were assigned to dexamethasone 0.7 mg at day 1 and month 5 with the option of retreatment at month 10 or 11, or ranibizumab 0.5 mg at day 1 and monthly through month 5 with subsequent as-needed injections at month 6–month 11. The primary efficacy outcome was the mean change from baseline in best-corrected visual acuity at month 12; secondary outcomes included average change in best-corrected visual acuity, proportion of eyes with ≥10- and ≥15-letter gain/loss, change in central retinal thickness, and change in Vision Functioning Questionnaire-25 score.

Results: In all, 307 of a planned 400 patients were enrolled in the study and received (mean) 2.5 dexamethasone injections (n = 154) and 8.0 ranibizumab injections (n = 153) over 12 months. The mean change from baseline in best-corrected visual acuity at month 12 was 7.4 letters for dexamethasone versus 17.4 letters for ranibizumab (least-squares mean difference (dexamethasone minus ranibizumab), −10.1 letters; 95% confidence interval, −12.9, −7.2; $p = 0.0006$).

Conclusion: Dexamethasone and ranibizumab improved best-corrected visual acuity and anatomical outcomes; however, dexamethasone did not show non-inferiority to ranibizumab in this under-powered study. Dexamethasone was associated with an increased risk of intraocular pressure elevation and cataract progression, but a lower injection burden, compared to ranibizumab.

Keywords

Branch retinal vein occlusion, dexamethasone intravitreal implant, non-inferiority study, ranibizumab

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Introduction

Thrombotic occlusion of the retinal vein is the second most common retinal vascular disorder after diabetic retinopathy.[1] With consequences that include increased intracapillary pressure, capillary leakage, retinal hemorrhage and edema, and accompanying capillary closure and retinal ischemia, retinal vein occlusion (RVO) is an important cause of vision loss.[2–4] Macular edema secondary to branch RVO (BRVO) is typically associated with reduced visual acuity.[5] Current treatment options include laser photocoagulation, intravitreal

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corticosteroids, and anti-vascular endothelial growth factor (VEGF) agents.[6]

Dexamethasone (DEX) intravitreal implant (Ozurdex®; Allergan plc, Dublin, Ireland) is a sustained delivery, biodegradable implant that releases drug for up to 6 months post-injection.[7] In two identical registration studies (the GENEVA studies), the efficacy and safety of DEX implant were compared with sham injection in patients with macular edema secondary to branch or central RVO (CRVO).[8,9] In the randomized, 6-month, double-masked, sham-controlled phase, a single injection of DEX implant 0.7 or 0.35 mg reduced the risk of vision loss and improved the speed of visual improvement.[8] A 6-month open-label extension phase allowed the option of repeat DEX implant injection in eyes meeting prespecified retreatment criteria. Overall, single and repeat DEX implant had a favorable safety profile over the 12-month study period, and the efficacy of the second implant was similar to that of the initial implant.[9] Another registration study (the BRAVO study) compared the efficacy and safety of intravitreal ranibizumab with sham injection in BRVO.[10,11] During the randomized, 6-month, double-masked, sham-controlled phase, monthly injections of ranibizumab 0.5 or 0.3 mg provided rapid improvements in best-corrected visual acuity (BCVA), with low rates of ocular events;[10] these benefits were maintained during a subsequent 6-month phase of as-needed ranibizumab treatment.[11]

Differences in patient populations and study methodologies preclude direct comparison of the GENEVA and BRAVO findings. In addition to enrolling patients with BRVO, the GENEVA studies included patients with CRVO.[8] Enrollees in GENEVA were required to have a central retinal thickness (CRT) ≥300 μm compared with ≥250 μm in BRAVO.[8,10] In addition, the duration of macular edema was longer in GENEVA than in BRAVO (mean ~5 vs 3.5 months). This study was designed as a head-to-head comparison to evaluate the efficacy and safety of DEX implant versus ranibizumab in patients with BRVO.

Methods

Study design and participants

The COMO (COmparison of intravitreal dexamethasone implant and ranibizumab for Macular Oedema in BRVO) study was a 12-month, multicenter, randomized, open-label study conducted in France, Germany, Israel, Italy, Spain, and the United Kingdom. The study complied with the tenets of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice and was approved by independent ethics committees at each study center. The study is registered with the identifier NCT01427751 at clinicaltrials.gov.

Subjects were randomized 1:1 to treatment with DEX implant or intravitreal ranibizumab and stratified based on the pre-enrollment BCVA (≤55 vs >55 letters) of their study eye. DEX implant 0.7 mg was administered at day 1 and month 5, with the option of a single retreatment at month 10 or 11. Intravitreal ranibizumab 0.5 mg was administered at day 1 and monthly through month 5, with subsequent as-needed injections at months 6–11. Retreatment criteria included BCVA <70 Early Treatment Diabetic Retinopathy Study (ETDRS) letters; CRT >300 μm, as assessed by optical coherence tomography (OCT); more than five letters loss of BCVA from any previous visit; >40 μm increase in CRT from the previous visit; or likely benefit, in the investigator's opinion, from retreatment. If no improvement in visual acuity was evident by month 3, continued treatment was discouraged.

Male or female subjects ≥18 years of age, with macular edema secondary to BRVO, CRT ≥300 μm, recent-onset (<3 months) visual symptoms, and BCVA ≥20 to ≤70 ETDRS letters (20/40 to 20/400 Snellen equivalent) in the study eye, in the absence of severe macular ischemia, were eligible for study inclusion. Exclusion criteria included ocular hypertension, defined as an intraocular pressure (IOP) >22 mm Hg, and recent (<3 months) laser photocoagulation, intravitreal anti-VEGF, or intravitreal corticosteroid therapy. All subjects provided written informed consent prior to study entry.

Efficacy endpoints

The primary efficacy endpoint was the mean change from baseline in BCVA at month 12. Secondary endpoints comprised the average change from baseline in BCVA to month 12; the proportion of study eyes with ≥10- and ≥15-letter gain or loss at month 12; time to ≥15-letter gain or loss; change from baseline in CRT at month 12; change from baseline in composite (near-vision, far-vision, and vision-related dependency) score of the Vision Functioning Questionnaire-25 (VFQ-25)[12] at months 3, 6, and 12; and treatment failure (study discontinuation before month 12 due to lack of efficacy). Safety endpoints included assessment for adverse events and IOP changes.

Statistical analyses

This was designed as a non-inferiority study using a non-inferiority margin of five ETDRS letters, with an intergroup difference in BCVA score within +5 and −5 ETDRS letters representing equivalent efficacy, consistent with the non-inferiority margin used in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) study.[13] The null hypothesis was that the mean improvement from baseline in BCVA at month 12 was more than five letters less with DEX implant than with ranibizumab. Applying a non-inferiority margin of five ETDRS letters

and assuming a common standard deviation (SD) of 10 ETDRS letters for a study with 80% power, the number of subjects required for each treatment arm was 176. Based on an anticipated dropout rate of 10%, the planned study enrollment was 400 patients. The primary endpoint of mean change in BCVA at month 12 was evaluated by analysis of covariance (ANCOVA). Because of large numbers of mis-stratifications of baseline BCVA and treatment imbalance in the actual strata, baseline BCVA was used as a covariate instead of baseline BCVA category (≤55 vs >55 letters). A two-sided 95% confidence interval (CI) for the least-squares (LS) mean difference in BCVA response between the two treatment groups (DEX implant minus ranibizumab) was calculated from the ANCOVA model. If the lower bound of the 95% CI was greater (i.e. less negative) than −5 ETDRS letters, the null hypothesis was rejected and DEX implant declared non-inferior to ranibizumab. A supportive analysis was based on the average change from baseline in BCVA over time using an area-under-the-curve (AUC) approach. Analysis of CRT and VFQ-25 outcomes was based on ANCOVA, using terms for treatment, baseline VFQ-25 composite score, lens status (pseudophakic/phakic), machine type (Spectralis OCT/Cirrus OCT), and baseline CRT. For all efficacy analyses, missing data were imputed using the last-observation-carried-forward approach.

Results

Patient disposition and baseline characteristics

Recruitment difficulties restricted study enrollment to 307 of the planned 400 patients. Consequently, the statistical power of the primary analysis to detect non-inferiority was reduced from 80% to 73%, thereby increasing the possibility of non-rejection of the null hypothesis. All 307 patients were randomized to treatment (154 to DEX implant and 153 to ranibizumab; intent-to-treat (ITT) population), of whom 303 patients received more than one dose of study drug (safety population). The ITT population was of mean age 67.0 years and predominantly presented with unilateral BRVO (95.7%) and a phakic study eye (82.1%). The study arms were generally well-balanced for demographic and baseline clinical characteristics, apart from baseline BCVA (mean 56.6 and 59.2 ETDRS letters in DEX implant- and ranibizumab-treated eyes, respectively; Table 1). Patients assigned to DEX implant received a mean of 2.5 (median 3; range, 0–3) injections, with 19 (12.3%), 41 (26.6%), and 93 (60.4%) eyes receiving 1, 2, and 3 injections, respectively, over the 12-month study period. Patients assigned to ranibizumab received a mean of 8.0 (median 8; range, 0–12) injections, with 64% of eyes receiving ≥8 injections. The distribution of intravitreal treatment administration over the study period is depicted in Figure 1. In total, 42 patients in the DEX implant arm and 14 patients in the ranibizumab arm failed to complete the study; reasons included adverse events (DEX, n = 18; ranibizumab, n = 2), protocol violation (DEX, n = 6; ranibizumab, n = 4), no expectation of further treatment benefit (DEX, n = 5; ranibizumab, n = 1), loss to follow-up (DEX, n = 3; ranibizumab, n = 1), withdrawal of consent (DEX, n = 2; ranibizumab, n = 2), or other (DEX, n = 8; ranibizumab, n = 1).

Change from baseline in BCVA

For the ITT population, the LS mean improvement from baseline in BCVA at month 12 was 7.4 ETDRS letters for DEX implant compared with 17.4 ETDRS letters for ranibizumab (LS mean difference (DEX implant minus ranibizumab), −10.1 ETDRS letters; 95% CI, −12.9, −7.2; $p = 0.0006$); accordingly, the lower bound of the 95% CI for the treatment difference was less (i.e. more negative) than −5 letters (Supplementary Table). Post hoc analysis of those DEX implant-treated patients who received treatment beyond month 5 (n = 94) likewise indicated that the lower bound of the 95% CI for the treatment difference extended below −5 letters (LS mean improvement in BCVA at month 12 of 6.1 vs 17.3 ETDRS letters for DEX implant and ranibizumab, respectively; LS mean difference, −11.2 ETDRS letters; 95% CI, −14.2, −8.1; $p < 0.0001$). In the supportive AUC analysis of average change in BCVA from baseline, the LS mean difference for the ITT population was −2.8 ETDRS letters (95% CI, −4.5, −1.1; $p = 0.0096$) at month 3 ($AUC_{0–3}$) and −6.3 ETDRS letters (95% CI, −8.3, −4.2; $p = 0.2190$) at month 12 ($AUC_{0–12}$) (Supplementary Table). Accordingly, the lower bound of the 95% CI for the treatment difference was greater than −5 letters over the first 3 months, but less than −5 letters over 12 months. Among pseudophakic study eyes (n = 53), the LS mean improvement from baseline in BCVA at month 12 was 4.4 ETDRS letters in the DEX implant group compared with 11.7 ETDRS letters in the ranibizumab group (LS mean difference, −7.4 ETDRS letters; 95% CI, −16.0, +1.3; $p = 0.5829$), mirroring the findings of the overall ITT population (Supplementary Table). The mean changes from baseline in BCVA over time for the overall study population and for the subset of pseudophakic eyes are shown in Figure 2(a) and (b), respectively.

Percentage of eyes with ≥10-letter and ≥15-letter gain and loss from baseline

At any time during the study, BCVA gains of ≥10 and ≥15 letters were achieved in 86.4% and 67.5% of DEX implant-treated eyes and 87.6% and 76.5% of ranibizumab-treated eyes, respectively. BCVA losses of ≥10 and ≥15 letters were seen in 19.5% and 14.9% of DEX implant-treated eyes and 5.2% and 4.6% of ranibizumab-treated eyes, respectively. The percentage of study eyes with ≥10-letter and ≥15-letter gains over time is shown in Figure 3. At

Table 1. Patient demographics and baseline clinical characteristics (ITT population).

	DEX implant (N = 154)	Ranibizumab (N = 153)	Total (N = 307)
Age, years			
Mean (±SD)	68.4 (10.6)	65.5 (12.0)	67.0 (11.4)
Gender, n (%)			
Male	92 (59.7)	87 (56.9)	179 (58.3)
Race, n (%)			
Caucasian	147 (95.5)	148 (96.7)	295 (96.1)
Black	2 (1.3)	3 (2.0)	5 (1.6)
Asian	4 (2.6)	1 (0.7)	5 (1.6)
Other	1 (0.6)	1 (0.7)	2 (0.6)
BRVO, n (%)			
Unilateral	147 (95.5)	147 (96.0)	294 (95.7)
Bilateral	6 (3.9)	5 (3.3)	11 (3.6)
Unknown	1 (0.6)	1 (0.7)	2 (0.7)
Study eye lens status, n (%)			
Phakic	127 (82.5)	125 (81.7)	252 (82.1)
Pseudophakic	26 (16.9)	27 (17.6)	53 (17.3)
Unknown	1 (0.6)	1 (0.7)	2 (0.7)
Baseline BCVA, ETDRS letters[a]			
Mean (±SD)	56.6 (10.9)	59.2 (10.9)	
Baseline BCVA, n (%)[b]			
≤55 ETDRS letters	61 (39.6)	47 (30.7)	108 (35.2)
>55 ETDRS letters	93 (60.4)	106 (69.3)	199 (64.8)
Baseline CRT, µm[a]			
Mean (±SD)	547 (163)	544 (168)	
Time from onset of symptoms to first treatment, days[c]			
Mean (±SD)	49.4 (28.7)	46.1 (25.9)	47.8 (27.3)

DEX: dexamethasone; SD: standard deviation; BRVO: branch retinal vein occlusion; BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CRT: central retinal thickness; ITT: intent-to-treat.
[a]Baseline BCVA and CRT data were available for 306 study eyes (DEX implant, n = 153; ranibizumab, n = 153).
[b]After correction for mis-stratifications.
[c]Time to treatment data were available for 290 study eyes (DEX implant, n = 146; ranibizumab, n = 144).

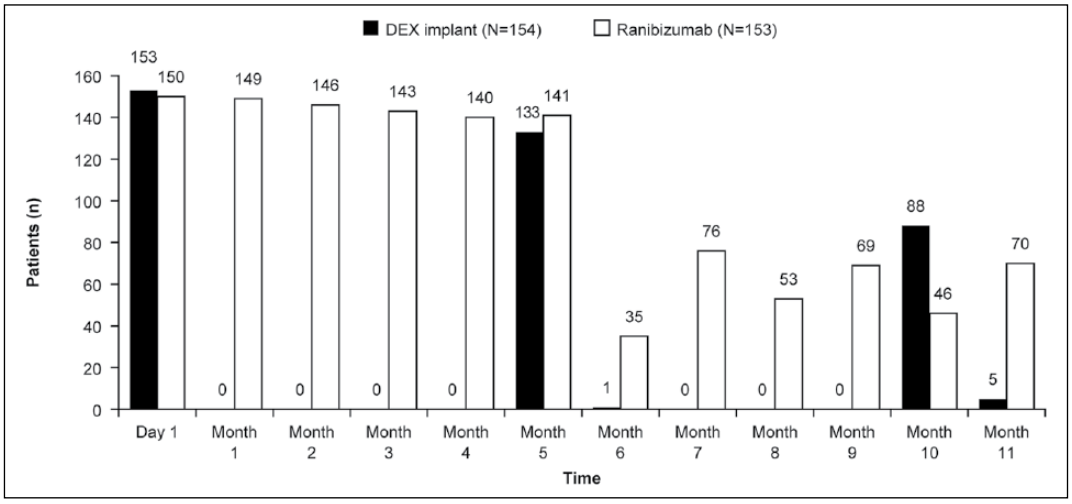

Figure 1. Number and distribution of study treatments administered over the study period.

month 12, the proportion of study eyes with ≥10-letter gain was 51.3% in the DEX implant arm versus 73.2% in the ranibizumab arm (odds ratio (OR), 0.30; 95% CI, 0.20, 0.55; $p < 0.0001$), while the proportion with ≥15-letter gain was 33.8% in the DEX implant arm versus 59.5% in the ranibizumab arm (OR, 0.30; 95% CI, 0.18, 0.48;

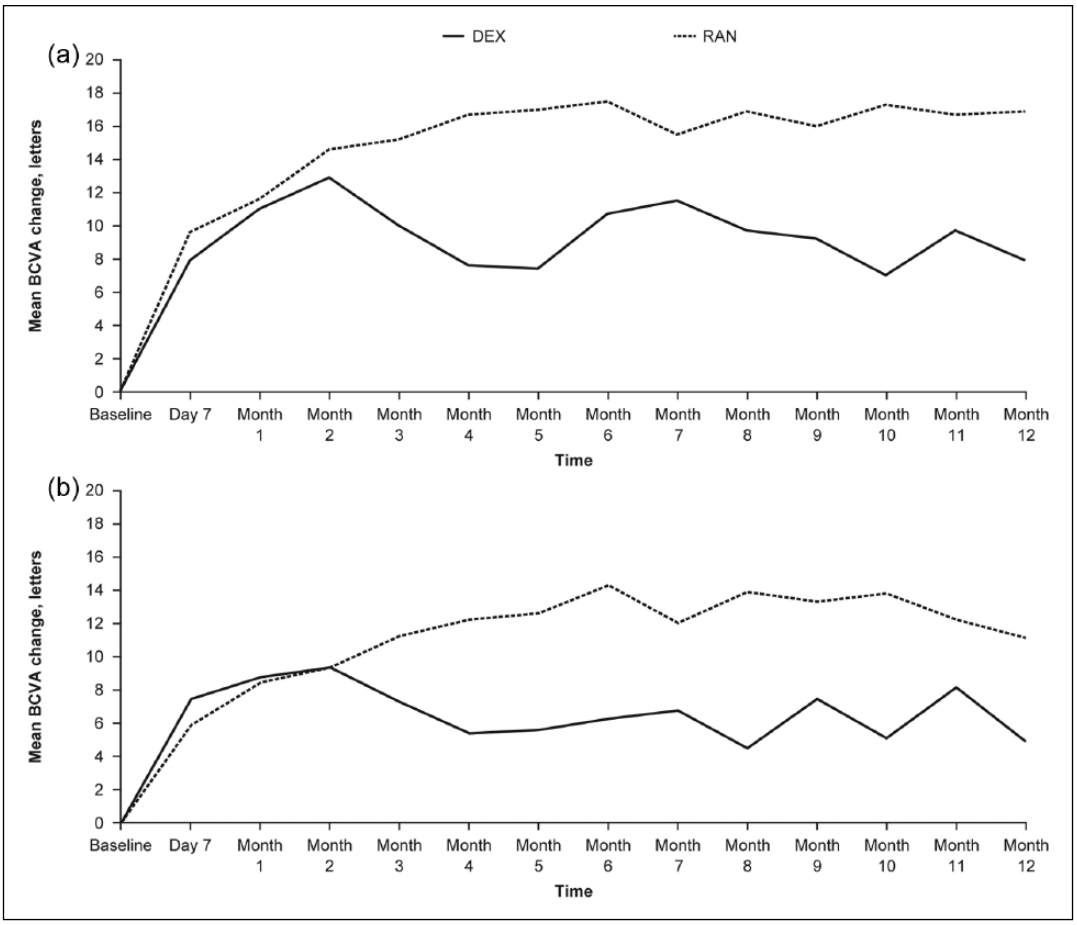

Figure 2. Mean change from baseline in BCVA (ETDRS letters) over 12 months: (a) overall ITT population (DEX implant, n = 153; ranibizumab, n = 153) and (b) pseudophakic eyes, ITT population (DEX implant, n = 26; ranibizumab, n = 27).

$p < 0.0001$). The proportion of study eyes with ≥10-letter loss was 11.7% in the DEX implant versus 2.0% in the ranibizumab arm (OR, 6.2; 95% CI, 1.8, 21.4; $p = 0.0043$), while the proportion with ≥15-letter loss was 9.1% in the DEX implant versus 0.7% in the ranibizumab arm (OR, 14.4; 95% CI, 1.9, 111.6; $p = 0.0104$).

Change from baseline in CRT

For the ITT population, the mean (±SD) baseline CRT was 547 (±163) μm in the DEX implant arm and 544 (±168) μm in the ranibizumab arm. The mean change from baseline in CRT versus time profile over 12 months is shown in Figure 4. The LS mean change from baseline in CRT at month 12 was −227 μm for DEX implant versus −252 μm for ranibizumab (LS mean difference, 24.7 μm; 95% CI, −3.3, +52.8; $p = 0.0839$).

Change from baseline in VFQ-25 composite score at month 12 and treatment failure

For the ITT population, the mean (±SD) baseline VFQ-25 composite score was 78.1 (±16.6) in the DEX implant arm and 80.7 (±14.3) in the ranibizumab arm. The LS mean change from baseline in VFQ-25 composite score at month 12 was 2.9 for DEX implant versus 7.2 for ranibizumab (LS mean difference, 4.3; 95% CI, −6.9, −1.8; $p = 0.0011$). Treatment failure rate was 4.5% in the DEX implant arm compared with 0.7% in the ranibizumab arm ($p = 0.0668$).

Ocular and systemic safety

The most common treatment-emergent ocular adverse events with either DEX implant or ranibizumab were increased IOP, conjunctival hemorrhage, macular edema, reduced visual acuity, cataract, lenticular opacities, ocular hypertension, and blepharitis; all occurred more frequently with DEX implant than with ranibizumab (Table 2). Dry eye, vitreous floaters, and nasopharyngitis occurred at similar frequency (≥5%) in the two treatment groups, whereas eye pain, conjunctivitis, hypertension, and headache occurred more frequently with ranibizumab. Contrasting IOP profiles were noted, with DEX implant-treated eyes showing a saw-tooth pattern and ranibizumab-treated eyes exhibiting a linear change over time (Supplementary Figure). IOP elevations ≥10 mm Hg from

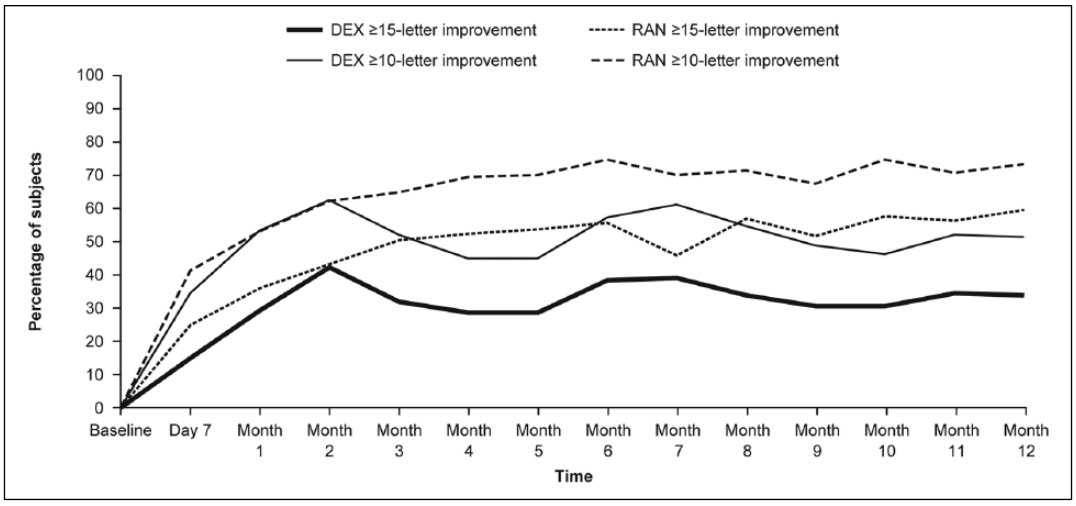

Figure 3. Proportion of study eyes with ≥10-letter and ≥15-letter gain from baseline in BCVA over 12 months, ITT population (DEX implant, n = 153; ranibizumab, n = 153).

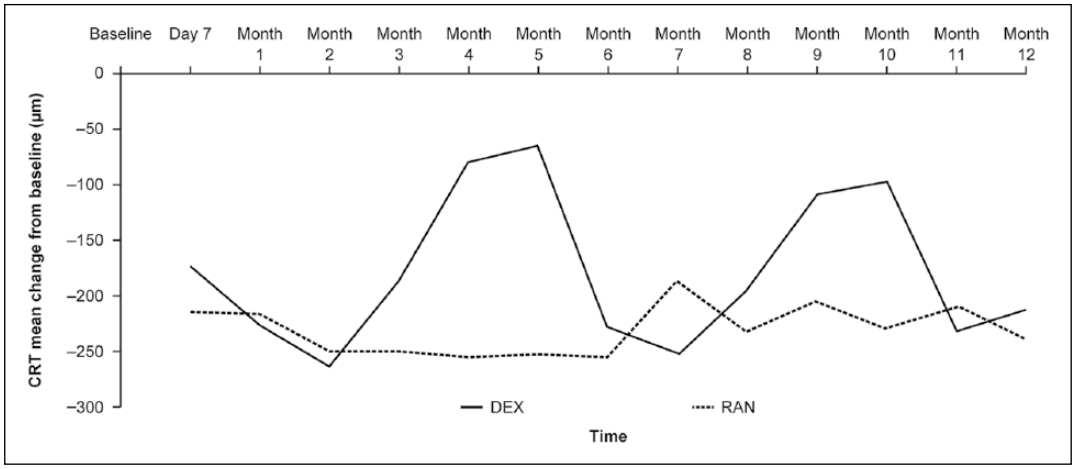

Figure 4. Mean change from baseline in central retinal thickness over 12 months, ITT population (DEX implant: n = 153; ranibizumab, n = 153).

baseline were more common with DEX implant than with ranibizumab (38.6% vs 5.3%), as were cataract progression, defined as an increase in lens opacity (59.8% vs 30.9%), and cataract surgery (3.1% vs 0%).

Discussion

Based on the primary outcome of change from baseline in BCVA at month 12, the null hypothesis of a more than five-letter difference in BCVA gain between DEX implant and ranibizumab at month 12 was not rejected, indicating that DEX implant did not demonstrate non-inferiority vis-à-vis ranibizumab in the treatment of macular edema secondary to BRVO. The difference in average change in BCVA from baseline to month 3 ($AUC_{0–3}$) was within the five-letter non-inferiority margin for the supportive analysis, although $AUC_{0–3}$ was significantly greater with ranibizumab than with DEX implant. At 12 months, the proportions of eyes with ≥10- and ≥15-letter gains were significantly greater, and the proportions with ≥10- and ≥15-letter losses significantly lower, for ranibizumab compared with DEX implant. Furthermore, the improvement in VFQ-25 composite score was significantly greater with ranibizumab than with DEX implant. Despite the overall superior improvement in visual acuity achieved with ranibizumab, DEX implant showed comparable efficacy with respect to time to ≥10- and ≥15-letter gain, CRT reduction, and treatment failure rate. Unlike ranibizumab, which was associated with consistent changes from baseline in CRT, DEX implant resulted in a fluctuating pattern of CRT, which may have contributed to the more modest improvement in visual acuity. To place this finding in context, the present results were achieved with a median of eight ranibizumab injections and three DEX implant injections over 12 months. As a reflection of

Table 2. Summary of most frequent (≥5% incidence) treatment-emergent ocular adverse events, safety population.

Treatment-emergent adverse event, n (%)	DEX implant (N = 153)	Ranibizumab (N = 150)
Increased IOP	50 (32.7)	16 (10.7)
Conjunctival hemorrhage	28 (18.3)	17 (11.3)
Macular edema	20 (13.1)	4 (2.7)
Reduced visual acuity	18 (11.8)	3 (2.0)
Cataract	13 (8.5)	2 (1.3)
Lenticular opacities	10 (6.5)	0
Ocular hypertension	9 (5.9)	1 (0.7)
Blepharitis	9 (5.9)	3 (2.0)
Dry eye	9 (5.9)	7 (4.7)
Vitreous floaters	9 (5.9)	9 (6.0)
Nasopharyngitis	8 (5.2)	5 (3.3)
Eye pain	6 (3.9)	9 (6.0)
Conjunctivitis	6 (3.9)	9 (6.0)
Hypertension	5 (3.3)	10 (6.7)
Headache	4 (2.6)	9 (6.0)

DEX: dexamethasone; IOP: intraocular pressure.

the low rate of retreatment with DEX implant, 12% of study eyes did not receive a second implant and 40% did not receive a third implant; in contrast, almost two-thirds (64%) of ranibizumab-treated eyes received eight or more-injections. The saw-tooth pattern of CRT response seen with DEX implant suggests that some patients may benefit from more frequent DEX implant injections.

Consistent with a postulated cataract-associated attenuation of BCVA response to DEX implant in phakic eyes,[9] narrowing of the differential in treatment efficacy was noted in pseudophakic eyes. No conclusion can be drawn, however, as to whether DEX implant is non-inferior to ranibizumab in pseudophakic eyes, since the study was under-powered for this particular analysis. Restoration of BCVA gains would be expected after cataract surgery in eyes with lens opacities. However, in this study cataract surgery was uncommon in both DEX implant- and ranibizumab-treated eyes (3% vs 0%, respectively), despite the high incidence of increased lens opacity (59.8% vs 30.9% of phakic DEX implant- and ranibizumab-treated eyes).

The ocular safety profile of DEX implant was consistent with previously published reports of its use in RVO.[8,9,14] Treatment with DEX implant was associated with a higher risk of IOP elevation/ocular hypertension, lenticular opacities, and cataract progression or surgery than treatment with ranibizumab. The IOP elevation observed with DEX implant was transient but recurrent.

Recent short-term (6-month), head-to-head controlled comparisons in BRVO (COMRADE B) and CRVO (COMRADE C) have demonstrated superior BCVA outcomes with monthly ranibizumab compared with single-dose DEX implant.[15,16] Whereas ranibizumab maintained its efficacy over 6 months, the efficacy of single-dose DEX implant declined over this period. In clinical practice, DEX implant is often re-administered at approximately 4- or 5-month intervals, and the observed BCVA improvements in RVO are greater with multiple-dose than with single-dose DEX implant.[17] In RVO, the visual acuity response to DEX implant is influenced by the duration of macular edema,[18] with the greatest BCVA gain being achieved in recent-onset BRVO.[19] This study extends these findings by demonstrating, in a controlled clinical trial, a visual acuity advantage with ranibizumab compared with multiple-dose DEX implant over a 12-month treatment period in BRVO. However, since anti-VEGF dosing intensity and treatment efficacy are greater in controlled trials than in clinical practice,[20] a real-world comparison of DEX implant and ranibizumab would be instructive.

A strength of this study is its head-to-head treatment comparison. However, the study also has several limitations. Compared with real-world scenarios, the frequency of ranibizumab retreatment was high. For those DEX implant-treated eyes that did not receive a third implant, the interval from treatment administration to 12-month efficacy assessment was excessive. Patients and investigators were not masked to treatment assignment, which introduces potential bias. Patient recruitment was lower than planned, reducing the statistical power to detect non-inferiority. Furthermore, despite randomization to treatment, intergroup imbalances occurred through mis-stratification of baseline BCVA. Collectively, these limitations prevent generalization of the study findings.

In conclusion, the primary analysis findings fail to demonstrate that DEX implant is non-inferior to intravitreal ranibizumab in improving visual acuity in BRVO. This suggested efficacy disadvantage, together with the added risk of IOP elevation and cataract progression, is partly mitigated by the lower treatment burden associated with DEX implant.

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Supplementary Material

Supplementary Material for this article is available online.

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Appendix 1

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