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

Francesco Bandello¹, Albert Augustin², Adnan Tufail³ and Richard Leaback⁴

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

Date received: 4 October 2017; accepted: 4 December 2017

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

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. 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). 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. A 6-month open-label extension phase allowed the option of repeat DEX implant injection in eyes meeting pre-specified 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. Another registration study (the BRAVO study) compared the efficacy and safety of intravitreal ranibizumab with sham injection in BRVO. 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; these benefits were maintained during a subsequent 6-month phase of as-needed ranibizumab treatment.

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. Enrollees in GENEVA were required to have a central retinal thickness (CRT) ≥300 µm compared with ≥250 µm in BRAVO. 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) 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 inter-group 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. 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 population (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 mean change from baseline in BCVA at month 12 was 7.4 ETDRS letters for DEX implant compared with 11.7 ETDRS letters in the ranibizumab group (LS mean difference, −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 (AUC0.3) and −6.3 ETDRS letters (95% CI, −8.3, −4.2; p = 0.2190) at month 12 (AUC0.12) (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
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;
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
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
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.

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.
Acknowledgements
The authors thank the study site personnel who participated in this study (see Appendix I). Medical writing and editorial assistance was provided to the authors by Andrew Fitzon, PhD, of Evidence Scientific Solutions (Horsham, UK) and funded by Allergan plc, Dublin, Ireland.

Declaration of conflicting interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: F.B. reports financial support from Allcon, Allergan, Alimera Sciences, Bayer, Bausch & Lomb, Boehringer-Ingelheim, Farmila Thea, Roche/Genentech, Novartis, Sanofi, Santen, SIFI SpA, SOOFT Italia, Thrombogenics, and Zeiss; A.A. reports financial support from Allergan; A.T. reports consultancy fees from Allergan, Bayer, Novartis, and Roche/Genentech. R.L. is an employee of Allergan Limited.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was sponsored by Allergan plc, Dublin, Ireland. All authors met the ICMJE authorship criteria. No honoraria or payments were made for authorship.

Supplementary Material
Supplementary Material for this article is available online.

References
1. 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(2): 313–319.e1.
2. Jaulim A, Ahmed B, Khanam T, et al. Branch retinal vein occlusion: epidemiology, pathogenesis, risk factors, clinical features, diagnosis, and complications. An update of the literature. Retina 2013; 33(5): 901–910.
3. Ota T, Tsujikawa A, Murakami T, et al. Subfoveal serous retinal detachment associated with extramacular branch retinal vein occlusion. Clin Ophthalmol 2013; 7: 237–241.
4. Flammer J and Konieczka K. Retinal venous pressure: the role of endothelin. EMA J 2015; 6: 21.
5. Rogers SL, McIntosh RL, Lim L, et al. Natural history of branch retinal vein occlusion: an evidence-based systematic review. Ophthalmology 2010; 117(6): 1094–1101.e5.
6. Regnier SA, Larsen M, Bezlyak V, et al. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis. BMJ Open 2015; 5(6): e007527.
7. Chang-Lin JE, Attar M, Acheampong AA, et al. Pharmacokinetics and pharmacodynamics of a sustained-release dexamethasone intravitreal implant. Invest Ophthalmol Vis Sci 2011; 52(1): 80–86.
8. Haller JA, Bandello F, Belfort R, et al. OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010; 117(6): 1134–1146.e3.
9. Haller JA, Bandello F, Belfort R, et al. OZURDEX GENEVA Study Group. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion: twelve-month study results. Ophthalmology 2011; 118(12): 2453–2460.
10. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010; 117(6): 1102–1112.e1.
11. Brown DM, Campochiaro PA, Bhistikul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology 2011; 118(8): 1594–1602.
12. Marella M, Pesudovs K, Keeffe JE, et al. The psychometric validity of the NEI VFQ-25 for use in a low-vision population. Invest Ophthalmol Vis Sci 2010; 51(6): 2878–2884.
13. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011; 364(20): 1897–1908.
14. Mayer WJ, Wolf A, Kernt M, et al. Twelve-month experience with Ozurdex for the treatment of macular edema associated with retinal vein occlusion. Eye 2013; 27(7): 816–822.
15. Hattenbach LO, Feltsge N, Bertlmann T, et al. Head-to-head comparison of ranibizumab PRN versus single-dose dexamethasone for branch retinal vein occlusion (COMRADE-B). Acta Ophthalmol 2018; 96(1): e10–e18.
16. Hoerauf H, Feltsge N, Weiss C, et al. Clinical efficacy and safety of ranibizumab versus dexamethasone for central retinal vein occlusion (COMRADE C): a European label study. Am J Ophthalmol 2016; 169: 258–267.
17. Sallam AAI, Stratton I. UK Dexamethasone Implant for Retinal Vein Occlusion Study Group. UK Dexamethasone Implant for Retinal Vein Occlusion Study Group. United Kingdom national database study of intravitreal dexamethasone implant (Ozurdex) for retinal vein occlusion-related macular edema: visual outcome and safety of treatment. Invest Ophthalmol Vis Sci 2015; 56(7): 5805.
18. Yeh WS, Haller JA, Lanzetta P, et al. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. Ophthalmology 2012; 119(6): 1190–1198.
19. Yoon YH, Kim JW, Chang DJ, et al. A 12-month, open-label, multicenter study to assess the safety and efficacy of Ozurdex 0.7 mg for the treatment of macula edema related to branch retinal vein occlusion in Korea: the COBALT study. Poster presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Seattle, WA, USA, 1–5 May 2016. Available at: http://www.docplayer.net/39897605-Arvo-2016-annual-meeting-abstracts.html (accessed 28 February 2018).
20. Kiss S, Liu Y, Brown J, et al. Clinical utilization of anti-vascular endothelial growth-factor agents and patient monitoring in retinal vein occlusion and diabetic macular edema. Clin Ophthalmol 2014; 8: 1611–1621.

Appendix I
Names and affiliations of the principal investigators who participated in the COMO study: Luis Arias, Hospital Universitari de Bellvitge, Barcelona, Spain; Félix
