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## **Eplerenone for chronic central serous chorioretinopathy in patients with active, previously untreated disease for more than 4 months (VICI): a randomised, double-blind, placebo-controlled trial**

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## **Efficacy of eplerenone to treat central serous chorioretinopathy in previously untreated adults with active disease for more than four months - the VICI multicentre, double-blind placebo-controlled randomised trial.**

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## **Summary**

### **Background:**

In chronic central serous chorioretinopathy (CSCR), fluid accumulates in the sub-retinal space. It is a common visually disabling condition in individuals of working age. There is no definitive treatment. Previous research suggests the mineralocorticoid receptor antagonist, eplerenone, is effective for treating CSCR but it is not licensed for this indication. We evaluated whether eplerenone is superior to placebo for treating chronic CSCR.

### **Methods:**

We conducted a placebo-controlled parallel-group randomised trial in 22 United Kingdom hospitals. Participants were aged  $\geq 18$  and  $\leq 60$  years with treatment naïve CSCR for  $\geq 4$  months. Randomisation stratified by best-corrected visual acuity (BCVA) and hospital was performed online, with participants randomised to receive oral eplerenone (25 mg/day for one week, increasing to 50 mg/day for up to 12 months) plus usual care or placebo plus usual care. Participants, care teams, outcome assessors, pharmacists and the trial management group were masked. The primary outcome was BCVA at 12 months. All outcomes apart from safety were analysed on a modified intention-to-treat basis. The trial is registered: ISRCTN92746680.

### **Findings:**

Between 11/01/2017 and 22/02/2018, 57 participants were randomised to eplerenone and 57 to placebo; 57 and 54 participants respectively were included in the final analysis. Modelled mean BCVA at 12 months in the placebo and eplerenone groups were 79.5 (SD 4.5) and 80.4 (SD 4.6) letters, with an adjusted estimated difference (eplerenone minus placebo) of 1.73 letters (95% confidence interval -1.12 to 4.57,  $p=0.24$ ) at 12 months. Hyperkalaemia occurred in eight participants in each group (14%). No serious adverse events occurred in the eplerenone group; three unrelated serious adverse events occurred in the placebo group.

### **Interpretation:**

Eplerenone was not superior to placebo in improving BCVA in people with chronic CSCR during 12 months follow-up.

### **Funding**

Efficacy and Mechanism Evaluation Programme, National Institute for Health Research and Social Care.

## Introduction

Central serous chorioretinopathy (CSCR) is the fourth most common retinal disease after neovascular age-related macular degeneration, diabetic macular oedema, and retinal venous occlusion.<sup>1</sup> Each year, 10 per 100,000 men and 2 per 100,000 women in the population develop CSCR.<sup>2</sup> The condition is characterised by the occurrence of subretinal fluid (SRF) which when located subfoveally results in central visual disturbance. The condition is frequently bilateral with most patients exhibiting signs of CSCR in both eyes.<sup>3</sup> In most patients, the first episode of CSCR resolves spontaneously within 3 months of onset. When there is persistence of SRF beyond three months, the condition is considered to be chronic and may lead to permanent vision loss in up to one third of patients. CSCR can occur in families and some genetic associations have been reported.<sup>5-8</sup>

Little progress has been made in understanding CSCR since it was first described. A variety of treatments have been used despite limited high quality evidence as to their effectiveness. Photodynamic laser therapy (PDT) with a drug called verteporfin (vPDT) is used in some cases; randomised controlled trials (RCT) with half dose vPDT have shown some encouraging results in the short-term.<sup>10, 11</sup> However, most hospitals do not have access to this treatment as it requires a specialised laser. Further, verteporfin is not licensed for this indication and is expensive. Other laser treatments have been tried but have limited evidence of effectiveness and are not supported by placebo-controlled RCTs.<sup>10, 12, 13</sup>

Recent advances in retinal imaging show that eyes with CSCR have a thickened choroid and dilated choroidal vessels. In addition, studies suggest that CSCR is associated with choroidal hyperpermeability.<sup>14, 15</sup> In a rat model of CSCR, choroidal vasodilation was induced by aldosterone, a mineralocorticoid receptor (MR) activator, acting via an endothelial vasodilatory potassium channel KCA2.3. Blockade of this pathway prevented aldosterone-induced choroidal thickening, suggesting MR activation may contribute to the pathogenesis of CSCR.<sup>16</sup> Subsequently, case-series of patients with chronic CSCR treated with oral MR antagonists such as eplerenone, a specific MR antagonist licensed for use in heart failure, and spironolactone, a non-specific MR antagonist, have reported resolution of SRF and reduction of choroidal thickening as well as improvement in visual acuity in the short-term. A recent meta-analysis of RCTs that used MR antagonists in CSCR found a modest benefit in visual acuity and suggests that blockade of MRs could be therapeutically beneficial for CSCR. As CSCR predominantly affects males, eplerenone has been preferred to spironolactone because the adverse effect of gynaecomastia is less prevalent with eplerenone.<sup>19</sup>

Despite a lack of robust clinical trial data, MR antagonists are widely used by ophthalmologists as first line therapy for treatment of CSCR. As these drugs can have serious systemic side effects such as hyperkalaemia, it is important to determine their efficacy and safety profile.

Therefore, we performed the first adequately powered randomised, double-masked, placebo-controlled trial to determine whether eplerenone is safe and efficacious for treating CSCR.

## Methods

### *Study design and participants*

The VICI trial was a placebo-controlled, parallel group randomised superiority trial undertaken in 22 secondary care NHS hospitals in the United Kingdom (appendix p 5). Patients with chronic CSCR attending outpatient ophthalmology clinics were screened in two stages, first from their medical records. Then, if initially eligible and after obtaining consent, trial-specific assessments were carried out to determine eligibility in relation to additional criteria. Eligibility was determined by experienced ophthalmologists and consent was obtained by ophthalmologists or experienced research nurses.

The eligibility criteria have been described previously.<sup>20</sup> In brief, patients aged  $\geq 18$  and  $\leq 60$  years with treatment naïve CSCR of  $\geq 4$  months duration were eligible to take part. Patients were excluded if they had: choroidal neovascularisation, or any other disease which could affect visual acuity or cause retinal fluid or SRF to accumulate, or myopia  $> -6$  dioptres, or hyperkalaemia (blood serum potassium  $> 5.0$  mmol/L).

All participants provided written informed consent. The trial was sponsored by University Hospitals Southampton NHS Trust and approved by the Wales Research Ethics Committee (16/WA/0069) and the Medicines and Healthcare products Regulatory Agency (MHRA; Eudract 2016-000113-70). The protocol has been published.<sup>20</sup>

### *Randomisation and masking*

Participants were randomly allocated (1:1) to eplerenone plus usual care or placebo plus usual care. Usual care was included in both groups to ensure participants could receive additional treatments if necessary, administered at the clinician's discretion. Randomisation was blocked (random block sizes of 2 and 4) and stratified by hospital and visual acuity (54-67 or 68-85 letters read on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart). The allocation list was generated by the trial statistician using Stata 14.0 (StataCorp, College Station, TX, US) before starting recruitment and supplied to Newcastle Specials Pharmacy Production Unit (Newcastle-Upon-Tyne, UK). This pharmacy was responsible for over-encapsulating eplerenone tablets, manufacturing identical placebo capsules, packaging capsules in plastic bottles and labelling the bottles identically as clinical trial Investigational Medicinal Product (IMP), with a unique bottle number to assign bottles of IMP to participants according to their allocation whilst maintaining masking. Production pharmacists had no role in trial design or conduct. Participants, clinical teams, outcome assessors, hospital pharmacists and the trial management group were masked to participants' allocations. Unmasking was permitted only if required to administer emergency treatment and required permission from AL or SS. Unmasking was done using a secure internet-based IMP management system (IMP-Track) or, in the event of internet failure, by code-break envelopes held at hospital pharmacies.<sup>20, 21</sup>

Before randomisation, information to identify the participant and confirm eligibility was entered into a secure internet-based randomisation system (Genesys, Bristol Trials Centre (CTEU), Bristol, UK), accessible only to approved trial personnel. Randomisation was performed by ophthalmologists or research nurses within four weeks of screening. The randomisation system provided the bottle number to be dispensed.

### *Procedures*

Participants were prescribed 25 mg/day eplerenone for the first week, increasing to 50 mg/day for up to 12 months if blood serum potassium was  $\leq 5.0$  mmol/L. Participants allocated to placebo followed the same schedule to maintain masking. Capsules were taken orally with no restrictions on time of day or food consumption. Participants were followed up at 1 week, 4 weeks and 3, 6, 9 and 12 months (appendix p 70).<sup>20</sup> Sufficient capsules were dispensed at each visit to last until the next follow-up visit. Participants returned unused capsules at each follow-up visit and the difference was calculated between the expected and actual number of capsules returned given the interval between visits. Participants were classified as 'adherent' if they took  $> 70\%$  of the capsules that they were prescribed between follow-up visits. Participants ceased the study drug if SRF had completely resolved at any follow-up visit and re-started the study drug if SRF recurred at a subsequent follow-up visit. If the study drug was re-started, the same dose escalation procedure was followed. If serum potassium exceeded 5.0 mmol/L at any follow-up visit, the study drug was stopped permanently and the participant was invited to continue with follow-up to 12 months.

We used a custom-designed database to collect the data, which also provided the randomisation (Genesys). The database allowed (a) sites to enter their own data and to review and correct data queries and (b) the central trial team to carry out central monitoring. We used a separate software application (IMP-Track) to manage the distribution, tracking and accounting of the investigational medicinal product over the lifetime of the study.<sup>21</sup>

### *Outcomes*

The primary outcome was best corrected visual acuity (BCVA) at 12 months, measured by ETDRS charts according to a standard protocol for medical retina trials.<sup>20, 23</sup> BCVA was measured at all follow-up visits, except week 1, by accredited optometrists at sites who were masked to BCVA results at previous visits as well as participants' allocations. Optometrists were certified to perform BCVA assessments in clinical trials during site set up.

Secondary outcomes were: low luminance BCVA (LLA); central subfield retinal thickness (CSRT); change in SRF thickness from baseline; systemic and ocular adverse events; macular atrophy of the retinal pigment epithelium; sub-foveal choroidal thickness; choroidal permeability; time-to-resolution of SRF; classification of SRF resolution as complete, partial or none; classification of SRF resolution as early, late or none; time-to-recurrence of SRF; fundus fluorescein angiography (FFA) phenotype; incidence of CSCR in the fellow eye; and patient-reported visual function. Outcome measurements and time points are detailed in the appendix (p 48). All retinal images were graded by masked, trained and quality assured independent graders in the Network of Ophthalmic Reading Centres UK (NetwORC UK).

### *Adverse events*

Adverse events and reactions were recorded throughout the 12-month follow-up period. Participants' general practitioners were notified of their participation, with a request to inform the local research team about any suspected adverse events or reactions.

At each visit participants were asked to report any adverse events experienced since the previous visit. All events were recorded on a form which coded them by the Medical Dictionary for Regulatory Activities (MedDRA) categories (version 14.1), which were used for reporting (appendix p 35).<sup>20</sup>

### *Statistical analysis*

A target sample size of 104 patients was chosen for the trial to have 90% power to detect a difference of  $\geq 5$  letters at a 5% significance level (2-tailed), given an anticipated dropout rate of  $<15\%$  during follow-up. The following assumptions were made: one study eye per participant; standard deviation 9 letters; correlation between baseline and any follow-up assessment 0.5; minimum of two follow-up assessments per participant with a correlation between BCVA on follow-up visits of 0.8.

Analyses were directed by a pre-specified statistical analysis plan (SAP; appendix p 46) and performed on a modified intention-to-treat (ITT) basis. Continuous data are summarised using mean and standard deviation (or median and interquartile range (IQR) if distributions were skewed) and categorical data as number and percentage. Outcomes were compared using linear regression (continuous outcomes), proportional hazards parametric survival models for interval-censored data (time-to-event outcomes) or mixed effects regression (continuous longitudinal outcomes). Model fit was assessed using standard methods and transformations were performed or alternative methods sought if model fit was inadequate. Analyses were adjusted for the stratification factors; baseline visual acuity (54-67 letters versus 68-85 letters) fitted as a fixed effect and centre fitted as a random effect. Centres with a small number of participants were combined to ensure estimation (appendix p 77). For time-to-event outcomes, a clustered sandwich estimator was used to adjust the standard errors for clustering within centre, as it was not possible to fit centre as a random effect. For continuous outcomes measured at baseline as well as subsequently, baseline values were modelled as a covariate. Longitudinal outcomes included both time and time by treatment interaction terms fitted as fixed effects which allowed the treatment effect at 12 months to be estimated. Different variance/covariance structures were explored and the structure that provided the best fit in terms of likelihood ratio tests was used to model within patient errors. An unstructured covariance structure provided the best fit in all models. Multiple imputation (10 imputed data sets) was used to account for missing data. Placebo with usual care was the reference group in all analyses. Likelihood ratio tests were used to determine statistical significance where possible and results are reported as effect estimates with 95% confidence intervals (CI). A pre-specified exploratory analysis was

performed to assess the effect of adherence and treatment on the primary outcome. Sensitivity analyses (a) adjusting time-to-event outcomes for baseline imbalances in prognostic factors and (b) reassessing the effect of adherence and treatment on the primary outcome after imputing pill counts for lost bottles were performed. Two post-hoc analyses (a) re-estimated the treatment effects for BCVA, CSRT, SRF thickness and choroidal thickness after adjusting for PDT administered during follow-up, and (b) analysed choroidal thickness in the fellow eye.

To set our findings in context, we did a systematic review and meta-analysis, searching for other trials comparing eplerenone and placebo (identified by Medical Subject Headings ‘central serous choroidal retinopathy’ AND (‘eplerenone’ OR ‘mineralocorticoid receptor antagonists’) AND ‘publication type = randomized controlled trial’). We assessed the risk of bias,<sup>25</sup> and re-analysed data reported by the trials to obtain treatment effects for BCVA and SRF thickness using the same metric, i.e. the difference between groups in the change in BCVA and SRF thickness from baseline to the end of treatment. If it was not possible to calculate the SD of the mean change from baseline for a group, an average of the SDs from the other studies was used. The treatment effects were synthesised in a fixed effects meta-analysis, to estimate weighted mean differences between eplerenone and placebo groups according to the inverse variance method.

All analyses were performed in Stata version 15.1 (StataCorp, LP, College Station, TX, US). Further details are given in the SAP (appendix p 46).

The trial was overseen by an independent data monitoring and safety committee (DMSC) who reported their recommendations to an independent trial steering committee (TSC) (appendix p 68).

The trial is registered as ISRCTN92746680.

The funder and the sponsor of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

One hundred and fourteen participants were randomised between January 11, 2017 and February 22, 2018, 57 to the eplerenone group and 57 to the placebo group (figure 1). A total of 402 patients were screened for inclusion and 305 were initially eligible; 223 were approached and 179 consented to participate but 64 were subsequently found to be ineligible and one patient withdrew consent (appendix p 69).

One hundred and eleven participants attended at least one post-randomisation visit where the primary outcome, BCVA, was measured. Adherence to taking the capsules was similar between groups (appendix p 76). There were no instances of a participant receiving the wrong drug and very few other protocol deviations, apart from visits attended outside the prespecified visit window (appendix p 72-73). During follow-up, nine participants received PDT and one participant received subthreshold laser therapy (appendix p 76) as usual care.

Participants' characteristics are described by allocated group in table 1. There was no apparent difference between groups in the proportion of time they were taking their allocated capsules (appendix p 74-75).

Modelled mean BCVA at 12 months was 80.4 letters (SD 4.6) in the eplerenone group and 79.5 letters (SD 4.5) in the placebo group. On average, BCVA increased by about four letters in both groups during follow-up (figure 2). There was no difference in BCVA at 12 months between the groups (mean difference (MD) eplerenone minus placebo = 1.73 letters, 95% CI (-1.12, 4.57),  $p=0.24$ ; table 2). The exploratory analysis found no effect of adherence and treatment on BCVA, irrespective of whether pill counts were imputed for lost IMP bottles (appendix p 92). The post-hoc analysis adjusting the estimated difference in BCVA between groups for PDT administered during follow-up did not change the finding (appendix p 91).

Findings for secondary outcomes by group, and treatment effects, are described in table 2 and the appendix p 78-85). There were no statistically significant differences between groups favouring eplerenone. There were no apparent differences between groups for the pattern of complete resolution of SRF or recurrence of CSCR, without or with adjustment for baseline SRF thickness (appendix p 91). CSRT at 12 months did not differ significantly between groups (MD = 24.35 microns, 95% CI (-7.86, 56.56),  $p=0.14$ ) but there was a statistically significant difference in SRF thickness favouring placebo at 12 months (MD = 48.08 microns, 95% CI (-13.34, 82.73),  $p=0.007$ ).

Serum potassium levels were very similar in both groups during follow-up (appendix p 75). Levels  $>5.0$  mmol/L triggered discontinuation of IMP in eight participants in each group (14%). All serious adverse events and other adverse events are tabulated in the table 3, categorised by the MedDRA system organ class. There were three serious adverse events; none was considered related to IMP, and all occurred in participants in the placebo group.

The results of the systematic review and meta-analysis can be found in the appendix (p 92-96). The four trials compared eplerenone and placebo in 40, 21, 19 and 111 eyes over one, two, three and 12 months of treatment, respectively. We found a pooled difference in mean change in BCVA of 0.06 logMAR (equivalent to 3.0 letters, 95% CI, -0.09, 0.02, equivalent to -4.5 to -1.0 ETDRS letters, I-squared 31%) and a pooled difference in SRF thickness of -26.7 microns (95% CI, -63.1, 9.8, I-squared 84%).



## Discussion

The primary analysis of the VICI trial excludes the target difference that the VICI trial was powered to detect (upper 95% confidence limit, 4.57 letters), showing that treatment with eplerenone did not result in an improvement of BCVA by 5 letters or more when compared with placebo at 12 months after randomisation. There was no difference between groups in complete resolution of SRF or subsequent recurrence of CSCR, nor any benefit with respect to several measurements of retinal morphology. If anything, time-to-resolution of SRF and recurrence of CSCR favoured placebo, but not significantly so. Surprisingly, two morphological outcomes, SRF thickness and choroidal thickness, significantly favoured placebo. It is unclear why this was the case. The findings for BCVA, time-to-event outcomes, and key morphological outcomes were unaltered in sensitivity, exploratory or post-hoc analyses. The failure to find a difference cannot be explained by weaknesses in trial conduct. The primary analysis included 97% of randomised participants and participants attended 94% of all scheduled visits. There were no protocol deviations affecting the treatment comparison.

The meta-analysis and VICI results are consistent in that the VICI point estimates lie within the 95% confidence intervals for the pooled estimates. The pooled BCVA estimate also excludes the target difference that the VICI trial was powered to detect (upper 95% confidence limit, -4.5 letters). The SRF thickness results, however, show substantial heterogeneity and the VICI treatment effect is in the opposite direction to the results of the other three trials. There is no obvious reason for the latter inconsistency. It is possible that the effect of eplerenone on SRF is short-lived and a shorter interval of follow-up, e.g. every 4 weeks, might have provided more data and allowed a more detailed comparison on response to treatment with eplerenone and placebo.

Notwithstanding the risk of bias assessment, we have concerns about the quality of the three small trials (appendix p 93). One was not registered despite publication in 2016. We could not find a published protocol or prespecified analysis plan for any of the trials and the reported analyses of treatment effects were unusual, suggesting selection of the reported result. In our meta-analysis, we avoided bias from selection of the reported result by re-analysing the published data.

The VICI trial had several strengths. All but three participants contributed to the primary analysis and participants attended almost all scheduled visits. There were no protocol deviations compromising the treatment comparisons. The trial was powered to detect a clinically important difference in BCVA targeted by several large multi-centre trials of treatments for retinal conditions and, in fact, had more power than anticipated due to participants attending almost all scheduled visits.<sup>29, 30</sup>

Limitations included the need to discontinue treatment if CSCR completely resolved during follow-up or an elevated serum potassium was detected. Hyperkalaemia was not a common side-effect in this group of patients who are younger and fitter than patients who are usually prescribed eplerenone for heart failure. These issues may have reduced the observed treatment effect but were required to ensure the safety of participants; we also compared recurrence of CSCR after complete resolution and found no difference between groups. Our inability to control the use of co-treatments, could have introduced bias if these were used differentially by group and we observed that more participants in the placebo group were treated with PDT compared to the eplerenone group. However, co-interventions (including PDT) were used rarely and the post-hoc analysis showed no effect on the results after adjusting for the slight imbalance in treatment with PDT.

In summary, the VICI trial found no evidence of a clinically important benefit of eplerenone for the treatment of CSCR. This is an important practice-changing outcome. The trial results should prompt ophthalmologists to stop treating CSCR with eplerenone and to participate in future trials of other potential interventions. CSCR remains a devastating condition for people who are affected, often of working age, and a challenging condition for ophthalmologists to manage.

## Contributors

AL conceived the trial; AL, SS, BCR, AC, CR, LC obtained funding; AL, SS, BCR, LC and CR designed the trial; AO, LE and LC managed the trial with input from AL, SS, AC, BCR and CR; UC, TP and FBC provided expert input; AL, SS, TP, UC and SM developed the retinal image grading protocols and managed the grading process; RH and CR analysed the data; AL, SS, RH, UC, TP, CR and BCR interpreted the data; AO, BCR and

RH wrote the first draft of the manuscript. All authors reviewed the manuscript and amended/approved the final version. AL was responsible for the decision to submit the manuscript.

### **Declaration of interests**

AL has received speaker fees and attended advisory board meetings of Novartis, Bayer, Roche, Allergan, Gyroscope Therapeutics and Boehringer Ingelheim; SS has received research grants, speaker fees and attended advisory board meetings of Novartis, Bayer, Roche, Allergan, Optos, Heidelberg Engineering and Boehringer Ingelheim; FBC is an inventor on a patent protecting the use of mineralocorticoid receptor antagonists for retinal edema; TP received research grants, speaker fees and attended advisory board meetings of Novartis, Bayer, Roche, Optos, Heidelberg Engineering, Welch Allyn and Boehringer Ingelheim. All other authors have no interests to declare.

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### **Data sharing statement**

Following publication, anonymised individual patient data will be made available upon request to the corresponding author for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review, approved by a UK REC or other similar, approved ethics review body. Patient identifiers will not be passed on to any third party.

## **Research in Context**

### **Evidence before this study**

Little progress has been made in treating CSCR over 150 years. Our proposal to do the VICI trial was founded on a literature review of possible treatments for CSCR, which identified no conclusive evidence about the effectiveness of postulated treatments published between March 1969 to January 2010. Our search identified articles in MEDLINE which were indexed with Medical Subject Headings (MeSH) for: CSC, chorioretinopathies, and central serous retinopathies. We restricted the search using MeSH subheadings ‘pathophysiology of central serous chorioretinopathy’, ‘treatment of central serous chorioretinopathy’, and ‘photodynamic treatment in central serous chorioretinopathy’. We searched for additional references from reference lists of included articles and review articles. We also searched the clinicaltrial.gov database for relevant studies using the same search terms. We identified some small phase 1 studies of aflibercept, photodynamic laser therapy and eplerenone but no definitive statistically powered studies. The available studies were not large enough to detect a clinically important benefit in visual acuity, i.e. five letters or more. Consequently, the standard of care varies. Photodynamic laser therapy and eplerenone are the treatments that are most frequently offered to affected patients.

### **Added value of this study**

This is the first randomised, double-masked, placebo-controlled trial with adequate power to detect a clinically important benefit in visual acuity to treating CSCR with eplerenone. This is a functional outcome of key relevance to patients, whereas two of the three previous trials prioritised structural changes in the retina as the primary outcome. Neither the primary or secondary outcomes such as time to resolution of CSCR, or recurrence of CSCR after resolution, found any benefit of eplerenone. By virtue of its size, the trial also provides more than double the evidence about the safety of using eplerenone to treat CSCR; instances of hyperkalaemia, a known adverse effect of eplerenone, arose in as many patients taking placebo as eplerenone.

### **Implications of all the available evidence**

The VICI trial found no evidence of a clinically important benefit of eplerenone for the treatment of CSCR. This is an important practice-changing outcome as eplerenone is commonly used by ophthalmologists as first line treatment for CSCR. The trial results should prompt ophthalmologists to stop treating CSCR with eplerenone and to participate in future trials of other potential interventions.

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## **Figure 1 CONSORT diagram**

<sup>1</sup>Reasons for patients being excluded before randomisation are detailed in the appendix (p 69).

**Table 1 Baseline participant characteristics by randomised allocation (entire trial population, 114 randomised participants)**

		Randomised to placebo (n=57)	Randomised to eplerenone (n=57)	Overall (n=114)
<b>Non-ocular history</b>				
Age at randomisation (years)		49.9 (7.9)	47.4 (7.1)	48.7 (7.6)
Male		43/57 (75%)	42.57 (74%)	85/114 (75%)
Ethnicity	White	53/57 (93%)	46/57 (81%)	99/114 (87%)
	Asian	4/57 (7%)	9/57 (16%)	13/114 (11%)
	Mixed	0/57 (0%)	1/57 (2%)	1/114 (1%)
	Other	0/57 (0%)	1/57 (2%)	1/114 (1%)
Systolic blood pressure (mmHg) ^		132 (125.0, 146.0)	129 (121.0, 141.0)	130 (122.0, 144.0)
Diastolic blood pressure (mmHg) ^		80 (75.0, 88.0)	80 (72.5, 88.5)	80 (73.0, 88.0)
Heart rate (bpm) ^		68 (60.0, 76.0)	73 (66.0, 80.0)	72 (63.0, 78.0)
Potassium (mmol/L)		4 (0.3)	4 (0.4)	4 (0.3)
Smoking	Current	10/57 (18%)	12/57 (21%)	22/114 (19%)
	Ex	16/57 (28%)	25/57 (44%)	41/114 (36%)
	Never	31/57 (54%)	20/57 (35%)	51/114 (45%)
Heart failure		0/57 (0%)	0/57 (0%)	0/114 (0%)
Myocardial infarction		1/57 (2%)	0/57 (0%)	1/114 (1%)
History of angina		0/57 (0%)	0/57 (0%)	0/114 (0%)
CCS class	No angina	57/57 (100%)	57/57 (100%)	114/114 (100%)
NYHA class	0	56/57 (98%)	57/57 (100%)	113/114 (99%)
	I	1/57 (2%)	0/57 (0%)	1/114 (1%)
Transient ischaemic attack		0/57 (0%)	0/57 (0%)	0/114 (0%)
Exposure to steroids		15/57 (26%)	12/57 (21%)	27/114 (23%)
Oral		1/15 (7%)	1/12 (8%)	2/27 (7%)
Inhalation		4/15 (27%)	6/12 (50%)	10/27 (37%)
Intramuscular injection		3/15 (20%)	0/12 (0%)	3/27 (11%)
Topical cream		5/15 (33%)	8/12 (67%)	13/27 (48%)
Other		4/15 (27%)	1/12 (8%)	5/27 (18%)
<b>Ocular history</b>				
CSCR duration (months)		9 (6.0, 18.0)	8 (6.0, 22.0)	9 (6.0, 19.0)
Family history of CSCR		1/57 (2%)	0.57 (0%)	1/114 (1%)
VA score	Low (54-67)	7/57 (12%)	7/57 (12%)	14/114 (12%)
	High (68-85)	50/57 (88%)	50/57 (88%)	100/114 (88%)
BCVA score		78 (73.0, 82.0)	77 (73.0, 80.0)	78 (73.0, 81.0)
Low luminance VA score ×		64 (57.0, 67.0)	57 (50.0, 64.0)	60 (52.5, 65.0)
Choroidal thickness (µm) *		461 (381.5, 534.5)	447 (398.0, 509.0)	447 (389.0, 521.0)
SRFT (µm)		119 (88.0, 178.0)	147 (93.0, 196.0)	134 (90.0, 194.0)
CSRT (µm)		322 (280.0, 394.0)	360 (290.0, 406.0)	349 (280.0, 401.0)
Macular atrophy of RPE		3/55 (5%)	2/56 (4%)	5/111 (5%)

Data are mean (SD), median (IQR) or n/N (%)

BCVA=best corrected visual acuity, VA=visual acuity, SRFT=subretinal fluid thickness, CSRT=central subfield retinal thickness, RPE=retinal pigment epithelium

Missing data (placebo, eplerenone): ^1 patient with missing data (0, 1), × 2 patients with missing data (1, 1), \* 1 patient with missing data (1, 0)

**Figure 2 Primary outcome best corrected visual acuity over time**



**Table 2 Primary and secondary outcomes by randomised allocation (analysis population, 114 participants)**

	Randomised to placebo (n=57)	Randomised to eplerenone (n=57)	Effect (95% CI)	p-value
<b>Primary outcome</b>				
BCVA at 12 months	79.5 (4.5)	80.4 (4.6)	MD=1.73 (-1.12, 4.57)	0.236
<b>Secondary outcomes</b>				
Low luminance VA at 12 months	65.3 (3.7)	63.9 (4.8)	MD=0.61 (-3.79, 5.02)	0.785
CSRT at 12 months	270.0 (38.0)	302.1 (43.7)	MD=24.35 (-7.86, 56.56)	0.142
SRFT at 12 months <sup>×</sup>	72.5 (6.2)	120.7 (6.0)	MD=48.08 (13.43, 82.73)	0.007
Macular atrophy of the RPE at 12 months	3/53 (6%)	4/49 (8%)		
Area change in macular RPE hypoautofluorescence at 12 months <sup>°</sup>	0.03 (0.03, 0.04)	0.72 (-0.73, 2.10)		
Choroidal thickness at 12 months <sup>×</sup>	451.4 (78.6)	478.0 (58.1)	MD=38.53 (12.31, 64.74)	0.004
Reduced choroidal permeability at 12 months	3/54 (6%)	1/49 (2%)		
VFQ-25 overall composite score at 12 months <sup>×</sup>	89.1 (4.4)	86.5 (5.3)	MD=2.39 (-5.45, 0.68)	0.127
Estimated median time to complete resolution of SRF (days) <sup>•</sup>	458.2 (214.1, 702.2)	603.3 (313.1, 893.5)	HR=0.78 (0.41, 1.51)	0.463
Estimated median time to complete or partial resolution of SRF (days) <sup>•</sup>	184.2 (122.3, 246.0)	141.1 (57.9, 224.4)	HR=1.23 (0.75, 2.01)	0.418
Estimated median time to recurrence of SRF (days) <sup>•†</sup>	192.1 (136.6, 247.6)	182.5 (117.7, 247.3)	HR=1.10 (0.45, 2.66)	0.836
New CSCR in the fellow eye	4/57 (7%)	5/57 (9%)		

Data are presented as median (interquartile range), mean (standard deviation) or n/N (%)

Formal statistical comparisons of treatment effects are not performed if less than 10 patients in total experienced the outcome.

BCVA=best corrected visual acuity, VA=visual acuity, CSRT=central subfield retinal thickness, SRFT=subretinal fluid thickness, RPE=retinal pigment epithelium, VFQ=visual function questionnaire, SRF=subretinal fluid, CSCR=central serous chorioretinopathy, CI=confidence interval, MD=mean difference, HR=hazard ratio

<sup>×</sup> Multiple imputation used to account for missing data; 10 imputed data sets were created

<sup>°</sup> Not formally tested as only eight patients in total had macular RPE hypoautofluorescence at baseline and/or 12 months

<sup>•</sup> Median time to resolution/recurrence predicted from interval-censored survival model

<sup>†</sup> Assumed resolution occurred in the middle of the interval between the last visit where the resolution status was 'No' and the first visit where the resolution status was 'Yes'.

**Table 3 Ocular and systemic adverse events by treatment received**

Event name	Received placebo (n=57)				Received eplerenone (n=57)			
	All events		SAEs		All events		SAEs	
	Patients (events)	%	Patients (events)	%	Patients (events)	%	Patients (events)	%
Any event (anticipated or otherwise)	31 (72)	54%	3 (3)	5%	30 (95)	53%	0 (0)	0%
Anticipated events listed in study protocol								
Study eye events	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Decrease in visual acuity $\geq$ 15 letters	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Incident choroidal neovascularisation	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Non-study eye events	0 (0)	0%	0 (0)	0%	1 (2)	2%	0 (0)	0%
Decrease in visual acuity $\geq$ 15 letters	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Incident choroidal neovascularisation	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Infections & infestations	3 (4)	5%	0 (0)	0%	8 (10)	14%	0 (0)	0%
Infection	3 (4)	5%	0 (0)	0%	8 (10)	14%	0 (0)	0%
Pharyngitis	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Pyelonephritis	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Eosinophilia	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Hypothyroidism	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Metabolism & nutrition disorders	9 (9)	16%	0 (0)	0%	8 (8)	14%	0 (0)	0%
Dehydration	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Hypercholesterolaemia	1 (1)	2%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Hyperkalaemia	8 (8)	14%	0 (0)	0%	8 (8)	14%	0 (0)	0%
Hypertriglyceridaemia	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Hyponatraemia	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Insomnia	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Nervous system disorders	8 (10)	14%	0 (0)	0%	7 (9)	12%	0 (0)	0%
Dizziness	3 (3)	5%	0 (0)	0%	4 (4)	7%	0 (0)	0%
Headache	6 (7)	11%	0 (0)	0%	3 (5)	5%	0 (0)	0%
Hypoesthesia	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Syncope	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Cardiac disorders	2 (2)	4%	1 (1)	2%	3 (5)	5%	0 (0)	0%
Atrial fibrillation	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Left ventricular failure	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Myocardial infarction	1 (1)	2%	1 (1)	2%	0 (0)	0%	0 (0)	0%
Tachycardia	1 (1)	2%	0 (0)	0%	3 (5)	5%	0 (0)	0%
Vascular disorders	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Arterial thrombosis limb	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Hypotension	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Orthostatic hypotension	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Cough	2 (2)	4%	0 (0)	0%	3 (3)	5%	0 (0)	0%
Gastrointestinal disorders	6 (10)	11%	0 (0)	0%	9 (19)	16%	0 (0)	0%
Constipation	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Diarrhoea	2 (3)	4%	0 (0)	0%	2 (2)	4%	0 (0)	0%
Flatulence	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Nausea	5 (7)	9%	0 (0)	0%	4 (7)	7%	0 (0)	0%
Vomiting	0 (0)	0%	0 (0)	0%	4 (8)	7%	0 (0)	0%
Skin & subcutaneous tissue disorders	1 (1)	2%	0 (0)	0%	5 (5)	9%	0 (0)	0%
Angioedema	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Hyperhidrosis	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Pruritus	0 (0)	0%	0 (0)	0%	2 (2)	4%	0 (0)	0%
Rash	1 (1)	2%	0 (0)	0%	2 (2)	4%	0 (0)	0%
Musculoskeletal & connective tissue disorders	5 (8)	9%	0 (0)	0%	11 (11)	19%	0 (0)	0%
Back pain	2 (3)	4%	0 (0)	0%	3 (3)	5%	0 (0)	0%

Event name	Received placebo (n=57)				Received eplerenone (n=57)			
	All events		SAEs		All events		SAEs	
	Patients (events)	%	Patients (events)	%	Patients (events)	%	Patients (events)	%
Muscle spasms	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Musculoskeletal pain	5 (5)	9%	0 (0)	0%	7 (7)	12%	0 (0)	0%
Renal impairment	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Cholecystitis	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Gynaecomastia	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
General disorders & administration site conditions	0 (0)	0%	0 (0)	0%	2 (2)	4%	0 (0)	0%
Asthenia	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Malaise	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Investigations	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Blood creatinine increased	0 (0)	0%	0 (0)	0%	1 (1)	2%	0 (0)	0%
Blood glucose increased	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Blood urea increased	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Epidermal growth factor receptor decreased	0 (0)	0%	0 (0)	0%	0 (0)	0%	0 (0)	0%
Any anticipated event	25 (46)	44%	1 (1)	2%	28 (75)	49%	0 (0)	0%
Any unanticipated event	16 (26)	28%	2 (2)	4%	13 (20)	23%	0 (0)	0%



