# Risk factors for MEK-associated retinopathy in patients with advanced melanoma treated with combination BRAF and MEK inhibitor therapy

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***Abstract***

**Background:** Retinopathy is a common adverse event with mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors. Little is known about the pathophysiology of MEK inhibitor-associated retinopathy (MEKAR). Since MEKAR has many similarities to central serous chorioretinopathy (CSCR), they may share common risk factors. The aim of this study was to evaluate the association between baseline characteristics and MEKAR in melanoma patients initiating MEK inhibitor treatment.

**Methods:** Data from patients treated with cobimetinib and vemurafenib for advanced melanoma in the coBRIM trial were subjected to secondary analysis. Consistent with CSCR risk factors, assessed baseline characteristics included: age, gender, past ocular disease, weight, hypertension, diabetes, dyslipidemia, glomerular filtration rate (eGFR) and corticosteroid use. Associations between characteristics and retinopathy events (any grade and symptomatic) were evaluated using univariate logistic regression and represented as odds ratios (OR).

**Results:** A total of 247 patients were treated with cobimetinib and vemurafenib, of whom 72 (29%) had retinopathy of any grade and 33 (13%) had symptomatic retinopathy. Patients with a history of ocular disease were at significantly higher risk of retinopathy (any grade, 44%; symptomatic, 22%) than those with no ocular disease history (any grade, 22%; symptomatic, 10%). Individuals with a history of ocular inflammation or infection were at highest risk: 4 of 5 developed symptomatic retinopathy during MEK inhibitor therapy. Increased age was associated with a higher risk of any grade retinopathy {decade increase OR [95% confidence interval (CI)] = 1.03 (1.01–1.05); $p = 0.009$}, while increasing eGFR was significantly associated with a decreased risk of any grade retinopathy [0.98 (0.96–0.99); $p = 0.004$]; the associations were not statistically significant with symptomatic retinopathy. Other assessed CSCR risk factors were not significantly associated with MEKAR.

**Conclusion:** Age, glomerular filtration rate and history of ocular disease (particularly inflammatory eye disease) were associated with a risk of MEK inhibitor induced retinopathy. Patients who are at increased risk of MEKAR may benefit from more regular ophthalmologic assessment during treatment.

***Keywords:*** baseline, characteristics, chorioretinopathy, cobimetinib, inhibitor, melanoma, MEK, MEKAR, retinopathy, vemurafenib

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## Introduction

New therapeutic agents have revolutionised the treatment of melanoma with mutations in the *BRAF* gene, which codes the protein kinase, B-Raf. The BRAF pathway inhibitors (i.e. vemurafenib, dabrafenib and encorafenib) have achieved significant improvement in the progression-free and overall survival of patients with melanoma, particularly amongst patients with metastatic disease and the BRAF V600 tumour gene mutation.[1] The use of BRAF inhibitors as monotherapy is limited by acquired resistance, occurring in approximately half of patients within 6 months of treatment, and likely due to mitogen-activated protein kinase (MAPK) pathway activation *via* mitogen-activated extracellular signal-regulated kinase (MEK).[2]

The MAPK signalling pathway plays a critical role in the regulation of cellular activities, which includes those that promote tumorigenesis, such as proliferation, survival, differentiation and motility. A dysregulation in the MAPK pathway occurs in roughly 30% of all malignancies. The MEK pathway is one component of the MAPK pathway, with inhibition of MEK targeting the signalling pathways of MAPK and thus inhibiting cell proliferation and promoting apoptosis.[3] The MAPK pathway also plays an important role in maintenance, protection, and repair of the retinal pigment epithelium (RPE).[4]

The combination therapy of a BRAF inhibitor and a MEK inhibitor decreases acquired resistance to BRAF inhibitors, while also improving progression-free and overall survival.[5] However, along with the benefits of the combination therapy, a new profile of adverse events has become apparent. A commonly reported adverse event associated with MEK inhibitor use has been retinopathy, and specifically, the accumulation of fluid between the neural retina and RPE, which is termed serous retinopathy.[6] Serous retinopathy occurs in 26% of individuals on combination treatment, and resolves in approximately 52% of individuals.[7] It usually resolves within 5 weeks of commencing treatment, only sometimes requiring reduction in dose and or drug withdrawal, and typically has no sequelae.[8] Retinopathy is considered a class effect of MEK inhibitors, with unique clinical and morphologic characteristics distinct from central serous chorioretinopathy (CSCR).[9] The pathophysiologic mechanisms underlying MEK-associated retinopathy (MEKAR) are not well understood,[10] and at present only sparse data are available on adverse retinal effects from long-term MEK inhibition.[11]

MEKAR shares a similar pathology with CSCR, with similar signs and symptoms. The drug-induced condition is characterised by detachment of the neurosensory retina, which is caused by accumulation of serous fluid between the photoreceptor outer segments and the RPE, in combination with unifocal or multifocal changes in the RPE.[12] The detachment should not be attributable to retinal tears or holes, neovascularization, inflammation, neoplasia or specific hereditary diseases. Optical coherence tomography shows that MEKAR is distinct from CSCR, but the specific pathophysiological cause of the fluid accumulation in MEKAR is not well understood. Retinal vein occlusion is a known risk factor and complication of MEKAR.[13] One leading theory for the mechanism of MEKAR suggests MEK-pathway inhibition leads to disruption of aquaporin channels in membranes of the RPE, leading to fluid accumulation.[14]

Risk factors for developing CSCR include: hypertension, vascular disease, increased sympathetic nervous system activation,[15] use of corticosteroid and/or Cushing's syndrome, type A personality, gastro-oesophageal reflux disease, and use of phosphodiesterase-5 inhibitors such as sildenafil.[16] Our study aimed to identify the risk factors for retinopathy in advanced melanoma patients treated with both BRAF and MEK pathway inhibitors (i.e. vemurafenib plus cobimetinib) in the coBRIM clinical trial.

## Methods

### *Study design and patients*

This study was a secondary analysis of adults with advanced melanoma positive for the BRAF V600 mutation who participated in the coBRIM clinical trial.[17,18] The coBRIM trial was a phase III randomised controlled trial comparing the first line use of vemurafinib monotherapy with vemurafenib and cobimetinib. Vemurafenib was dosed at 960 mg orally twice daily for days 1–28, and cobimetinib was dosed at 60 mg orally four times daily for days 1–21, during each 28-day treatment cycle. De-identified participant-level data for the coBRIM trial was analysed in a secure environment managed by clinicalstudydatarequest.com, and all participants from the coBRIM trial combination therapy with vemurafinib plus cobimetinib were included in the analysis. This secondary analysis of the trial data was approved by the Southern Adelaide

Clinical Human Research Ethics Committee (SAC HREC EC00188).

The coBRIM trial inclusion criteria required adults with a life expectancy of greater than 3 months from the expected time of treatment commencement and adequate organ function at baseline. Relevant exclusion criteria included any history of prior BRAF or MEK pathway inhibitor treatment, other malignancies that were not in remission, and history or ophthalmoscopic evidence of retinal disease that was considered a risk factor for neurosensory retinal detachment, central serous retinopathy, retinal vein occlusion or neovascular macular degeneration. Exclusions also included risk factors for retinal vein occlusion, such as poorly controlled glaucoma with intraocular pressure above 20 mmHg, elevated serum cholesterol, hypertriglyceridemia and fasting hyperglycemia above grade 1.

### *Adverse events*

In the coBRIM trials, patients were monitored for adverse events every 2 weeks during the first two cycles of treatment, and then prior to each cycle, as deemed medically necessary, for the remainder of the study. Adverse events were coded in the coBRIM trial using MedDRA, and adverse event toxicity data were presented using the NCI CTCAE grading (v4.0).[17,18] Patients who experienced the same adverse event on more than one occasion were counted once and scored as the highest NCI CTCAE grade.

Patients with serous retinopathy were identified using the umbrella term 'retinopathy', which comprises a group of preferred terms from the medical Dictionary for Regulatory Activities (MedDRA).[7] The high-level terms grouped together as retinopathy include chorioretinopathy, retinal detachment, detachment of retinal pigment epithelium, macular oedema, macular fibrosis, retinal disorder, retinopathy, detachment of macular retinal pigment epithelium, subretinal fluid, cystoid macular oedema and macular detachment.

Retinopathy adverse events were graded based on visual acuity measurements and impact on activities of daily living, with grade 1 being asymptomatic and only visible *via* slit lamp examination and/or optical coherence tomography (OCT). Grades 2–4 indicated deterioration of the visual acuity and/or impact to the patient's ability to carry out their activities of daily living, with changes appreciable on slit lamp examination and or optical coherence tomography. This present study distinguishes between grade 1 asymptomatic retinopathy events and symptomatic retinopathy events of grade 2 and higher (considered to be severe) by evaluating the maximum grade of retinopathy event experienced by a patient during the study and forming two distinct groups based on that adverse event grade. Retinopathy events occurring while on vemurafenib and cobimetinib therapy were considered MEKAR events in this study.

### *Ophthalmologic assessment*

In the coBRIM trial, ophthalmologic examinations were performed at screening, on day 1 of cycle 2, and on day 1 of cycles 5, 8, 11, 15, 19, 23, 29, 35, 41 and 47. The ophthalmologic examinations were performed by a qualified ophthalmologist according to a defined study protocol,[17,18] which described briefly included visual acuity testing, intraocular pressure measurement *via* tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral- (or when unavailable, time-domain-) OCT.

For ocular adverse events, the coBRIM study protocol outlined that the combination medication should be interrupted, pending complete ophthalmologic examination, which guided dosing, including continuation of the current dose, dose adjustment, or permanent discontinuation of the medications. Visual symptoms of grade $\geqslant 2$ prompted a complete ophthalmological examination and interruption of the combination medication until resolution to grade $\leqslant 1$, with dose reduction if the grade $\geqslant 2$ visual symptoms reoccurred. Treatment was permanently discontinued in cases of retinal vein occlusion, lack of resolution of visual symptoms to grade $\leqslant 1$ within 28 days, or reoccurrence of grade $\geqslant 2$ visual symptoms despite dose reduction.

### *Baseline characteristics*

CSCR risk factors guided the potential predictor variables analysed in this study. Baseline characteristics evaluated included age, sex, body mass index (BMI), estimated glomerular filtration rate [eGFR; determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR formula], and medical histories documenting concomitant hyperlipidaemia (additionally considered individuals with lipid levels grossly

**Table 1.** Summary of demographics of patients enrolled in the coBRIM trial.

| | *n* (%)/median (IQR) |
|---|---|
| Treatment | |
| Vemurafenib monotherapy | 246 (50%) |
| Vemurafenib + Cobimetinib | 247 (50%) |
| BRAF V600 gene mutation | |
| V600E | 170 (69%) |
| V600K | 25 (10%) |
| Missing | 52 (21%) |
| Disease stage | |
| IIIc unresectable | 21 (9%) |
| M1a | 40 (16%) |
| M1b | 40 (16%) |
| M1c | 146 (59%) |
| Missing | 0 |
| Age (years) | 56 (45–65) |
| Sex | |
| Male | 146 (59%) |
| Female | 101 (41%) |
| Race | |
| White | 227 (92%) |
| Other | 4 (2%) |
| Missing | 16 (6%) |
| Weight (kg) | 81 (69–95) |
| Missing | 1 (1%) |
| BMI | 27 (24–31) |
| Missing | 6 (2%) |
| eGFR | 89 (76–104) |
| Missing | 1 (1%) |

BMI, body mass index (kg/m$^2$); eGFR, estimated glomerular filtration rate (ml/min/1.73 m$^2$); IQR, interquartile range (the first quartile to the third quartile).

outside of the reference range), diabetes mellitus, hypertension, and ocular disease. Concomitant corticosteroid use was also assessed.[16] Baseline values refer to values taken pre-treatment (i.e. prior to initiation of vemurafenib plus cobimetinib therapy).

Past medical history of ocular disease was stratified into categories based on anatomical regions and pathological causes. The distinct groups of eye disease evaluated included any eye disease overall, posterior segment eye disease, ocular vascular disease, ocular inflammation, and vision disorders. Posterior segment eye disease included disorders of the vitreous, retinal and macula. Inflammatory disease of the eye included periorbital, ocular and conjunctival infection.

### *Statistical analysis*

Univariate logistic regression was used to model the association between baseline characteristics and occurrence of retinopathy events; including by any grade and by only severe (grade $\geqslant$2). All the statistical analyses were performed using R (version 3.4).

## Results

### *Patient population*

The coBRIM clinical trial included a total of 493 patients, of whom 247 were treated with vemurafenib plus cobimetinib. A summary of patient demographic data is shown in Table 1.

### *Retinopathy adverse events*

Of the 247 study participants, 72 (29%) experienced retinopathy; of these, 39 experienced a maximum of grade 1 (asymptomatic) retinopathy, and 33 reported symptoms of grade $\geqslant$2 (symptomatic) retinopathy. There were 101 distinct retinopathy adverse events experienced across the 72 patients, with 49 of these patients having only one event, 21 having 2–3 events, and 2 having 4 or more events.

### *Dose adjustment and adverse event resolution*

Seven patients withdrew from the vemurafenib plus cobimetinib arm of coBRIM due to retinopathy adverse events. A total of 30 patients had temporary dose reductions and or dose interruptions, and 5 of these patients did not recover from the retinopathy event by the conclusion of data collection. Retinopathy of any grade had a median time to first onset of 1 month in the combination therapy arm (versus 4 months in the vemurafenib

plus placebo arm). Median time to resolution for the first retinopathy event was 3 months in the combination treatment arm.

Of the 5 the patients who still had active retinopathy at data censoring, the median follow up was 16 months after the initial retinopathy onset. Further, one of these patients was documented as still having ongoing macula detachment. This provides important information that not all cases of retinopathy resolve quickly, and that the condition can worsen.

### *Association between putative predictors and retinopathy adverse events*

The associations between baseline characteristics and retinopathy are summarised in Tables 2 and 3. Increasing age was significantly associated with the occurrence of any grade retinopathy {OR [95% confidence interval (CI)] for a decade increase = 1.03 (1.01–1.05); $p = 0.009$]. However, no significant association between age and symptomatic retinopathy was observed. eGFR was a significant predictor of retinopathy of any grade [OR (95% CI) = 0.98 (0.96–0.99); $p = 0.004$], but no association with symptomatic retinopathy was observed. Sex, diabetes mellitus, hypertension, cholesterol and other lipid disorders and blood glucose level at entry to the clinical trial and use of corticosteroid were not significantly associated with the occurrence of retinopathy.

Presence of any eye disorder at baseline was significantly associated with any grade retinopathy [OR (95% CI) = 2.82 (1.59–5); $p < 0.001$], and symptomatic retinopathy [OR (95% CI) = 2.6 (1.24–5.48); $p = 0.012$]. A history of inflammation, infection or irritation of the eye was significantly associated with the occurrence of symptomatic retinopathy [OR (95% CI) = 29.4 (3.17–272); $p = 0.003$]. Of the patients with a history of inflammation, infection or irritation of the eye, 80% experienced symptomatic retinopathy, as compared with 28% of those who did not have a history.

## Discussion

Our study highlights several patient characteristics that are significantly associated with the occurrence of the maximum grade of retinopathy experienced by patients treated for advanced melanoma with combined BRAF and MEK inhibitor therapy.

The results of this study confirmed age as a significant risk factor for MEKAR, along with decreased eGFR, prior ocular disease and inflammatory disorders of the anterior eye being predictive of MEKAR. While our study found no significant correlation between sex and MEKAR, the data showed a trend towards females experiencing more severe grades of retinopathy, which is not consistent with the sex risk factor for CSCR of being male.[16] Hypertension, systemic vascular disease, and corticosteroid use were not identified as significant risk factors for MEKAR, likely due to the underlying differences in disease pathophysiology as well as the exclusion criteria of the primary study.

Decreased eGFR was determined using the CKD-EPI formula to estimate GFR, which has been shown to be a more accurate predictor of CKD and its use in risk prediction compared with the classic formula MDRD.[19] While there was a significant correlation between lower eGFR and incidence of retinopathy, the exclusion criteria of the coBRIM trial limited true evaluation of kidney insufficiency as a baseline risk factor. The correlation between eGFR and retinopathy may either be due to small changes in drug clearance leading to slightly higher accumulation of the MEK inhibitor, or be indicative of older age and/or other risk factors for retinopathy.

Past studies have highlighted key differences in the pattern of subretinal fluid leakage between MEKAR and CSCR, relating to microvascular involvement and changes in RPE barrier function.[9] These differences have been further reinforced given the differing baseline risk factors between MEKAR and CSCR demonstrated by our study. The accumulation of the drug at major vessels within the retina is thought to be responsible for the unique characteristic of MEKAR, causing bilateral macular foci of fluid without gravitational dependency, located between the RPE and interdigitation zone of the neural retina.[9]

Although this analysis comprises a large cohort of patients treated with combined BRAF and MEK inhibitor therapy with detailed information on ocular conditions and retinopathy outcomes, the evaluation of some baseline characteristics was limited by sample size. As larger cohorts of data emerge, baseline characteristics that have low prevalence may be evaluated, for example the presence of vascular and

**Table 2.** Summary of univariate associations of baseline characteristics predicting asymptomatic retinopathy (grade 1) in patients treated with the combination of vemurafenib and cobimetinib.

| | Events/patients (%) | OR | 95% CI | *p*-value |
|---|---|---|---|---|
| Age (decades) | | 1.32 | 1.07–1.62 | 0.009 |
| Age (years) | | | | 0.015 |
| (23, 50) | 16/88 (18%) | 1.00 | | |
| (50, 65) | 33/95 (35%) | 2.40 | 1.21–4.76 | |
| (65, 88) | 23/64 (36%) | 2.52 | 1.20–5.31 | |
| Sex | | | | 0.900 |
| Male | 43/146 (29%) | 1.00 | | |
| Female | 29/101 (29%) | 0.96 | 0.55–1.69 | |
| BMI | | 1.00 | 0.96–1.05 | 0.872 |
| eGFR (continuous variable) | | 0.98 | 0.96–0.99 | 0.004 |
| eGFR | | | | 0.005 |
| (90, 155) | 8/19 (42%) | 1.00 | | |
| (75, 90) | 10/37 (27%) | 0.51 | 0.16–1.63 | |
| (60, 75) | 31/73 (42%) | 1.01 | 0.37–2.82 | |
| (40.1, 60) | 23/117 (20%) | 0.34 | 0.12–0.93 | |
| Diabetes | | | | |
| No | 57/205 (28%) | | | |
| Yes | 10/33 (30%) | 1.13 | 0.51–2.52 | 0.767 |
| Hypertension | | | | |
| No | 42/159 (26%) | | | |
| Yes | 30/88 (34%) | 1.44 | 0.82–2.53 | 0.205 |
| Lipid disorder | | | | |
| No | 63/213 (30%) | | | |
| Yes | 9/34 (26%) | 0.86 | 0.38–1.94 | 0.711 |
| Any eye disorder | | | | |
| No | 37/168 (22%) | | | |
| Yes | 35/79 (44%) | 2.82 | 1.59–5.00 | <0.001 |
| Posterior segment eye disease | | | | |
| No | 57/211 (27%) | | | |
| Yes | 15/36 (42%) | 1.93 | 0.93–4.00 | 0.077 |

*(Continued)*

**Table 2.** (Continued)

| | Events/patients (%) | OR | 95% CI | *p*-value |
|---|---|---|---|---|
| Retinopathy | | | | |
| No | 67/235 (29%) | | | |
| Yes | 5/12 (42%) | 1.79 | 0.55–5.84 | 0.334 |
| Ocular vascular disease | | | | |
| No | 67/236 (28%) | | | |
| Yes | 5/11 (45%) | 2.10 | 0.62–7.12 | 0.233 |
| Ocular inflammation | | | | |
| No | 68/242 (28%) | | | |
| Yes | 4/5 (80%) | 10.2 | 1.12–93.2 | 0.039 |
| Vision disorders | | | | |
| No | 64/225 (28%) | | | |
| Yes | 8/22 (36%) | 1.44 | 0.58–3.59 | 0.437 |
| Steroid Use | | | | |
| No | 25/90 (28%) | | | |
| Yes | 47/157 (30%) | 1.11 | 0.63–1.97 | 0.719 |

BMI, body mass index (kg/m$^2$); CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73 m$^2$); OR, odds ratio.

other systemic diseases at baseline which are known risk factors for CSCR.

It is recommended that patients on a MEK inhibitor have baseline ophthalmologic review by an ophthalmologist, including OCT and dilated posterior eye examination to assess the retina and identify any subretinal fluid, and that risk factors predisposing to retinopathy are identified before starting a MEK inhibitor. The type of ophthalmic assessment is clearly important and, in addition to OCT, a volume scan may reveal more subtle pathology that is not detected by straight line or low image raster scans. Current guidelines suggest interrupting therapy for cases of symptomatic retinopathy until visual symptoms resolve, and to resume therapy at a reduced dose only if symptoms improve within 4 weeks. For recurrence of symptomatic retinopathy or incidence of retinal vein occlusion, cobimetinib should be discontinued permanently.[20] The purpose of our study was to define the baseline characteristics that were risk factors for developing retinopathy events, in order to highlight patients who were relatively more likely to suffer from this complication. These patients might benefit from more frequent ophthalmologic assessment to monitor severity and progression, and to guide dose changes if necessary. Patients should have further ophthalmologic evaluations during the first cycle of treatment and at the start of every alternate cycle. If baseline and inter-cycle monitoring is not feasible, patients on MEK inhibitors who present with visual symptoms should be clinically assessed for retinopathy.

## Conclusion

This study highlights that increased age, decreased eGFR, overall eye disease, posterior segment eye disease and ocular inflammatory conditions are associated with MEKAR. In comparison to CSCR risk factors, MEKAR was not significantly associated with being male, overweight or the use of corticosteroid. Given the potential consequences of progressing to severe MEKAR, this study provides important information on patient subgroups who may benefit from more frequent

**Table 3.** Summary of univariate associations of baseline characteristics predicting symptomatic retinopathy (grade ⩾2) in patients treated with the combination of vemurafenib and cobimetinib.

| | Events/patients (%) | OR | 95% CI | *p*-value |
|---|---|---|---|---|
| Age (decades) | | 1.19 | 0.91–1.55 | 0.215 |
| Age (years) | | | | 0.542 |
| (23, 50) | 9/88 (10%) | 1.00 | | |
| (50, 65) | 14/95 (15%) | 1.52 | 0.62–3.71 | |
| (65, 88) | 10/64 (16%) | 1.63 | 0.62–4.27 | |
| Sex | | | | 0.185 |
| Male | 16/146 (11%) | 1.00 | | |
| Female | 17/101 (17%) | 1.64 | 0.79–3.43 | |
| BMI | | 0.99 | 0.92–1.05 | 0.667 |
| eGFR (continuous variable) | | 0.99 | 0.97–1.01 | 0.201 |
| eGFR | | | | 0.462 |
| (90, 155) | 2/19 (11%) | 1.00 | | |
| (75, 90) | 8/37 (22%) | 2.34 | 0.45–12.3 | |
| (60, 75) | 10/73 (14%) | 1.35 | 0.27–6.75 | |
| (40.1, 60) | 13/117 (11%) | 1.06 | 0.22–5.13 | |
| Diabetes | | | | |
| No | 26/205 (13%) | | | |
| Yes | 3/33 (9%) | 0.69 | 0.20–2.42 | 0.560 |
| Hypertension | | | | |
| No | 17/159 (11%) | | | |
| Yes | 16/88 (18%) | 1.86 | 0.89–3.89 | 0.101 |
| Lipid disorder | | | | |
| No | 28/213 (13%) | | | |
| Yes | 5/34 (15%) | 1.14 | 0.41–3.19 | 0.804 |
| Any eye disorder | | | | |
| No | 16/168 (10%) | | | |
| Yes | 17/79 (22%) | 2.60 | 1.24–5.48 | 0.012 |
| Posterior segment eye disease | | | | |
| No | 26/211 (12%) | | | |
| Yes | 7/36 (19%) | 1.72 | 0.68–4.32 | 0.250 |

*(Continued)*

**Table 3.** (Continued)

| | Events/patients (%) | OR | 95% CI | *p*-value |
|---|---|---|---|---|
| Retinopathy | | | | |
| No | 31/235 (13%) | | | |
| Yes | 2/12 (17%) | 1.32 | 0.28–6.29 | 0.731 |
| Ocular vascular disease | | | | |
| No | 31/236 (13%) | | | |
| Yes | 2/11 (18%) | 1.47 | 0.30–7.12 | 0.633 |
| Ocular inflammation | | | | |
| No | 29/242 (12%) | | | |
| Yes | 4/5 (80%) | 29.4 | 3.17–272 | 0.003 |
| Vision disorders | | | | |
| No | 31/225 (14%) | | | |
| Yes | 2/22 (9%) | 0.63 | 0.14–2.81 | 0.541 |
| Steroid Use | | | | |
| No | 8/90 (9%) | | | |
| Yes | 25/157 (16%) | 1.94 | 0.84–4.51 | 0.123 |

BMI, body mass index (kg/m$^2$); CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73 m$^2$); OR, odds ratio.

ophthalmologic assessments when taking a MEK inhibitor to ensure early detection of an often-manageable condition.

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## Data sharing statement

Data were accessed according to Roche's policy and process for clinical study data sharing at https://clinicalstudydatarequest.com/.

## Ethics approval

This study was a secondary analysis of coBRIM trial data approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188). Data is accessible *via* clinicalstudydatarequest.com, according to Roche's policy and process for data sharing. coBRIM, conducted by Roche, was performed in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.[17,18] Protocol approval was obtained from an independent ethics committee at each study site.[17,18] All patients provided written informed consent to participate in the coBRIM trial.[17,18]

## Conflict of interest statement

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