BMJ Open Ophthalmology

Dexamethasone intravitreal implant in diabetic macular oedema refractory to anti-vascular endothelial growth factors: the AUSSIEDEX study

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To cite: Mitchell P, Arnold J, Fraser-Bell S, *et al*. Dexamethasone intravitreal implant in diabetic macular oedema refractory to anti-vascular endothelial growth factors: the AUSSIEDEX study. *BMJ Open Ophthalmology* 2023;**8**:e001224. doi:10.1136/bmjophth-2022-001224

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjophth-2022-001224).

This work was partially presented at the EURETINA 2019 Congress (5 September 2019–8 September 2019, Paris, France), American Academy of Ophthalmology 2019 meeting (12 October 2019–15 October 2019, San Francisco, California, USA), and Saudi Ophthalmology 2020 Symposium (6 August, Riyadh, Saudi Arabia, virtual congress).

Received 9 December 2022
Accepted 26 April 2023

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ABSTRACT

Aim To evaluate effectiveness of dexamethasone intravitreal implant 0.7 mg (DEX) monotherapy in the AUSSIEDEX study non-responder subgroup, defined by diabetic macular oedema (DME) refractory to anti-vascular endothelial growth factor (anti-VEGF) agents.

Methods This prospective, open-label, observational, real-world study included pseudophakic and phakic (scheduled for cataract surgery) eyes that did not achieve a ≥5-letter best corrected visual acuity (BCVA) gain and/or clinically significant central subfield retinal thickness (CRT) improvement after 3–6 anti-VEGF injections for DME (N=143 eyes), regardless of baseline BCVA and CRT. After an initial DEX injection (baseline visit), reinjection was permitted at ≥16-week intervals. Primary endpoints: changes in mean BCVA and CRT from baseline to week 52. Safety assessments included adverse events.

Results Of 143 eyes, 53 (37.1%) and 89 (62.2%) switched to DEX after 3–6 (early) and >6 (late) anti-VEGF injections, respectively; 1 (0.7%) had missing information. With 2.3 injections (mean) over 52 weeks, the change in mean BCVA from a baseline of 57.8 letters was not significant at week 52. Mean CRT improved significantly from a baseline of 417.8 µm at week 52 (mean change –60.9 µm; p<0.001). Outcomes were similar in eyes switched to DEX early and late. No unexpected adverse events were reported; no filtration surgeries were required.

Conclusion To date, AUSSIEDEX is the largest prospective, real-world study of DEX monotherapy for treatment-naïve or anti-VEGF-refractory DME. Following early or late switch from anti-VEGF agents, DEX significantly improved anatomic outcomes at 52 weeks without new safety concerns, supporting use in anti-VEGF-refractory DME.

Trial registration number NCT02731911.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Intravitreal anti-vascular endothelial growth factor (VEGF) agents have become the standard of care for diabetic macular oedema (DME), but not all eyes respond optimally.

⇒ By providing broader anti-inflammatory effects than anti-VEGF agents, corticosteroids such as the dexamethasone intravitreal implant 0.7 mg (DEX; Ozurdex) have the potential to treat a wider range of patients.

WHAT THIS STUDY ADDS

⇒ AUSSIEDEX is to date the largest prospective, real-world study of DEX monotherapy for treatment-naïve or anti-VEGF-refractory DME.

⇒ In this subgroup analysis of patients with anti-VEGF-refractory DME, DEX significantly improved anatomic outcomes at 52 weeks without new safety concerns, supporting DEX use following early (after 3–6 anti-VEGF injections) or late (after >6 anti-VEGF injections) switch from anti-VEGF agents.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Early-switch patients also had better best corrected visual acuity (on average) than late-switch patients at 52 weeks, suggesting that earlier treatment of DME with DEX is one factor that could improve functional outcomes as well.

INTRODUCTION

Diabetes is a major public health issue,[1 2] partly because diabetic macular oedema (DME) is a leading cause of vision loss among working individuals.[2] Intravitreal anti-vascular endothelial growth factor (VEGF) agents have become DME's standard of care,[3 4] but not all eyes respond optimally.[4] Intravitreal corticosteroids such as the dexamethasone intravitreal implant 0.7mg (DEX; Ozurdex, Allergan, an AbbVie company) inhibit synthesis of VEGFs and other proinflammatory mediators that cause DME.[5] By providing broader anti-inflammatory effects than anti-VEGF agents, corticosteroids can potentially treat a wider range of patients.

In 2014, DEX was approved as DME treatment by the US Food and Drug Administration and European Medicines Agency. In 2015, DEX was approved as DME treatment (first indication) by the Australian Therapeutic Goods Administration and Pharmaceutical Benefits Scheme, with reimbursement for pseudophakic and phakic (scheduled for cataract surgery) eyes. Approval was based on

results from two identically designed, randomised, multicentre, masked, sham-controlled, phase 3 studies, in which patients with DME refractory to anti-VEGF or laser treatments experienced statistically significant improvements in visual and anatomic outcomes from baseline (vs sham treatment) with 4.1 DEX injections (mean) over 3 years (permitted every 6 months if retreatment criteria were met), with an acceptable safety profile.[6]

The AUSSIEDEX study was designed to assess DEX effectiveness and safety as treatment for DME (treatment-naïve or refractory to anti-VEGF therapy) in Australian clinics, and to advance understanding of DEX monotherapy as individualised DME treatment. To date, it is the largest prospective, real-world study of DEX monotherapy for DME, and one of the first to prospectively, directly compare the effects of early vs late switch from anti-VEGF therapy to DEX on anatomic and functional outcomes.[7–12] Outcomes in the overall population and subgroup of treatment-naïve eyes were previously published.[13] Reported here are outcomes in anti-VEGF non-responders, defined by a failure to achieve a ≥5-letter best corrected visual acuity (BCVA) gain and/or clinically significant central subfield retinal thickness (CRT) reduction after 3–6 anti-VEGF injections.

METHODS

AUSSIEDEX study design

This prospective, observational, multicentre, open-label, non-randomised, phase 4 study (ClinicalTrials.gov identifier: NCT02731911) was conducted as previously described.[13]

AUSSIEDEX study population

Details of the study population were previously published.[13] Briefly, eligible patients had vision-threatening, treatment-naïve or previously treated DME in pseudophakic or phakic (scheduled for cataract surgery) eyes. There were no eligibility restrictions regarding baseline BCVA and CRT. For patients treated bilaterally, the first eye treated was analysed.[14]

Enrolled patients were stratified by prior therapy: treatment-naïve eyes[13] or anti-VEGF non-responders (defined above and analysed here). The decision to treat with DEX had to be made by the investigator before the patient could be screened for participation in the study. In the non-responder subgroup, the decision was based on the investigator's assessment of the patient's clinical response to anti-VEGF therapy (ie, failure to achieve a ≥5-letter BCVA gain and/or clinically significant CRT reduction after 3–6 injections) and medical history.

Patient and public involvement

The study patients and public were not involved in the design, conduct, reporting or dissemination plans of this research.

Intervention and procedures

DEX was administered intravitreally per product information.[14] Following initial injection (baseline visit), reinjection was permitted at ≥16-week intervals[15 16] until week 52, per physician judgement.[13 14] Laser photocoagulation was allowed, per physician judgement, starting at week 16. Patients who received laser treatment for DME could receive additional DEX treatment and were to be evaluated at week 52.

Baseline measurements were obtained on the day of the first DEX injection. Mandatory follow-up visits were at 16 and 52 weeks (±4 weeks); the treating physician determined the timing of other follow-up visits. BCVA and CRT assessments, biomicroscopy and ophthalmoscopy were performed as previously described.[13] Adverse events (AEs), use of DME-related laser treatment, intraocular pressure (IOP), IOP-lowering medication use and ocular surgeries performed during the study[13] were recorded.

Outcomes and analyses

The mean number of DEX injections per eye by week 52 was recorded. Effectiveness endpoints included the changes in mean BCVA and CRT from baseline to weeks 6, 16, 24 and 52 (primary endpoint); patients (%) with a >15-letter, >10-letter and >5-letter gain or loss, or no BCVA change; patients (%) with central foveal threatening lipid deposition at each visit (based on the combined presence of hard exudates and central foveal involvement); and change in mean BCVA from baseline at each visit, stratified by baseline BCVA level (≥70 letters/driving vision standard and ≤34 letters/legal blindness). Effectiveness analyses included all patients who received ≥1 DEX injection(s) in the study eye and attended the baseline visit and ≥1 post-baseline visit(s), mandatory or other. If multiple visits occurred around weeks 6, 16, 24 and 52 (±4 weeks), the assessments closest to the target day were analysed.

The primary effectiveness endpoints are presented for non-responders overall and the subset of pseudophakic non-responders at baseline. Post hoc analyses of effectiveness variables were performed in non-responder subsets who switched to DEX early, after 3–6 anti-VEGF injections, or late, after >6 anti-VEGF injections.

Safety endpoints included the incidence of AEs and AEs of special interest (previously defined[13]); IOP at each visit; patients (%) with IOP change ≥10, ≥25 or ≥35 mmHg from baseline at any time; and patients (%) requiring IOP-lowering medications and/or glaucoma-related laser or incisional surgical treatment during the study.

Statistical analyses were performed as previously described,[13] without imputation for missing values, unless otherwise indicated. Analyses of effectiveness endpoints were based on Student's paired t-tests, with two-sided p values for continuous variables or the Clopper-Pearson method, with 95% CIs for categorical variables. A $p<0.05$ indicated statistical significance.

RESULTS

Patient disposition, demographics and baseline characteristics

The AUSSIEDEX study was conducted in 25 Australian ophthalmology clinics.[13] Of 200 patients enrolled, 143 (71.5%) were non-responders to anti-VEGF therapy; 113/143 (79.0%) completed the study (online supplemental figure 1). The non-responder safety and effectiveness populations included 141 (98.6%) and 139 (97.2%) patients, respectively. Two patients were excluded from both populations, having received no DEX treatment. Two additional patients were excluded from the effectiveness population, having attended no post-baseline visits.

In the safety population, 103/141 (73.0%) patients were pseudophakic at baseline, and 20 (14.2%) underwent cataract surgery during the study. Although no formal statistical comparisons were performed, demographics and baseline characteristics of the non-responder subgroup and total AUSSIEDEX study population appeared comparable (online supplemental table 1).

Treatment in non-responders

The mean number of DEX injections over 52 weeks was 2.3 (95% CI 2.2 to 2.5), ranging from 1 to 4 (median 2.0); 36 (25.5%), 37 (26.2%), 53 (37.6%) and 15 (10.6%) received 1, 2, 3 and 4 injections, respectively. Among non-responders who received >1 DEX injection, the mean (SD) injection interval was 148.6 (56.5) days. No study eye received laser photocoagulation for DME.

Effectiveness analyses in non-responders overall

The change in mean BCVA from baseline was statistically significant at weeks 6, 16 and 24, with 4.1, 2.4 and 4.1 letters, respectively (p≤0.048), but not at week 52, the primary endpoint (figure 1A). Over 72% reported a BCVA gain or no change from baseline at weeks 6, 16, 24 and 52 (figure 2A). At week 52, 37.4% of patients gained ≥5 letters, 35.3% had unchanged BCVA (gain or loss ≤4 letters) and 27.3% lost ≥5 letters.

When non-responders were analysed by BCVA at baseline (online supplemental table 2), baseline BCVA ≥70 or ≤34 letters were not statistically significant predictors of BCVA outcomes at week 52. However, there was a consistent trend for BCVA improvement among patients with baseline BCVA ≤34 letters, with statistical significance at weeks 16 and 24. Among pseudophakic non-responders, the change in mean BCVA from baseline was statistically significant at week 6 only, with 5.2 letters (p<0.001; online supplemental table 3).

The change in mean CRT from baseline was statistically significant at weeks 6, 16, 24 and 52 (primary endpoint), with reductions of 99.2, 32.7, 62.9 and 60.9 µm, respectively (figure 3A). Similarly, the change in mean CRT from baseline was statistically significant at weeks 6, 16, 24 and 52 in pseudophakic non-responders, with reductions of 102.6, 35.1, 71.4, and 67.1 µm, respectively (online supplemental table 3). The proportion of patients with central foveal threatening lipid deposition was 29.8% (n=42/141), 33.3% (n=47/141), 19.9% (n=28/141) and 23.4% (n=33/141) at weeks 6, 16, 24 and 52, respectively, compared with 36.2% (n=51/141) at baseline.

Effectiveness analyses in non-responders stratified by early and late switch

Of the 143 anti-VEGF non-responders, 53 (37.1%) and 89 (62.2%) were early-switch and late-switch patients, with mean (SD) DME duration of 2.9 (2.7) and 4.0 (3.0) years at baseline, respectively (p=0.001). The timing of the switch was missing for 1 (0.7%) patient. Consistent with findings in non-responders overall, the change in mean BCVA from baseline was not statistically significant at week 52 in either subset (figure 1B,C); statistical significance was observed at weeks 6 and 16 in early-switch patients, with mean changes of 6.1 and 5.8 letters, respectively (p≤0.021; figure 1B), and at week 6 in late-switch patients, with a mean change of 2.9 letters (p=0.022; figure 1C). The early switch–late switch difference in BCVA (letters) was not statistically significant (p≥0.056) at baseline (2.15; 95% CI −4.59 to 8.89), week 6 (3.03; 95% CI −4.84 to 10.91), week 16 (6.80; 95% CI −0.17 to 13.77) and week 24 (4.89; 95% CI −2.97 to 12.75), but was statistically significant at week 52 (9.41; 95% CI 1.85 to 16.96; p=0.015), suggesting that early-switch patients had greater BCVA improvement at week 52 than late-switch patients.

Also similar to observations in non-responders overall, at least 75% and 71% of early-switch and late-switch patients, respectively, reported a BCVA gain or no change from baseline at weeks 6, 16, 24 and 52 (figure 2B,C); 50.0% and 30.6% gained ≥5 letters, 25.0% and 40.3% had unchanged BCVA, and 25.0% and 29.0% lost ≥5 letters, respectively.

The change in mean CRT from baseline was statistically significant at weeks 6, 16, 24 and 52 in both early-switch (p≤0.019) and late-switch (p≤0.030) patients, being −63.5 and −59.8 µm, respectively, at week 52 (figure 3B,C). Among early-switch patients, 28.8% (n=15/52), 34.6% (n=18/52), 19.2% (n=10/52) and 19.2% (n=10/52) had central foveal threatening lipid deposition at weeks 6, 16, 24 and 52, respectively, compared with 38.5% (n=20/52) at baseline. At those visits among late-switch patients, 30.7% (n=27/88), 33.0% (n=29/88), 20.5% (n=18/88) and 26.1% (n=23/88) had central foveal threatening lipid deposition, respectively, compared with 35.2% (n=31/88) at baseline.

Safety analyses in non-responders

Among anti-VEGF non-responders (N=141), 78 (55.3%) experienced ≥1 treatment-emergent AE(s) in the study eye, including 31 (22.0%) with ≥1 treatment-related AE(s). Of those, one serious treatment-related AE (table 1), increased IOP from baseline, was reported.

Increased IOP was the most common treatment-emergent AE and AE of special interest, reported in 27 (19.1%) non-responders (table 1) and leading to

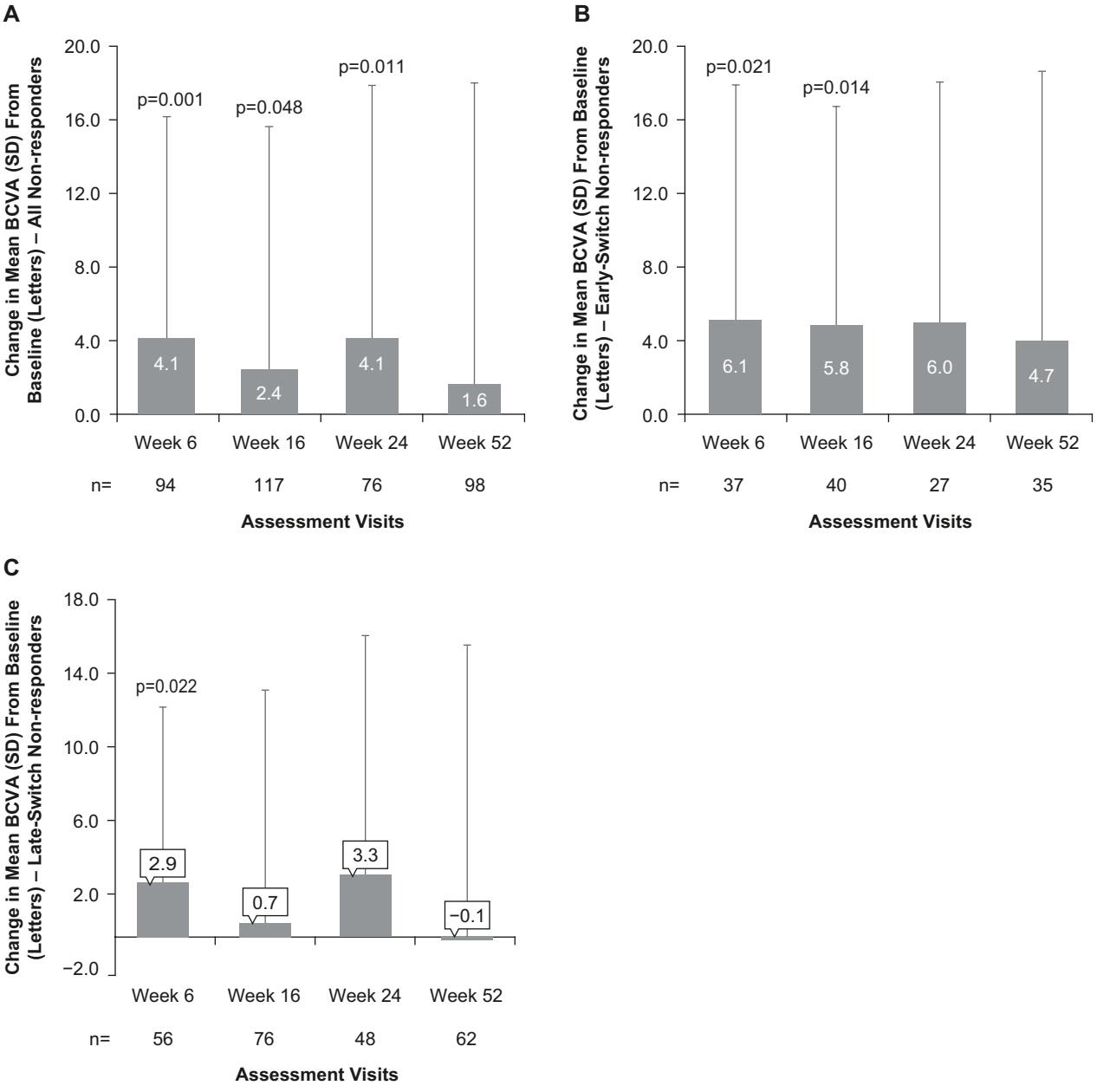

Figure 1 Change in mean BCVA from baseline over time in (A) all non-responders to anti-VEGF agents treated with DEX, (B) non-responders to anti-VEGF agents who switched to DEX treatment after 3–6 anti-VEGF injections (early switch) and (C) non-responders to anti-VEGF agents who switched to DEX treatment after >6 anti-VEGF injections (late switch). BCVA, best corrected visual acuity; DEX, dexamethasone intravitreal implant; VEGF, vascular endothelial growth factor.

one study discontinuation. The mean change in IOP from baseline was ≤1.7 mmHg at each visit. At week 52, 11.5% (n=12/104) of non-responders exhibited IOP ≥21 mmHg, compared with 6.5% (n=9/138) at baseline (table 2). The proportion of non-responders with IOP increases ≥10 mmHg from baseline was ≤7.7% at weeks 6, 16, 24 and 52 (table 2). There was one report of IOP increase ≥25 mmHg at week 24 (table 2), but no reports of IOP increase ≥35 mmHg. Among non-responders with available IOP data at week 52 (n=104), 20 (19.2%) required IOP-lowering medication, compared with 27/138 (19.6%) at baseline (table 2). Of the 20 eyes/patients requiring IOP-lowering medication at week 52, 7 were already being treated with such medication at baseline. No eyes required laser treatment or glaucoma filtration surgery during the 12-month period. The IOP increase ≥25 mmHg, serious treatment-related AE and IOP-related discontinuation were reported in different patients.

In early-switch and late-switch patients with available data at week 52, 7/39 (17.9%) and 12/64 (18.8%) required IOP-lowering medication, compared with 11/51 (21.6%) and 15/86 (17.4%) at baseline, respectively. These findings are consistent with those observed in non-responders overall.

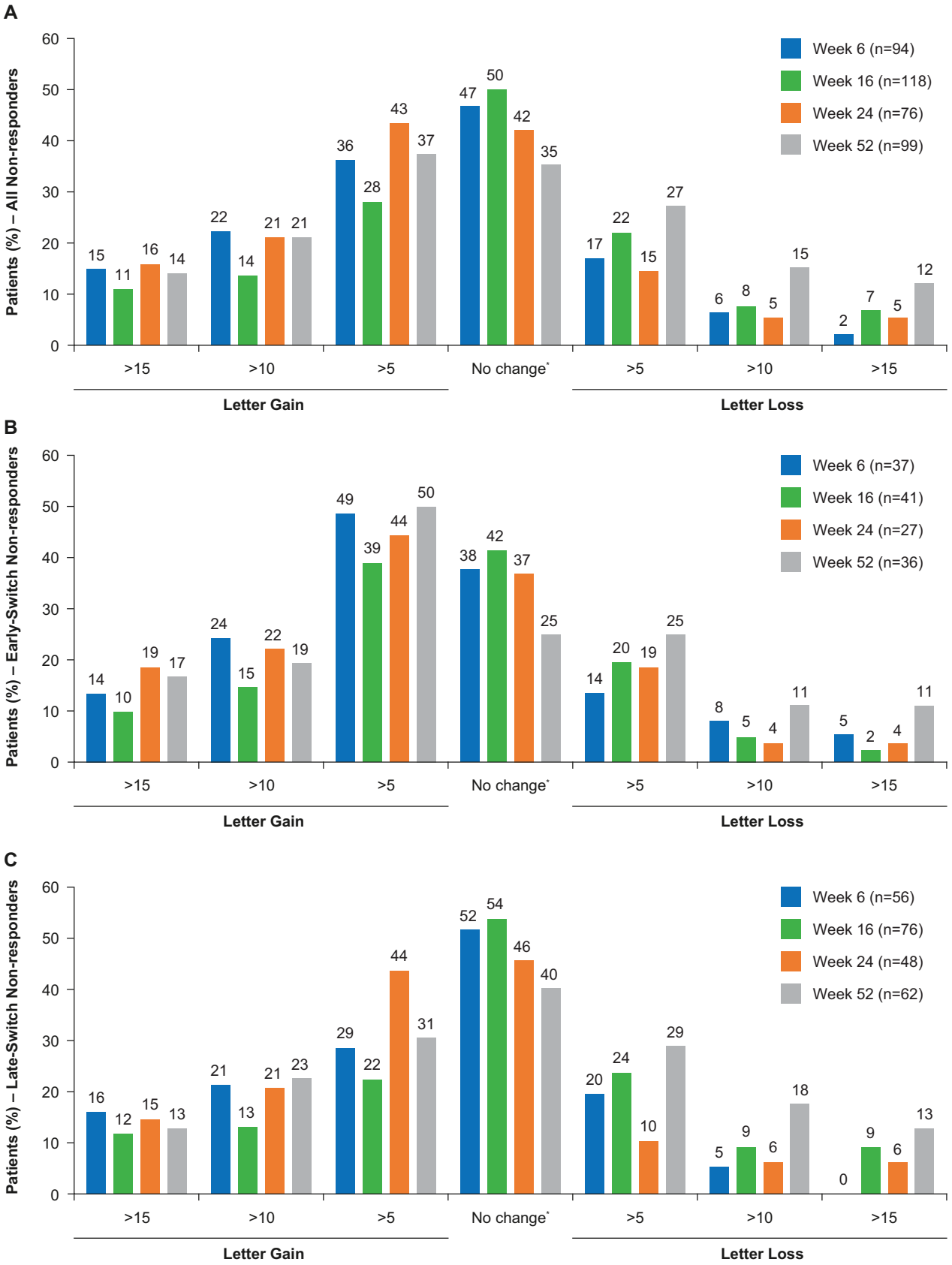

Figure 2 Proportions of non-responders to anti-VEGF agents treated with DEX with a ≥15-letter, ≥10-letter and ≥5-letter gain, no change, or ≥15-letter, ≥10-letter and ≥5-letter loss from baseline at each visit. Data are shown for (A) all non-responders, (B) non-responders to anti-VEGF agents who switched to DEX treatment after 3–6 anti-VEGF injections (early switch) and (C) non-responders to anti-VEGF agents who switched to DEX treatment after >6 anti-VEGF injections (late switch). *No change means a gain or loss of 4 letters or less. DEX, dexamethasone intravitreal implant; VEGF, vascular endothelial growth factor.

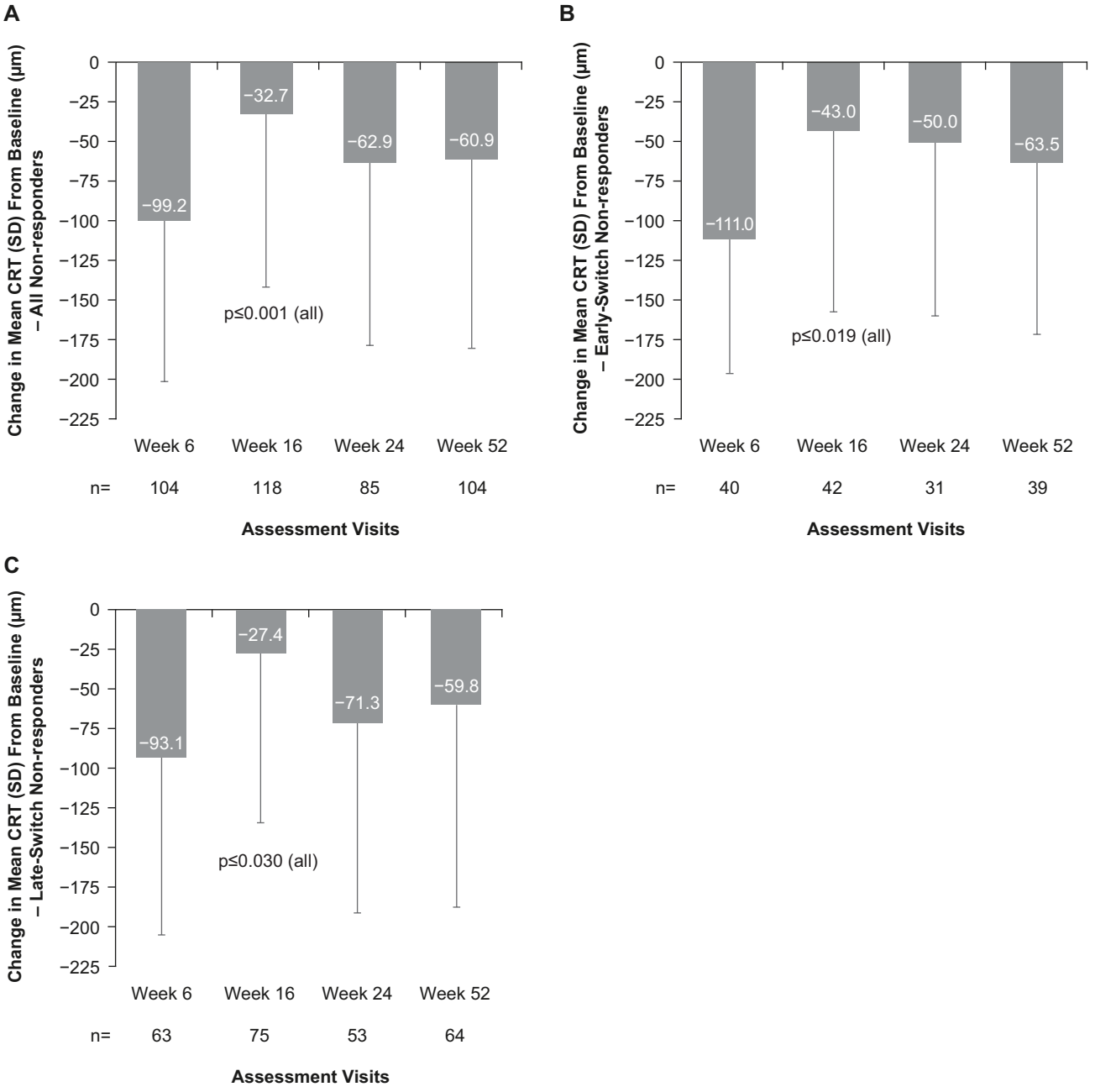

Figure 3 Change in mean CRT from baseline over time in (A) all non-responders to anti-VEGF agents treated with DEX, (B) non-responders to anti-VEGF agents who switched to DEX treatment after 3–6 anti-VEGF injections (early switch) and (C) non-responders to anti-VEGF agents who switched to DEX treatment after >6 anti-VEGF injections (late switch). CRT, central retinal/macular thickness; DEX, dexamethasone intravitreal implant; VEGF, vascular endothelial growth factor.

DISCUSSION

The AUSSIEDEX study prospectively evaluated the effectiveness and safety of DEX monotherapy in DME in clinical settings to refine understanding of DEX as individualised DME treatment. In this anti-VEGF non-responder subgroup, 2.3 DEX injections (mean) over 12 months statistically significantly improved mean CRT from baseline at weeks 6, 16, 24 and 52, with similar results in early-switch and late-switch patients. Notably, DEX's effect on CRT peaked at week 6, consistent with previous reports showing peak CRT reductions 4–8 weeks post-injection.[17–21]

DEX's effect on mean BCVA was not statistically significant at week 52 (primary timepoint) before and after stratification (early vs late switch). The early–late switch difference in BCVA, however, was statistically significant at week 52, suggesting that early-switch patients had greater BCVA improvement at week 52 than late-switch patients. The proportions of early-switch and late-switch patients with central foveal threatening lipid deposition decreased by 50% and 26%, respectively, from baseline to week 52, also suggesting greater treatment benefits following an early switch. Notably, clinical evidence and expert consensus support switching from anti-VEGF

Table 1 Treatment-emergent adverse events reported in >2% of non-responders to anti-VEGF agents treated with DEX

Treatment-emergent adverse events, n (%)	Non-responders (N=141)
Total	78 (55.3)
Treatment-related	31 (22.0)
Serious*	1 (0.7)
Increase in intraocular pressure†	27 (19.1)
Conjunctival haemorrhage	6 (4.3)
Cystoid macular oedema	4 (2.8)
Vitreous haemorrhage	4 (2.8)
Influenza	4 (2.8)
Pneumonia	4 (2.8)
Fall	4 (2.8)
Lower respiratory tract infection	4 (2.8)
Urinary tract infection	4 (2.8)
Eye irritation	3 (2.1)
Cataract	3 (2.1)
Posterior capsule opacification	3 (2.1)
Foot fracture	3 (2.1)

*Increase in intraocular pressure from baseline, which was resolved with medication without sequalae and did not lead to discontinuation from the study.
†Compared with baseline.
DEX, dexamethasone intravitreal implant; VEGF, vascular endothelial growth factor.

therapy to DEX early, after three anti-VEGF injections.[7 9 10 22 23] However, randomised clinical trials and meta-analyses are awaited to guide clinical practice.

Although the CRT-related findings are consistent with observations in the randomised, masked, controlled, multicentre, phase 3 studies (MEAD) of DEX in DME,[6] the BCVA-related findings appear conflicting, possibly due to differences in eligibility criteria. Indeed, there were no baseline BCVA or CRT restrictions in this study, whereas MEAD required patients to have a BCVA of 20/50 to 20/200 Snellen equivalent and CRT ≥300 µm at baseline.[6] Other notable differences between the MEAD study population and this AUSSIEDEX non-responder subgroup included baseline characteristics such as mean age (~62.4 years[6] and 66.7 years), lens status (~25%[6] and 73.0% were pseudophakic) and prior exposure to anti-VEGF agents (≤11.2%[6] and 100%), respectively. Whether these factors or others (eg, retreatment criteria) can explain the apparent discrepancy in functional outcomes between the studies is unclear at this time, but other (differently designed) studies have reported CRT reductions without visual improvement.[24 25]

In a prospective, interventional case series of 13 consecutively enrolled patients (18 eyes) with DME refractory to panretinal photocoagulation, focal/grid laser treatment and anti-VEGF agents, 2.2 DEX injections (mean) over 12 months produced statistically significant improvements in BCVA and CRT from baseline at week 52.[26] Whether the younger age (mean 60.5 years), requirement for baseline CRT to be ≥300 µm, or other factors might have contributed to the positive functional outcome in that study[26] is unknown, but it is worth noting the similarity in mean age and CRT requirements between MEAD[6] and the above case series,[26] compared with this analysis. In another interventional case series that included seven treatment-naïve patients/eyes and seven non-responders to laser (n=3), anti-VEGF (n=2) or both (n=2) with a mean age of 61 years and a required baseline CRT >300 µm, both BCVA and CRT statistically significantly improved from baseline at week 52, with 1.7 DEX injections (mean). In a prospective study of 113 eyes (84 patients), including 11 (9.7%) anti-VEGF-refractory eyes, statistically significant improvements in BCVA and CRT were observed at 1 and 3 months but not months 5, 9 and 12, which could be due to the older age (mean 69 years) and/or lower number of DEX injections (mean 1.44).[27] Considering evidence supporting age as a negative predictor of final visual outcome in anti-VEGF non-responders,[28] further research is needed to determine whether DEX treatment at a younger age might increase the odds of

Table 2 Mean IOP and related variables at each visit in non-responders to anti-VEGF treatment treated with DEX (N=141)

Visits	Mean (SD) IOP, mmHg	IOP ≥21 mmHg, n (%)	IOP increase ≥10 mmHg, n (%)	IOP increase ≥25 mmHg, n (%)	Patients who required 1 / 2 / 3 IOP-lowering medications, n (%)
Baseline	14.8 (3.7)	9 (6.5)	0 (0)	0 (0)	13 (9.4) / 6 (4.3) / 8 (5.8)
N	138	138	138	138	138
Week 6	16.3 (4.7)	19 (17.1)	6 (5.4)	0 (0)	9 (8.1) / 6 (5.4) / 7 (6.3)
N	111	111	111	110	111
Week 16	15.3 (4.6)	13 (10.9)	2 (1.7)	0 (0)	13 (10.9) / 5 (4.2) / 8 (6.7)
N	119	119	119	118	119
Week 24	16.5 (5.7)	10 (11.5)	5 (5.7)	1 (1.1)	10 (11.5) / 4 (4.6) / 6 (6.9)
N	87	87	87	87	87
Week 52	16.3 (4.5)	12 (11.5)	8 (7.7)	0 (0)	12 (11.5) / 3 (2.9) / 5 (4.8)
N	104	104	104	104	104

DEX, dexamethasone intravitreal implant; IOP, intraocular pressure; VEGF, vascular endothelial growth factor.

improving both BCVA and CRT outcomes at 1 year. Since there is no consensus definition of treatment-resistance in DME,[29] differences in definition among studies could also contribute to the apparent variability in outcomes.

When analysis excluded patients with baseline BCVA ≥70 letters, which is more in line with analyses performed in MEAD,[6] the mean BCVA gains from baseline were numerically larger at all visits in non-responders overall (≥2.1 letters), early-switch patients (≥3.2 letters) and late-switch patients (≥1.6 letters), suggesting that patients with worse vision at baseline are more likely to show an improvement in vision. In a retrospective study of 32 eyes (31 patients) that received ≥1 DEX injection(s), including 21.9% treatment-naïve and 78.1% anti-VEGF non-responders, associations between baseline characteristics and outcomes were also investigated.[30] In multivariate analyses, baseline BCVA was the only prognostic indicator of BCVA at 6 months, with an OR of 0.73 (p=0.01); with each positive increment of 0.1 logMAR at baseline, a patient was more likely to achieve vision gain at month 6.[30] There was no evaluation at 12 months, however, warranting further research.

At week 52 in this study, BCVA was either improved from baseline or maintained at baseline levels in 72% of patients, with similar results in early-switch (75%) and late-switch (71%) patients, supporting DEX effectiveness as monotherapy for anti-VEGF-refractory DME. Additionally, early-switch patients had better BCVA (on average) than late-switch patients at 52 weeks, suggesting that earlier treatment of DME with DEX is one factor that could have improved functional outcomes. Further investigation in non-responders with a more homogeneous baseline BCVA (as in MEAD[6]) might thus prove informative. It is also worth noting that no patients required laser rescue for DME in this study, whereas 37%, 56% and 46% of patients required it following treatment with aflibercept, bevacizumab and ranibizumab in the Protocol T study.[31]

A potential limitation of the AUSSIEDEX study was that only the week-16 and week-52 follow-up visits were mandatory (reflecting real-world settings) and that use of laser photocoagulation and the frequency of injections were based on clinical judgement, which likely introduced clinical response heterogeneity and could have biased the outcomes. The more favourable outcomes at week 6 (maximum time of DEX effectiveness) and less favourable outcomes at week 16 (diminution of DEX effectiveness) suggest that a more regimented trial design could have demonstrated greater effects. Similarly, inclusion of phakic eyes (38/141 in the non-responders subgroup) scheduled for cataract surgery without a set deadline for procedure completion may have increased population heterogeneity, leading to underestimating the BCVA change from baseline.[28] However, an analysis of the BCVA change from baseline in pseudophakic non-responders found no statistically significant change from baseline at week 52, arguing against it. Additionally, the absence of minimal BCVA and CRT requirements at baseline could have introduced a 'ceiling effect' and led to smaller and/or less consistent effects of DEX on BCVA and CRT over time. However, our study was designed to include a broad population, as typically encountered in ophthalmology clinics, compared with clinical trials. It is also possible that early-switch patients achieved better BCVA than late-switch patients because they had DME for a shorter time and/or their vision had not yet plateaued by the time treatment with anti-VEGF agents was stopped. These findings should thus be interpreted with caution, especially as the early- vs late-switch subgroups were not compared in a randomised study in which—for example—patients who do not respond to the initial loading doses (3) of anti-VEGF would be randomised to early switch or late switch (based on predetermined numbers of anti-VEGF injections) before non-responders are identified and switched to treatment with DEX. Finally, although the study completion rate was not ideal (79.0%), it is worth noting that the number of patients who completed the current study (n=113) is higher than that included in various retrospective studies reporting real-world evidence on the effects of early vs late switch (n≤69 patients).[7 9 10 32] Additionally, it is higher than that previously published for the treatment-naïve subgroup (72%) of the prospective AUSSIEDEX study.[13]

In this subgroup analysis, DEX monotherapy was shown to effectively improve CRT from baseline at weeks 6, 16, 24 and 52 in patients with anti-VEGF-refractory DME, whether they switched to DEX early, after 3–6 anti-VEGF injections, or late, after >6 anti-VEGF injections. There were no unexpected treatment-related AEs during the study, and no reports of endophthalmitis (despite a previous report of increased risk).[33] The incidence of treatment-related AEs (22.02%) was also much lower than that reported in a previous study of DEX (65.7%) vs ranibizumab (22.5%)[18]; the investigators' experience with DEX at the time of study start (March 2012[18] vs April 2016 [this study]), number of centres involved (60[18] vs 25 [this study]), differences in patient baseline characteristics, and/or other factors may have influenced this observation. Increased IOP, the most frequent treatment-emergent AE, was manageable with IOP-lowering medications. No glaucoma-related laser treatments or glaucoma filtration surgeries were required, and only one AE-related discontinuation was reported. Our findings thus indicate that DEX is an effective treatment option for patients with anti-VEGF-refractory DME, regardless of the timing of the switch from anti-VEGF agents to DEX. Randomised studies in which patients would be switched from anti-VEGF therapy to DEX early vs later (based on BCVA and CRT, as in the current study, and/or additional parameters such as hyperreflective retinal foci and neurosensory detachment, recently discussed by Sorour *et al*[34]) are warranted to verify these findings in controlled settings.

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Acknowledgements We acknowledge the following institutions (researchers) for their participation in the study: Adelaide Eye & Retina Centre (Jagjit Gilhotra), Essendon Retina (Elvis Ojaimi), Hobart Eye Surgeons (Nitin Verma), Lions Eye Institute (Ian McAllister), Marsden Eye Research (Jennifer Arnold), Mona Vale Eye Doctors (Paul Beaumont), Moreton Eye Group (Graham Hay-Smith, Gurmit Uppal [formerly at Caboolture Eye Surgery]), Nepean Valley Eye Specialists (Gayatri Banerjee), Queensland Eye Institute (Tony Kwan), Retina & Vitreous Centre (Hyong Kwon Kang), Retina & Vitreous Centre Strathfield (Mark Gorbatov), Retina and Macula Specialists (Adrian Fung, Rajeev Chalasani), Retina Associates - South West Retina (Tim Nolan), Retina Specialists Victoria (Sanj Wickremasinghe), Royal Adelaide Hospital (Grant Raymond), Strathfield Retina Clinic (James Wong), Sydney Hospital and Sydney Eye Hospital (Samantha Fraser-Bell), Sydney Retina Clinic & Day Surgery (Andrew Chang), Sydney West Retina (Paul Mitchell), Tasmanian Eye Institute (Brendon Vote), Terrace Eye Centre (Mark Donaldson), Victoria Parade Eye Consultants (Mark Daniell), and Vision Eye Institute (Nandor Jaross).The authors would like to thank all the patients who participated in this study, as well as Hongxin Lai (AbbVie Inc.) for providing additional support with statistics. Writing and editorial assistance was provided to the authors by Michele Jacob, PhD, CMPP, of Evidence Scientific Solutions, Inc (Philadelphia, PA), and funded by AbbVie Inc. All authors met ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

Contributors Study concept and design: SS, SF-B, PM, JA and JT. Data analysis and/or interpretation: SF-B, HKK, PM, JA, AAC, JT and SS. Drafting of the manuscript: SF-B, HKK, PM, JA, AAC, JT and SS. Review and editing of the manuscript: SF-B, HKK, PM, JA, AAC, JT and SS. All authors gave final approval of the version to be published and agreement to be accountable for all aspects of the work. The guarantor, PM, accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and approved the decision to publish.

Funding The study was sponsored by Allergan (prior to its acquisition by AbbVie).

Disclaimer The sponsor participated in the study design, data management, analysis and interpretation, and preparation, review, and approval of the manuscript.

Competing interests Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. PM, MD, PhD: Advisory board member for and honoraria from Allergan (an AbbVie company), Bayer, and Novartis. JA, MD: Advisory board member for and honoraria from Alcon, Allergan (an AbbVie company), Apellis, Bayer, Novartis, and Roche. SF-B, MD, PhD: Consultant for Allergan (an AbbVie company), Bayer, Novartis, and Roche. HKK, MD: Scientific advisory member for Allergan (an AbbVie company). AAC, MD, PhD: Advisor for Alcon, Allergan (an AbbVie company), Apellis, Bayer, Novartis, and Roche. JT, RN: Employee of Allergan (an AbbVie company) at the time the study was conducted, and current employee of Pfizer. SS, BS, RN: Employee of Allergan (an AbbVie company) at the time the study was conducted.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study protocol was approved by the Central Adelaide Local Health Network (CALHN) Royal Adelaide Hospital, Human Research Ethics Committee (CALHN reference number, R20160701; HREC reference number, HREC/16/RAH/250) and a centralised independent institutional review board, Bellberry (application/approval number, 2016-02-140). All patients provided written informed consent before taking part in the study and initiating treatment.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

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