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List of abbreviations

Acronym	Details
AE	Adverse event
AF	Autofluorescence
AKI	Acute kidney injury
BCVA	Best corrected visual acuity
CEN	Central optical involvement
CF	Counting fingers
CI	Confidence interval
CMT	Central macular thickness
COR	Cortical
CRF	Case report form
CSCR	Central serous chorio-retinopathy
CSRT	Central subfield retinal thickness
CTEU	Clinical Trials and Evaluation Unit
DBP	Diastolic blood pressure
DMSC	Data monitoring and safety committee
eGFR	Estimated glomerular filtratin rate
ETDRS	Early treatment diabetic retinopathy study
FFA	Fundus fluorescein angiogram
FP	Fundus photography
GM	Geometric mean
GMR	Geometric mean ratio
Hct	Haematocrit
HM	Hand movements
HR	Hazard ratio
ICGA	Indocyanine green angiography
IQR	Inter quartile range
ITT	Intention to treat
LP	Light perception
MAR	Missing at random
MD	Mean difference
NLP	No light perception
NUC	Nuclear sclerosis
OCT	Optical coherence tomography
OR	Odds ratio
PDT	Photodynamic laser therapy
PH	Proportional hazards
PIL	Patient information leaflet
PSC	Posterior subcapsular
RCT	Randomised controlled trial
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure

Acronym	Details
SD	Standard deviation
SFF	Subfoveal fluid
SRF	Subretinal fluid
TR	Time ratio
VA	Visual acuity
VFQ	Visual function questionnaire

1. INTRODUCTION TO SAP

1.1 Scope

This statistical analysis plan (SAP) details information regarding the statistical analysis of the VICI randomised controlled trial (RCT) and covers all analyses of study data outlined in the study protocol.

1.2 Editorial changes

Any changes made to this SAP after approval must be clearly justified and documented as an amendment at the end of this document. The SAP should then be re-approved.

1.3 SAP document approval

The co-director of the Clinical Trials and Evaluation Unit (CTEU) must authorise this document.

1.4 Skeleton tables and figures

Throughout this document references are made to skeleton tables and figures to be used in the reporting of the study (e.g. **Figure F1** or **Table T1**). Such tables and figures can be found in **Appendix A** of this document and are intended as a guide for study reporting. Final versions of the tables/figures may differ: tables may be combined, and/or their layout or numbering may differ. However, the content should be consistent with **Appendix A.**

2. STUDY BACKGROUND AND OBJECTIVES

2.1 Study background

The VICI study is a multi-centre double-blind parallel-group RCT. It aims to test the superiority of eplerenone therapy with usual care to placebo with usual care in adult patients with chronic central serous chorio-retinopathy (CSCR).

2.2 Study objectives

The primary objective is to evaluate whether best corrected visual acuity (BCVA) following eplerenone therapy with usual care is superior to placebo with usual care in eyes with chronic CSCR.

Secondary objectives are:

(a) To evaluate whether eplerenone treatment with usual care is better than placebo with usual care for resolution of subretinal fluid (SRF)

(b) To describe the safety profile of eplerenone treatment with usual care (compared to placebo with usual care)

(c) To evaluate whether participant-reported visual function improves with eplerenone treatment with usual care compared to placebo with usual care

(d) To describe how the choroid responds to treatment in CSCR

(e) To describe how retinal pigment epithelium (RPE) function changes over a year in CSCR as measured by autofluorescence (AF)

(f) To evaluate how low luminance visual acuity changes with eplerenone treatment

2.3 Primary outcome

The primary outcome is BCVA over a 12 month period.

2.4 Secondary outcomes

Secondary outcomes are listed in the study protocol as:

(1) Low luminance BCVA over a 12 month period.

(2) Central subfield retinal thickness (CSRT) as measured by optical coherence tomography (OCT) over a 12 month period

(3) Change in SRF thickness as measured by OCT

(4) Adverse events at any time during the 12-month follow-up period

(5) Proportion of patients with macular atrophy of the RPE defined as hypoautofluorescence at 12 months

(6) Area change in macular RPE hypoautofluorescence at 12 months

(7) Choroidal thickness as measured by enhanced depth imaging OCT over a 12 month period

(8) Proportion of patients with reduced choroidal permeability on indocyanine green angiography (ICGA) at 12 months

(9) Time to resolution of SRF

(10) Classification of all study eyes as complete, partial or no resolution of SRF at each time point of the study

(11) Patient-reported visual function using Visual Function Questionnaire VFQ 25 at 12 months adjusted for baseline

(12) Classification of all study eyes by each fundus fluorescein angiogram (FFA) phenotype

(13) Classification of all study eyes as early, late, or non-responder

(14) Incidence of CSCR in the fellow eye

(15) Time to disease recurrence

How *secondary* objectives link to secondary outcomes

Secondary objectives are as below. In parentheses are the secondary outcome(s) linked to the objective.

(a) *To evaluate whether eplerenone treatment with usual care is better than placebo with usual care for resolution of SRF [3,9,10,13]*

(b) *To describe the safety profile of eplerenone treatment with usual care (compared to placebo with usual care) [4]*

(c) *To evaluate whether participant-reported visual function improves with eplerenone treatment with usual care compared to placebo with usual care [11]*

(d) *To describe how the choroid responds to treatment in CSCR [7,8]*

(e) *To describe how RPE function changes over a year in CSCR as measured by autofluorescence (AF) [5,6]*

(f) *To evaluate how low luminance visual acuity changes with eplerenone treatment [1]*

2.5 Exploratory analyses

Additional exploratory analyses of the overall trial cohort will investigate:

(1) The association between final visual acuity and age of the patient

(2) The association between presence of granular/confluent hypoautofluorescence in the macula at randomisation and final visual acuity.

2.6 Changes to the study objectives during the course of the study

There have been no changes to the study objectives during the course of the study. OCT angiography was added partway through the study and is only available for a subset of participants being treated at centres where OCT angiograph equipment is available.

3. STUDY POPULATION

The study population is all patients recruited into the trial satisfying the main eligibility criteria: aged between 18 and 60 years who have had visual impairment due to CSCR for at least four months (defined as subfoveal presence of SRF on OCT, characteristic appearance of CSCR on FFA and ICGA, and an investigator believes there is sufficient evidence that CSCR has been present for at least 4 months). For specific inclusion/exclusion criteria see **Figure F1**.

Recruitment over time against targets will be presented overall (**Figure F2**).

The planned sample size for the VICI study is 104 patients. This sample size is sufficient to detect a difference of 5 letters in BCVA between the eplerenone and placebo groups with 90% power and 5% significance (2-tailed), assuming that: the standard deviation is 9 letters[(1)]; the correlation between baseline and any follow up assessment is 0.5[(2)]; on average, there will be a minimum of 2 follow up assessments per patient[(3)] with a correlation between BCVA on follow-up visits of 0.8; up to 15% dropout will occur over the 12 month period**.**

3.1 Flow of participants

Participant flow will be described via a flowchart (see **Figure F1**). Follow-up will last 12 months with follow-up visits planned at 1 week, 4 weeks, 3 months, 6 months, 9 months and 12 months post-randomisation.

3.2 Randomisation

Patients are randomised (1:1 ratio) to either eplerenone with usual care or placebo with usual care. Randomisations are in blocks of varying size and stratified by study centre and visual acuity level (high/low). Randomisation should take place within one month of the screening visit. The sequence of random allocations were generated by a computer in advance of starting to recruit.

3.3 Protocol deviations

The following will be considered a protocol deviation:

- Patient received the alternative drug to that allocated on at least one occasion
- Patient did not meet the study eligibility criteria but was treated in the study
- Patient did not attend a study visit (prior to study exit)
- Visit attended but outside of visit window
- Patients potassium exceeded 5.0mmol/L but patient was informed to continue treatment
- Incorrect dosage regimen followed
- Patient prescribed more medication than required at study visit
- Patients disease resolved but informed to continue treatment

Note it may be possible for patients to be classified as a protocol deviation for more than one reason.

The frequency of each type of deviation will be tabulated by treatment allocation (see **Table T1**).

3.4 Withdrawals

A patient (or a clinician on their behalf) can withdraw from the study at any time. Data from participants who consent to data collected prior to withdrawal being used will be included up to the point of withdrawal. Participants who do not consent to their data collected in the trial being used will be excluded, see **section 3.5** for further details.

Data on all withdrawals is captured on a specific case report form (CRF) and will be tabulated by treatment allocation; see **Table T2.**

3.5 Analysis population

The analysis population consists of all randomised patients excluding:

- Patients who died after randomisation but prior to any data collection.
- Patients withdrawn who were unwilling for data collected to be used.

The main study analyses will be performed on a (modified) ITT basis, modified to take into account exclusions listed above.

3.6 Safety population

The safety population is the same as the analysis population for the VICI trial. Participants will be grouped according to the treatment allocated and events in participants who were non-compliant, received the alternative treatment (e.g. study drug received by participant randomised to placebo or vice versa) or received no treatment will be detailed in footnotes.

4. DERIVATIONS

4.1 Primary outcome

The primary outcome is the BCVA in the study eye over a 12-month period. BCVA is measured at baseline, 4 weeks, 3, 6, 9 and 12 months, using validated Early Treatment Diabetic Retinopathy Study (ETDRS) vision charts with measurements made in accordance with a standardised protocol for trials in medical retina.

New variable	Rules
BCVA at standard luminance (study eye)	**At each visit:** = ETDRS letters read at standard luminance in study eye if ETDRS letters read at standard luminance not missing; OR = 0 if ETDRS letters read at standard luminance in study eye = missing AND count fingers = YES; OR = -15 if ETDRS letters read at standard luminance in study eye = missing AND hand movements = YES; OR = -30 if ETDRS letters read at standard luminance in study eye = missing AND perception of light = YES; OR = -45 if ETDRS letters read at standard luminance in study eye = missing AND perception of light = NO; ELSE = MISSING

A value of zero equates to no letters read at 1 metre. The other values (which equate to a doubling of the visual angle) are chosen to allow approximate numbers of letters to be assigned to the commonly-used categories of deteriorating visual function.

4.2 Secondary outcomes

1. BCVA at low luminance

Low luminance BCVA is measured in the study eye immediately after measuring BCVA and is measured at baseline, 4 weeks, 3, 6, 9 and 12 months.

New variable	Rules
BCVA at low luminance (study eye)	**At each visit:** = ETDRS letters read at low luminance in study eye if ETDRS letters read at low luminance not missing; OR = 0 if ETDRS letters read at low luminance in study eye = missing AND count fingers = YES; OR = -15 if ETDRS letters read at low luminance in study eye = missing AND hand movements = YES; OR = -30 if ETDRS letters read at low luminance in study eye = missing AND perception of light = YES; OR

	= -45 if ETDRS letters read at low luminance in study eye = missing AND perception of light = NO; ELSE = MISSING

2. CSRT

CSRT is measured in the study eye by OCT and is measured at baseline, 4 weeks, 3, 6, 9 and 12 months. CSRT is recorded directly (variable name: SE_OCT_CentralSubfieldRetinalThickness) and so no derivation is required.

3. Change in sub-retinal fluid thickness

Sub-retinal fluid thickness is measured in the study eye by OCT. Measurements at baseline and 12 months will be used to derive this outcome. Change in sub-retinal fluid thickness will be described; sub-retinal fluid thickness at 12 months will be compared between groups, adjusting for baseline.

New variable	Rules
Sub-retinal fluid thickness (study eye)	If 'Is maximum SRF at fovea?' (SE_OCT_IsMaxSRFAtFovea) = YES; then = 'Height of SRF at fovea' (SE_OCT_HeightSRFAtFovea) Else if 'Is maximum SRF at fovea?' = NO; then = 'If no, measure height of maximum SRF' (SE_OCT_HeightMaxSRF) Else = Missing
Change in sub-retinal fluid thickness	= (sub-retinal fluid thickness at 12 months – sub-retinal fluid thickness at baseline)

4. Adverse events

All adverse events occurring at any time during the 12-month follow-up period will be reported, with distinctions made between ocular and systemic (patient level) events.

New variable	Rules
Maximum intensity of SAE	Maximum of intensity variable on initial SAE form and all follow-up SAE forms

5. Proportion of patients with macular atrophy of the RPE

Macula atrophy of the RPE is defined as the presence of hypoautofluorescence in the study eye at 12 months and will be determined by AF.

New variable	Rules
Macular atrophy of the RPE (study eye)	**YES:** if at 12 month visit 'Is there homogenous hypo AF (representing atrophy) involving the fovea?' (SE_AF_HomogenousHypoAF) in study eye = YES **NO:** if at 12 month visit 'Is there homogenous hypo AF (representing atrophy) involving the fovea?' in study eye = NO **MISSING:** otherwise

6. Area change in macular RPE hypoautofluorescence

Macular RPE hypoautofluorescence will be measured in the study eye by AF. Measurements at baseline and 12 months will be used to derive this outcome. Area change will be described; area of macular RPE at 12 months will be analysed, adjusting for baseline.

New variable	Rules
Area of macular RPE (study eye)	Total area of hypo AF (atrophy) (SE_AF_HypoAFTotalArea)
Area change in macular RPE	= (area of macular RPE at 12 months – area of macular RPE at baseline)

7. Choroidal thickness

Choroidal thickness will be measured by enhanced depth imaging OCT at 12 months. Measurements will be made sub-foveally. Choroidal thickness is recorded directly as a continuous variable (variable name: SE_OCT_MaxChoroidalThickness) and so no derivation is required.

8. Proportion of patients with reduced choroidal permeability

Reduced choroidal permeability will be assessed by ICG at 12 months. Reduced choroidal permeability is recorded directly as yes or no (variable name: SE_ICG_ReducedChoroidalPermeability) and so no derivation is required.

9. Time to resolution of SRF

Resolution of SRF will be assessed in the study eye at 4 weeks, 3, 6, 9 and 12 months.

New variable	Rules
SRF resolved (study eye)	**YES:** if 'Are there any areas of hyporeflectivity separating the neurosensory retina and the RPE/Bruch's Complex on any scan?' (SE_OCT_HyporeflectivityOnAnyScan) = NO **NO:** if 'Are there any areas of hyporeflectivity separating the neurosensory retina and the RPE/Bruch's Complex on any scan?' = YES **MISSING:** otherwise
Time to resolution of SRF (study eye)	= (Date of SRF resolution – date of randomisation)

10. Classification of study eyes as complete, partial or no resolution of SRF

Classification of study eyes will be completed at each time point of the study. Partial resolution of SRF is defined as a decrease of >25% of CMT from baseline due to resolution of SRF. A non-responder is defined as having an increase in SRF or decrease in SRF ≤25% from baseline.

New variable	Rules
Central macular thickness (study eye)	Central subfield retinal thickness (SE_OCT_CentralSubfieldRetinalThickness)
Resolution of SRF (study eye)	**COMPLETE RESOLUTION:** if SRF has completely resolved **PARTIAL RESOLUTION:** if CMT has decreased by >25% from baseline **NON-RESPONDER:** if SRF increased or decreased by ≤25% from baseline **MISSING:** if CMT missing

11. Patient-reported visual function

Patient-reported visual function will be assessed using the visual function questionnaire VFQ-25 which will be completed at baseline and 12 months.

Data from the VFQ-25 questionnaires will be used to derive 12 sub-scale scores and an overall composite score, with a higher score indicating a better level of functioning.

The National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25) Version 2000 manual will be used to derive these scores [(4)].

To derive the sub-scores:

- Re-code original responses using the following scoring rules (**Table 1**) so all items are on a scale of 0 to 100.

Table 1 Scoring key: recoding of items

Item number	Original response	Re-coded response
1, 3, 4, 15c[1]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	1	100
	2	75
	3	50
	4	25
	5	0
	6	*

17, 18, 19, 20, 21, 22, 23, 24, 25	1	0
	2	25
	3	50
	4	75
	5	100

[1] Item 15c has four-response levels but is expanded to five-levels using item 15b. Note:
- If 15b = 1, then 15c should be recoded to 0
- If 15b = 2, then 15c should be recoded to missing
- If 15b = 3, then 15c should be recoded to missing

* Response choice 6 indicates that the person does not perform the activity because of non-visual related problems. If this choice is selected, the item is coded as missing.

To calculate the sub-scale scores, average the items within each sub-scale (Table 2). Items that are missing are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score.

Table 2 Averaging of items to calculate sub-scales

Scale		Number of items	Items to be averaged
General health		1	1
General vision		1	2
Ocular pain		2	4, 19
Near activities		3	5, 6, 7
Distance activities		3	8, 9, 14
Vision specific:	Social functioning	2	11, 13
	Mental health	4	3, 21, 22, 25
	Role difficulties	2	17, 18
	Dependency	3	20, 23, 24
Driving		3	15c, 16, 16a
Colour vision		1	12
Peripheral vision		1	10

To derive an overall composite score:

To calculate an overall composite score, average the vision-targeted sub-scale scores (excluding the general health scale).

12. Classification of all study eyes by each FFA phenotype

All study eyes will be classified by each FFA phenotype, e.g. smoke stack, ink-blot or chronic epitheliopathy at baseline and 12 months. FFA phenotype is recorded directly as smoke stack, ink-blot or chronic epitheliopathy for all participants (variable name: SE_FA_IfLeakageVisible) and so no derivation is required.

13. Classification of all study eyes as early, late, or non-responder

All study eyes will be classified as early, late or non-responder. An early responder is defined as complete or partial resolution of sub-foveal SRF by 3 months. A late responder is defined as complete or partial resolution of sub-foveal SRF after 6 months. Resolution of sub-foveal SRF will be measured at baseline, 4 weeks, 3, 6, 9 and 12 months.

14. Incidence of CSCR in the fellow eye

Incidence of CSCR in the fellow eye will be diagnosed by OCT, FFA, ICGA or AF at baseline, 4 weeks, 3, 6, 9 and 12 months. The proportion of patients with any CSCR in the fellow eye will be described and the proportion with new CSCR in the fellow eye will be compared between groups.

New variable	Rules
CSCR in fellow eye at baseline	**YES:** if right eye considered for eligibility = YES AND left eye considered for eligibility = YES **NO:** if either right eye considered for eligibility = NO or left eye considered for eligibility = NO **MISSING:** otherwise
Any CSCR (fellow eye)	**YES:** if either CSCR in fellow eye at baseline = YES OR CSCR in fellow eye = YES at any post-randomisation study visit **NO:** if CSCR in fellow eye at baseline = NO AND new CSCR in the fellow eye = NO at all post-randomisation study visits **MISSING:** otherwise
New CSCR (fellow eye)	**YES:** if CSCR in fellow eye at baseline = NO AND new CSCR in fellow eye = YES at any post-randomisation study visit **NO:** if either new CSCR in fellow eye = NO at all post-randomisation study visits OR CSCR in fellow eye at baseline = YES **MISSING:** otherwise

15. Disease recurrence

Disease recurrence will be defined as the appearance of new SRF in a study eye after complete resolution of SRF at any point. The proportion of participants with disease recurrence will be described and time to disease recurrence will be compared between groups.

New variable	Rules
Disease recurrence (study eye)	**YES:** if complete resolution of SRF in study eye at any study visit = YES AND new SRF in study eye at any study visit after complete resolution = YES **NO:** if Complete resolution of SRF in study eye at any study visit = YES AND new SRF in study eye at any point after complete resolution = NO **N/A:** if complete resolution of SRF in study eye at all study visits = NO **MISSING:** otherwise

Time to disease recurrence	= (date of disease recurrence – date of disease resolution)

4.3 Other variables

Details for any other variables which will be derived for use in any other figures or tables are given below:

New variable	Rules
Exclusion category	INELIGIBLE: any of the inclusion criteria are NO, or any of the exclusion criteria are YES NOT APPROACHED: patient is eligible, patient approached = NO DID NOT CONSENT: patient is eligible, patient approached = YES, patient consented = NO DID NOT ATTEND SCREENING VISIT: patient is eligible, patient approached = YES, patient consented = YES, screening visit attended = NO INELIGIBLE POST-CONSENT: patient is eligible, patient approached = YES, patient consented = YES, screening visit attended = YES, but any of the post-consent inclusion criteria = NO, or any of the post-consent exclusion criteria = YES OTHER: patient is eligible, patient approached = YES, patient consented = YES, screening visit attended = YES, post-consent eligibility = YES, randomised = NO
Treatment received	YES: if at least one prescription has been completed NO: if no prescriptions have been completed
Age (years)	= (date of randomisation – date of birth)/365.25
Protocol deviation 1 – patient received the alternative drug to that allocated on at least one occasion	YES: if a bottle on any prescription does not match their treatment allocation NO: if all bottles on all prescriptions match their treatment allocation MISSING: otherwise
Protocol deviation 2 – patient did not meet eligibility criteria but was treated in the study	YES: if patient was ineligible at screening visit or at post-consent visit but was randomised NO: if patient was eligible MISSING: otherwise Note: if a patient who was otherwise eligible was ineligible due to an allergy to fluorescein or indocyanine green, a decision was made by the chief investigator to include them in the study, allowing them to take part in all aspects except for the FFA or ICGA imaging. These patients will not be classed as a protocol deviation.
Protocol deviation 3 – missed visit	YES: if patient attended visit = NO for any of the study visits before study exit) NO: if patient attended visit = YES for all study visits (before study exit) MISSING: otherwise

Protocol deviation 4 – visit attended but outside of study window	YES: if any visit attended falls outside the visit window NO: if all attended visits are within the visit windows MISSING: otherwise Visit windows: 1 week and restarting one week (+/- 1 day) 4 weeks and restarting four weeks (+/- 5 days) All other follow-up visits (+/- 10 days) Note: all visit windows are calculated from the date of randomisation, except re-starting visits which are calculated from the date the patient was informed to restart treatment
Protocol deviation 5 – patient potassium exceeded 5.0mmol/L but patient was informed to continue treatment	YES: if patients potassium level was > 5.0mmol/L at any visit AND patient informed to continue treatment = YES NO: if patients potassium level was > 5.0mmol/L at any visit AND patient informed to continue treatment = NO OR patient potassium level ≤ 5.0mmol/L at all visits MISSING: otherwise
Protocol deviation 6 – incorrect dosage regimen followed	YES: if for any attended visit where the patient remained on the study treatment, the incorrect dose was prescribed. NO: if for all attended visits where the patient remained on the study treatment, the correct dose was prescribed. Correct dosage regimen: patient prescribed 25mg/day of treatment at baseline visit which is increased to 50mg/day after 1 week if the patients potassium level ≤ 5.0mmol/L. Patient continues on 50mg/day until there is evidence of complete resolution of SRF. If a patient restarts treatment during the study, the same dose escalation procedure will be followed i.e. patients will restart on 25mg/day increased to 50mg/day after 1 week.
Protocol deviation 7 – patient prescribed more bottles than required at study visit	YES: if either: • Patient prescribed more than one bottle at baseline visit, 1 week visit or restarting visit • Patient prescribed more than two bottles at 4 week visit or restarting week 4 visit • Patient prescribed more than three bottles at 3 month, 6 month or 9 month visit NO: if patient prescribed correct number of bottles at all study visits where treatment is continuing
Protocol deviation 8 – patients disease resolved but informed to continue treatment	YES: if at any study visit CSCR resolved = YES AND informed to continue treatment = YES NO: if either: • if CSCR resolved = NO at all attended study visits • if CSCR resolved = YES at any study visit AND informed to continue treatment = NO MISSING: otherwise
Systolic blood pressure (SBP)	= SBP at screening visit if potassium results were back on day of screening visit = SBP at baseline visit if potassium results were not back on day of screening visit

Diastolic blood pressure (DBP)	= DBP at screening visit if potassium results were back on day of screening visit = DBP at baseline visit if potassium results were not back on day of screening visit
Heart rate	= heart rate at screening visit if potassium results were back on day of screening visit = heart rate at baseline visit if potassium results were not back on day of screening visit
Study eye / non-study eye variables	For variables that are measured in right eye and left eye but are to be reported for study eye and non-study eye: STUDY EYE: If study eye = right eye then study eye variable = right eye measurement. Otherwise, if study eye = left eye then study eye variable = left eye measurement. NON-STUDY EYE: If study eye = right eye then non-study eye variable = left eye measurement. Otherwise, if study eye = left eye then non-study eye variable = right eye measurement.
Number of pills taken during time period	= (Total number of pills prescribed during time period) – (Total number of pills returned in prescribed bottles collected on IMP database) Note: if a bottle is confirmed as lost then it will be assumed that there were no pills remaining in the bottle
Number of pills expected to be taken during time period	= (Date of next study visit) – (Date patient informed to start/continue treatment after current study visit) If date patient informed to start/continue treatment is missing, then date of prescription will be used
Adherence for time period (for patients who received a prescription)	YES: if (number of pills taken during time period / number of pills expected to be taken during time period) *100 > 70 NO: if (number of pills taken during time period / number of pills expected to be taken during time period) *100 ≤ 70 MISSING: otherwise
Triiodothyronine (nmol/L)	Some triiodothyronine measurements have been recorded in pmol/L instead of nmol/L. To convert pmol/L to nmol/L: Triiodothyronine (nmol/L) = triiodothyronine (pmol/L) * 1000
Ta - Treatment and adherence indicator (for each post-randomisation study visit)	= 1 if prescribed treatment in previous period and took >70% of pills expected = 0 otherwise
Tna - Treatment and non-adherence indicator (for each post-randomisation study visit)	= 1 if prescribed treatment in previous period and did not take >70% of pills expected = 0 otherwise
NTres – No treatment as resolved indicator (for each post-randomisation study visit)	= 1 if at any point in previous period patient not on treatment as disease had resolved = 0 otherwise
NToth – No treatment other reason indicator (for each post-randomisation study visit)	= 1 if at any point in previous period patient not on treatment for any reason other than disease resolution = 0 otherwise
Presence of granular/confluent hypoautofluorescence in the macula	Recorded directly as yes/no (SE_AF_GranularHypoAF) so no derivation required

5. STATISTICAL ANALYSES

5.1 Baseline data

Baseline data (i.e. patient demography and past history) will be described by treatment group for patients in the analysis population. **Table T3** will be used as a template for this.

Continuous variables will be summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number and percentage. The summary statistic headings given in **Table T3** are those we expect to use based on a-priori knowledge of the clinical measurements gained from previous studies. However, if distributional assumptions are not valid, changes will be made.

Any imbalances in the characteristics of the patients at the start of the study will be described but statistical tests for baseline imbalance will not be carried out.

5.2 Additional descriptive data

Additional tables describing compliance, additional treatments, exposure to steroids, ocular examinations and results of tests performed throughout follow-up, by treatment group will be included (e.g. Tables T4-T15). The choice of summary statistics will be as for the baseline data. These data will only be described; no formal comparisons will be made.

5.3 Primary and secondary outcome data

Primary and secondary outcome data will be described by treatment group for patients in the analysis population. The choice of summary statistics will be as for the baseline data. Treatment effects will be reported graphically with 95% confidence intervals (CIs), and with numerical details alongside (cf. Forest plot). **Figures F3 to F5** will be used as templates for this.

5.3.1 Adjustment in models

The intention is to adjust all models for the stratification factors included in the randomisation: visual acuity level (low [54-67 ETDRS BCVA score] and high [68-85 ETDRS BCVA score]) as a fixed effect and centre as a random effect. If it is not possible to estimate a random effect for each centre due to small numbers of patients at some centres, these centres will be combined (e.g. centres with 1 or 2 patients will be grouped into one and centres with 3 or 4 patients will be grouped). If it is still not possible to estimate random effects for each of the (combined) centres, further groupings will be explored.

For continuous outcomes that are measured before the treatment has started at baseline as well as subsequently (e.g. BCVA); subsequent values will be modelled and the baseline value will be modelled as a covariate.

5.3.2 Analysis models

All outcomes listed in the study protocol will be presented as per the template tables **Table T14** to **T18.** General methods of presentation and assessing treatment effects are outlined below. For all treatment comparisons, the placebo with usual care group will be the reference group. Details specific to each outcome are described as appropriate.

Each outcome will be considered under a certain data type, as outlined in the table below:

Date type	Outcomes
Binary	Proportion of patients with macular atrophy of the RPE Proportion of patients with reduced choroidal permeability
Continuous	Sub-retinal fluid thickness Area of macular RPE hypoautofluorescence Patient-reported visual function (VFQ-25) Choroidal thickness
Time to event	Time to resolution of SRF Time to disease recurrence Time to complete or partial resolution Incidence of CSCR in fellow eye
Longitudinal	BCVA (primary) Low luminance BCVA CSRT
Descriptive	Systemic and ocular adverse events Classification of all study eyes as complete, partial or no resolution of SRF Classification of all study eyes by each FFA phenotype

Each type of data will be summarised and compared between the groups according to the following:

- **Binary outcomes** will be presented as numbers and percentages of patients in each treatment group experiencing the outcome at 12 months. Outcomes will be compared between treatment groups using logistic regression, with treatment comparison estimates presented as adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the outcome (with at least one event in each treatment group).
- **Continuous outcomes measured 12 months only (with or without baseline values)** will be summarised by the mean change and SD in each treatment group if distributions are approximately normal, or the median and IQR if data are non-normal. In patient-reported visual function, mean and SD at 12 months will be summarised and models adjusted for baseline. Outcomes will be compared using linear regression. For untransformed data treatment comparisons will be presented as adjusted differences in means with 95% CI, and for logarithmically transformed data as adjusted geometric mean ratios (GMRs) with 95% CI.
- **Time to event outcomes** will be summarised by the median and IQR in each treatment group, estimated from Kaplan Meier curves. Outcomes will be compared using proportional hazards parametric survival models for interval-censored data. If the assumption of proportional hazards does not hold, other methods will be considered as appropriate. The choice of model used will depend on the outcome event and model assumptions. Treatment comparisons will be presented as hazard ratios (HRs) and 95% CI if a proportional hazards model is used, time ratios (TRs) and 95% CI if an accelerated failure time model is used, or odds ratios (OR) and 95% CI if a discrete time proportional odds model is used. Times will be censored using censoring variables defined below:

Outcome	Censor variable
Time to resolution of SRF	Date of last visit, if SRF did not resolve
Time to disease recurrence	Date of last visit, if SRF did not recur
Time to response (complete or partial)	Date of last visit, if disease did not resolve completely or partially
Time to incidence of CSCR in fellow eye	Date of last visit, if CSCR not present in fellow eye at any point by the end of follow-up

- **Continuous longitudinal outcomes** will be summarised as means and SDs (or medians and IQRs if distributions are skewed) at each time point. Outcomes will be compared using linear mixed effects methodology where the outcome of interest is collected at baseline, 4 weeks, 3, 6, 9 and 12 months, with the treatment group and study design variables fitted as per section 5.2.1, and patient terms fitted as random effects. Separate parameter estimates will be incorporated into models for 1) the mean baseline response across both treatment groups and 2) at each post-intervention time point for each treatment (i.e. saturated model with time fitted as a categorical variable). If the time x treatment interaction (post-intervention) is not statistically significant at the 5% level an overall treatment effect will be reported. If the interaction is statistically significant the changes in treatment effect with time will be described. Different variance/covariance structures will be explored, and the structure that provides the best fit in terms of information criteria such as AIC, BIC and likelihood ratio tests will be used. Treatment comparisons will be presented as adjusted differences in means with 95% CI.
- **Descriptive outcomes** will be described using the mean and SD, the median and IQR (if data are non-normal) or numbers and percentages, by group and overall.

5.3.3 Statistical significance

For hypothesis tests two-tailed p-values<0.05 are considered statistically significant. Likelihood ratio tests will be used in preference to Wald tests for hypothesis testing.

5.3.4 Model assumptions

For all methods outlined underlying assumptions will be checked using standard methods, e.g. residual plots, tests for proportional hazards, etc. If assumptions are not valid then alternative methods of analysis will be sought.

5.3.5 Subgroup analyses

There are no planned subgroup analyses defined in the study protocol.

5.3.6 Exploratory analyses

An exploratory analysis to assess the effect of adherence and treatment on the primary outcome, BCVA will be performed.

Four indicators will be generated for each post-randomisation time point at which the primary outcome was assessed:

1. Patient on treatment and adhered
2. Patient on treatment and did not adhere
3. Patient not on treatment due to disease resolution
4. Patient not on treatment for any other reason

The proportion of time spent in each of the respective categories during the previous period will be calculated (e.g. 25% of period on treatment and adhered and 75% not on treatment due to disease resolution, would be coded as 0.25 for indicator 1 and 0.75 for indicator 3) as indicators of adherence. If possible, interactions between treatment group and each of these indicators will be added to the model and indicator status-specific effects will be estimated for each treatment group. If preliminary analyses suggest that some parameters cannot be estimated reliably a simpler model will be sought (e.g. fitting indicators of treatment and adherence, but not proportion of time on treatment etc.).

Additional exploratory analyses of the overall trial cohort will assess the association between:

(a) Age of the patient at randomisation and visual acuity;

(b) Presence of granular/confluent hypoautofluorescence in the macula at randomisation and final visual acuity

The analyses will be adjusted for treatment group.

5.3.7 Sensitivity analyses

There are no planned sensitivity analyses defined in the study protocol. In the exploratory analysis assessing adherence, when calculating adherence, the assumption will be made that if a bottle is confirmed as lost, there were no pills remaining in the bottle. A sensitivity analysis on this exploratory analysis will be carried out by imputing the number of pills remaining in bottles that are confirmed as lost.

A sensitivity analysis for binary outcomes measured at 12 months will be performed if there is differential drop-out between treatment groups. Note this analysis was not pre-specified in the protocol. This will be performed by: (a) assuming missing values = no, and (b) assuming missing values = yes.

An initial review of baseline data found imbalances between treatment groups in some prognostic factors. For analyses of outcomes which have a baseline measure, this imbalance will be taken into account. For other outcomes (e.g. time to event outcomes) no adjustment for baseline was planned; for these outcomes a post-hoc analysis will be performed adjusting for factor(s) imbalanced at baseline.

5.3.8 Missing data

In all tables missing data will be indicated by footnotes. If the amount of missing data differs substantially between treatment groups potential reasons will be explored.

Missing predictors:

There will be no missing data for any of the randomisation factors (by design). All other potential predictors are baseline measurements of continuous longitudinal outcomes, and due to the modelling approach described previously the handling of missing values for such data is considered in the context of missing longitudinal data (see below).

Missing outcomes measured at one time point:

- If the proportion of missing data is less than 5% then complete case analysis will be performed (i.e. excluding cases with missing data).

- If the proportion of missing data is above 5% multiple imputation methods will be considered. A general imputation model that uses an iterative procedure to generate imputed values will be used to generate multiple complete data sets (e.g. using Stata's mi impute). The model of interest will be the fitted to each of the complete data sets and effect estimates combined using Rubin's rules. If appropriate, methods such as predictive mean matching will be used in order to ensure that imputed values lie within specific ranges.

Missing longitudinal data:

- For continuous data measured at multiple time points baseline values will be modelled jointly with those measured during follow-up, as described previously, thereby allowing all cases with at least one observation to be included. If the proportion of cases that do not have at least one observation is above 5% then multiple imputation methods will be considered (see above). If appropriate (the level of missingness is >20%) then any variables that are predictive of missingness will be identified, and if there is reason to suggest that an assumption of missing at random (MAR) given these variables is reasonable (especially likely if the variable was measured at baseline) then such variables will be adjusted for in the models of interest. These models can be shown to provide unbiased estimates of the treatment effect and moreover multiple imputation approaches would not be expected to recover any additional information.

5.3.9 Multiple testing

No formal adjustment will be made for multiple testing. However as previously described formal statistical comparisons will not be made for outcomes with low event rates and only pre-specified subgroup analyses will be performed. Consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different outcomes.

5.4 Safety data

Adverse events (AEs) occurring in the study period for all patients in the safety population will be tabulated as per **Table T19 to T21**.

Table T19 summarises expected AEs listed in the study protocol, with events that meet the serious criteria[1] indicated. Such events are captured via the study CRFs.

Table T20 provides further details on the expected AEs that meet the serious criteria.

Table T21 summarises unexpected serious adverse events (SAEs), i.e. events that are not listed in the study protocol that meet the serious criteria. Such events are captured via separate SAE report forms.

No formal comparisons between treatment groups will be made, as numbers of events are expected to be small.

[1] An event is classified as serious if it meets one or more of the following criteria: a) resulted in death, b) was life threatening, c) resulted in persistent or significant disability/incapacity, d) prolonged an ongoing hospitalisation or resulted in hospitalisation

6. BIBLIOGRAPHY

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7. AMENDMENTS TO THE SAP

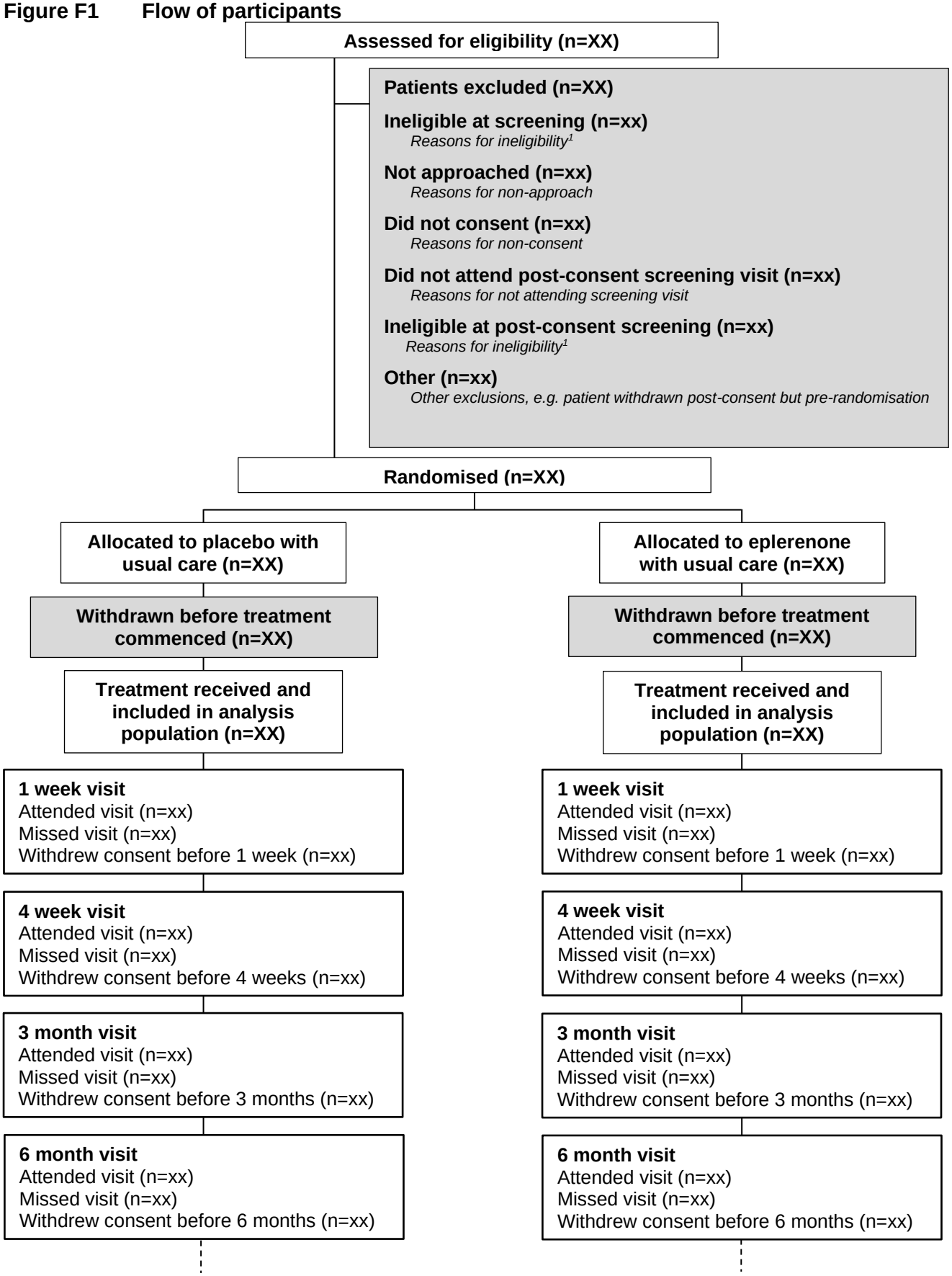
Previous version	Previous date	New version	New date	Brief summary of changes
1.0	29/03/2019	2.0	16/05/2019	Post-hoc additions after initial review of data: Choroidal thickness moved from longitudinal outcome to continuous as this was not graded at interim visits as previously thought. Choroidal thickness and SRF thickness removed from 'Differences in visual acuity and OCT features at baseline and at time of disease recurrence' table as this data was not graded at all visits. Some sites have a very small number of patients. Sentence added to 'adjustment in models' section to state if it is not possible to fit centre as a random effect, centres with a small number of patients will be combined. Some prognostic factors were found to be imbalanced between treatment groups. For time to event outcomes, where no adjustment for baseline was pre-specified, a post-hoc analysis will be performed adjusting for the imbalanced baseline prognostic factor(s).

APPENDIX A: SKELETON TABLES AND FIGURES

The following summarises the planned outputs:

Section	Outputs	
Section 1 Population	**Tables, figures and listings detailing the study population**	
	Figure F1	Flow of participants
	Figure F2	Predicted and actual recruitment
	Table T1	Protocol deviations
	Table T2	Withdrawals
Section 2 Baseline data	**Summary tables of demographic information**	
	Table T3	Patient demography and past history
Section 3 Additional descriptive information	**Summary tables of additional descriptive information**	
	Table T4	1 week visit data
	Table T5	4 week visit data
	Table T6	3 month visit data
	Table T7	6 month visit data
	Table T8	9 month visit data
	Table T9	12 month visit data
	Table T10	Study intervention
	Table T11	OCT angiography
	Table T12	Additional treatments as usual care
	Figure F3	Potassium levels over time
	Table T13	Adherence to study treatment
	Table T14	Unblinding
	Table T15	Differences in visual acuity and OCT features at baseline and at time of disease recurrence
Section 4 Primary and secondary outcome data	**Summary data and treatment estimates for primary and secondary outcomes**	
	Table T16	Primary outcome
	Figure F4	Change in BCVA over time
	Table T17	Secondary outcomes
	Table T18	Longitudinal secondary outcomes
	Table T19	VFQ-25 total and subscale scores
	Figure F5	Secondary outcomes
	Figure F6	Change in low luminance VA over time
	Figure F7	Change in CSRT over time
	Table T20	Descriptive secondary outcomes
	Figure F8	Exploratory analyses of trial cohort
	Table T21	Adverse events and serious adverse events
	Table T22	Details of expected serious adverse events
	Table T23	Details of unexpected serious adverse events
	Table T24	Exploratory analysis of primary outcome, BCVA
	Table T25	Adherence to study treatment by prescription (imputed)
	Table T26	Sensitivity analysis of exploratory analysis

Figure F1 Flow of participants



9 month visit
Attended visit (n=xx)
Missed visit (n=xx)
Withdrew consent before 9 months (n=xx)

12 month visit
Attended visit (n=xx)
Missed visit (n=xx)
Withdrew consent before 12 months (n=xx)

9 month visit
Attended visit (n=xx)
Missed visit (n=xx)
Withdrew consent before 9 months (n=xx)

12 month visit
Attended visit (n=xx)
Missed visit (n=xx)
Withdrew consent before 12 months (n=xx)

Notes:
[1] Some patients may be ineligible for more than one reason

Figure F2 Predicted and actual recruitment

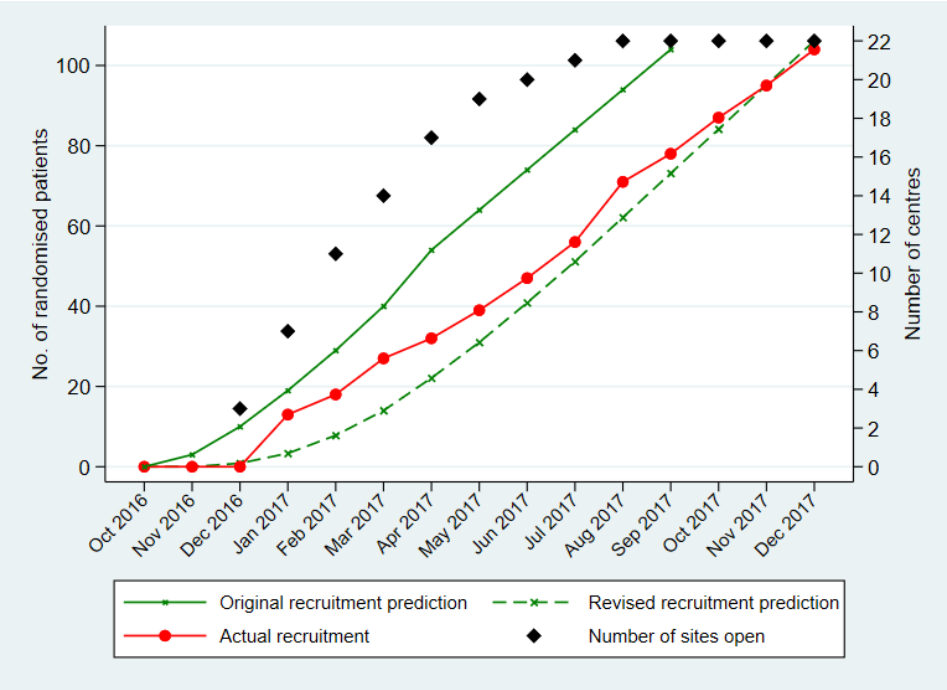


Table T1 Protocol deviations

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Any protocol deviation			
Patient did not receive allocated drug			
Patient ineligible but randomised			
Missed visit			
Visit attended but outside visit window			
Potassium > 5.0 mmol/L but patient informed to continue treatment			
Incorrect dosage regimen followed			

Patient prescribed more medication than required at any study visit	
Disease resolved but patient informed to continue treatment	

Notes:
Data are presented as n (%).

Table T2 Withdrawals

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Any withdrawal			
Timing of withdrawal			
Post-consent pre-randomisation			
Post-randomisation but before treatment			
After start of treatment			
Reason for withdrawal			
Clinician's advice			
SAE (including pregnancy)			
Other*			
Patient's decision			
Too ill to attend			
Unhappy with study procedures			
Unwilling to give a reason			
Wants standard NHS treatment			
Other			
Patient died			
Willing to participate in follow-up?			

Notes:
Data are presented as n (%).
Other clinical reasons will be provided in footnotes

Table T3 Patient demography and past history

		Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Non-ocular history				
Age at randomisation (years)				
Male				
Ethnicity	White			
	Black			
	Asian			
	Chinese			
	Mixed			

	Other
Systolic blood pressure (mmHg)	
Diastolic blood pressure (mmHg)	
Heart rate (bpm)	
TSH/Thyrotropin (mlU/L)	
Thyroxine (pmol/L)	
Triiodothyronine (nmol/L)	
HbA1c (mmol/mol)	
Haematocrit (Hct) (L/L)	
Platelets ($x10^9$ /L)	
WBC ($x10^9$ /L)	
Serum creatinine (µmol/L)	
Urea (mmol/L)	
Potassium (mmol/L)	
Sodium (mmol/L)	
Chloride (mmol/L)	
Bicarbonate (mmol/L)	
eGFR (ml/min)	
Bilirubin (µmol/L)	
ALT (units/L)	
Albumin (g/L)	
Protein (g/L)	
Smoking	Current
	Ex
	Never
Heart failure	
Myocardial infarction	
History of angina	
CCS class	No angina
	I
	II
	III
	IV
NYHA class	I
	II
	III
	IV
Transient ischemic attack	
Stroke	
DVT	
PE	
Claudication	
Diabetes	None
	Diet
	Oral

	Non-insulin injections	
	Insulin	
Ocular history		
VA score	Low (54-67)	
	High (68-85)	
CSCR duration (months)		
Family history of CSCR		
Pupils abnormal^		
Cornea abnormal^		
Anterior chamber cells present		
Anterior chamber flare present		
IOP measurement (mmHg)		
Lens status	Phakic	
	Pseudophakic	
	Aphakic	
Nuclear sclerosis (NUC)*	Grade NUC-0	
	Grade NUC-1	
	Grade NUC-2	
	Grade NUC-3	
	Grade NUC-9	
Cortical (COR)*	Grade COR-0	
	Grade COR-1	
	Grade COR-2	
	Grade COR-3	
	Grade COR-9	
Central Optical Involvement (CEN)*		
Posterior subcapsular (PSC)*	Grade PSC-0	
	Grade PSC-1	
	Grade PSC-2	
	Grade PSC-3	
	Grade PSC-9	
Macula abnormal^		
Peripheries abnormal ^		
Disc abnormal^		
Cup disc ratio		
Cataract surgery		

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).
** Only completed if lens status was phakic*
^ Details of any abnormal clinical findings will be provided in footnotes

Table T4 1 week visit data

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Blood sample taken			
Serum creatinine (µmol/L)			
Urea (mmol/L)			
Sodium (mmol/L)			
Chloride (mmol/L)			
Bicarbonate (mmol/L)			
Systolic blood pressure (mmHg)			
Diastolic blood pressure (mmHg)			
Heart rate (bpm)			
Rifampicin, finasteride or melatonin taken			
Exposed to steroids			
Oral			
Inhalation			
Intramuscular injection			
Topical cream			
Other			

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).

Table T5 4 week visit data

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Blood tests and cardiac measures			
Blood sample taken			
Serum creatinine (µmol/L)			
Urea (mmol/L)			
Sodium (mmol/L)			
Chloride (mmol/L)			
Bicarbonate (mmol/L)			
Systolic blood pressure (mmHg)			
Diastolic blood pressure (mmHg)			
Heart rate (bpm)			
Changes in medication			
Taken rifampicin, finasteride or melatonin			
Exposure to steroids			
Exposed to steroids			
Oral			
Inhalation			
Intramuscular injection			
Topical cream			
Other			
Ocular exam			

Anterior segment: clinical findings changed from previous visit?		
Pupils abnormal^		
Cornea abnormal^		
Anterior chamber cells present		
Anterior chamber flare present		
IOP measurement (mmHg)		
Lens status	Phakic	
	Pseudophakic	
	Aphakic	
Nuclear sclerosis (NUC)*	Grade NUC-0	
	Grade NUC-1	
	Grade NUC-2	
	Grade NUC-3	
	Grade NUC-9	
Cortical (COR)*	Grade COR-0	
	Grade COR-1	
	Grade COR-2	
	Grade COR-3	
	Grade COR-9	
Central Optical Involvement (CEN)*		
Posterior subcapsular (PSC)*	Grade PSC-0	
	Grade PSC-1	
	Grade PSC-2	
	Grade PSC-3	
	Grade PSC-9	
Posterior segment: clinical findings changed from previous visit		
Macula abnormal^		
Peripheries abnormal ^		
Disc abnormal^		
Cup disc ratio		

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).
** Only completed if lens status was phakic*
^ Details of any abnormal clinical findings will be provided in footnotes

Table T6 3 month visit data

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Blood tests and cardiac measures			
Blood sample taken			
Serum creatinine (µmol/L)			
Urea (mmol/L)			
Sodium (mmol/L)			
Chloride (mmol/L)			
Bicarbonate (mmol/L)			

Systolic blood pressure (mmHg)		
Diastolic blood pressure (mmHg)		
Heart rate (bpm)		
Changes in medication		
Taken rifampicin, finasteride or melatonin		
Exposure to steroids		
Exposed to steroids		
Oral		
Inhalation		
Intramuscular injection		
Topical cream		
Other		
Ocular exam		
Anterior segment: clinical findings changed from previous visit?		
Pupils abnormal^		
Cornea abnormal^		
Anterior chamber cells present		
Anterior chamber flare present		
IOP measurement (mmHg)		
Lens status	Phakic	
	Pseudophakic	
	Aphakic	
Nuclear sclerosis (NUC)*	Grade NUC-0	
	Grade NUC-1	
	Grade NUC-2	
	Grade NUC-3	
	Grade NUC-9	
Cortical (COR)*	Grade COR-0	
	Grade COR-1	
	Grade COR-2	
	Grade COR-3	
	Grade COR-9	
Central Optical Involvement (CEN)*		
Posterior subcapsular (PSC)*	Grade PSC-0	
	Grade PSC-1	
	Grade PSC-2	
	Grade PSC-3	
	Grade PSC-9	
Posterior segment: clinical findings changed from previous visit		
Macula abnormal^		
Peripheries abnormal ^		
Disc abnormal^		
Cup disc ratio		

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).
** Only completed if lens status was phakic*
^ Details of any abnormal clinical findings will be provided in footnotes

Table T7 6 month visit data

		Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Blood tests and cardiac measures				
Blood sample taken				
Serum creatinine (µmol/L)				
Urea (mmol/L)				
Sodium (mmol/L)				
Chloride (mmol/L)				
Bicarbonate (mmol/L)				
Systolic blood pressure (mmHg)				
Diastolic blood pressure (mmHg)				
Heart rate (bpm)				
Changes in medication				
Taken rifampicin, finasteride or melatonin				
Exposure to steroids				
Exposed to steroids				
Oral				
Inhalation				
Intramuscular injection				
Topical cream				
Other				
Ocular exam				
Anterior segment: clinical findings changed from previous visit?				
Pupils abnormal^				
Cornea abnormal^				
Anterior chamber cells present				
Anterior chamber flare present				
IOP measurement (mmHg)				
Lens status	Phakic			
	Pseudophakic			
	Aphakic			
Nuclear sclerosis (NUC)*	Grade NUC-0			
	Grade NUC-1			
	Grade NUC-2			
	Grade NUC-3			
	Grade NUC-9			
Cortical (COR)*	Grade COR-0			
	Grade COR-1			
	Grade COR-2			
	Grade COR-3			

	Grade COR-9
Central Optical Involvement (CEN)*	
Posterior subcapsular (PSC)*	Grade PSC-0
	Grade PSC-1
	Grade PSC-2
	Grade PSC-3
	Grade PSC-9
Posterior segment: clinical findings changed from previous visit	
Macula abnormal^	
Peripheries abnormal ^	
Disc abnormal^	
Cup disc ratio	

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).
** Only completed if lens status was phakic*
^ Details of any abnormal clinical findings will be provided in footnotes

Table T8 9 month visit data

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Blood tests and cardiac measures			
Blood sample taken			
Serum creatinine (µmol/L)			
Urea (mmol/L)			
Sodium (mmol/L)			
Chloride (mmol/L)			
Bicarbonate (mmol/L)			
Systolic blood pressure (mmHg)			
Diastolic blood pressure (mmHg)			
Heart rate (bpm)			
Changes in medication			
Taken rifampicin, finasteride or melatonin			
Exposure to steroids			
Exposed to steroids			
Oral			
Inhalation			
Intramuscular injection			
Topical cream			
Other			
Ocular exam			
Anterior segment: clinical findings changed from previous visit?			
Pupils abnormal^			
Cornea abnormal^			
Anterior chamber cells present			
Anterior chamber flare present			

IOP measurement (mmHg)		
Lens status	Phakic	
	Pseudophakic	
	Aphakic	
Nuclear sclerosis (NUC)*	Grade NUC-0	
	Grade NUC-1	
	Grade NUC-2	
	Grade NUC-3	
	Grade NUC-9	
Cortical (COR)*	Grade COR-0	
	Grade COR-1	
	Grade COR-2	
	Grade COR-3	
	Grade COR-9	
Central Optical Involvement (CEN)*		
Posterior subcapsular (PSC)*	Grade PSC-0	
	Grade PSC-1	
	Grade PSC-2	
	Grade PSC-3	
	Grade PSC-9	
Posterior segment: clinical findings changed from previous visit		
Macula abnormal^		
Peripheries abnormal ^		
Disc abnormal^		
Cup disc ratio		

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).
** Only completed if lens status was phakic*
^ Details of any abnormal clinical findings will be provided in footnotes

Table T9 12 month visit data

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Cardiac measures			
Systolic blood pressure (mmHg)			
Diastolic blood pressure (mmHg)			
Heart rate (bpm)			
Thyroid function tests			
Blood sample taken			
TSH/Thyrotropin (mlU/L)			
Thyroxine (pmol/L)			
Triiodothyronine (nmol/L)			
Full blood count and renal profile			
Blood sample taken			
HbA1c (mmol/mol)			
Haematocrit (Hct) (L/L)			

Platelets (x10^9 /L)	
WBC (x10^9 /L)	
Serum creatinine (µmol/L)	
Urea (mmol/L)	
Potassium (mmol/L)	
Sodium (mmol/L)	
Chloride (mmol/L)	
Bicarbonate (mmol/L)	
Liver function tests	
Blood sample taken	
Bilirubin (µmol/L)	
ALT (units/L)	
Albumin (g/L)	
Total protein (g/L)	
Changes in medication	
Taken rifampicin, finasteride or melatonin	
Exposure to steroids	
Exposed to steroids	
Oral	
Inhalation	
Intramuscular injection	
Topical cream	
Other	
Ocular exam	
Anterior segment: clinical findings changed from previous visit?	
Pupils abnormal^	
Cornea abnormal^	
Anterior chamber cells present	
Anterior chamber flare present	
IOP measurement (mmHg)	
Lens status	Phakic
	Pseudophakic
	Aphakic
Nuclear sclerosis (NUC)*	Grade NUC-0
	Grade NUC-1
	Grade NUC-2
	Grade NUC-3
	Grade NUC-9
Cortical (COR)*	Grade COR-0
	Grade COR-1
	Grade COR-2
	Grade COR-3
	Grade COR-9
Central Optical Involvement (CEN)*	
	Grade PSC-0

Posterior subcapsular (PSC)*	Grade PSC-1
	Grade PSC-2
	Grade PSC-3
	Grade PSC-9
Posterior segment: clinical findings changed from previous visit	
Macula abnormal^	
Peripheries abnormal ^	
Disc abnormal^	
Cup disc ratio	

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).
** Only completed if lens status was phakic*
^ Details of any abnormal clinical findings will be provided in footnotes

Table T10 Study intervention

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Overall (n=XX)
Duration of treatment (months)			
Discontinued treatment as resolved			
Discontinued treatment for safety reason			
Resumed treatment			
Number of bottles confirmed as lost			

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).

Table T11 OCT angiography

	Centre carried out imaging (n=XX)	Number of patients with imaging (n=XX)
Baseline imaging performed		
12 month imaging performed		
Overall		

Notes:
Data are presented as n (%).

Table T12 Additional treatments as usual care

Additional therapy	Randomised to placebo (n=XX)						Randomised to eplerenone (n=XX)					
	Therapy received		Received in study eye		Received whilst on study IMP		Therapy received		Received in study eye		Received whilst on study IMP	
	Treatments/ patients	%	Treatments /patients	%	Treatments /patients	%	Treatments/ patients	%	Treatments/ patients	%	Treatments/ patients	%
Photodynamic laser therapy												
Thermal laser therapy												
Other therapy[1]												

Notes:
[1] Details of other therapies received will be provided in footnotes

Figure F3 Potassium levels over time (mmol/L)

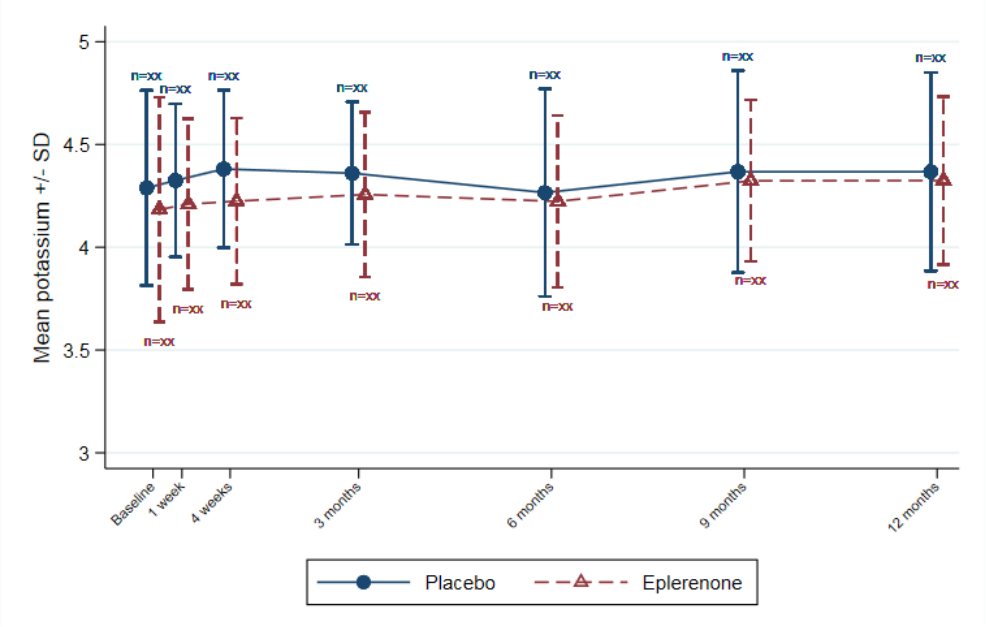


Table T13 Adherence to study treatment by prescription

Prescription	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)
Baseline		
1 week		
4 week		
3 month		
6 month		
9 month		
Restarting		
Restarting 1 week		
Restarting 4 week		

Notes:
Data are presented as n (%).
For bottles confirmed as lost, the assumption was made that no pills were remaining.

Table T14 Unblinding of patients and optometrists

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)
Patient unblinded		
Optometrist unblinded		

Notes:
Data are presented as n (%).

Table T15 Differences in visual acuity and OCT features at baseline and at time of disease recurrence

Feature	Baseline (n=XX)	Recurrence (n=XX)
BCVA		
Central subfield retinal thickness		

Notes:
Data are presented as median (interquartile range), mean (standard deviation) or n (%).

Table T16 Primary outcome

		Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Effect (95% CI)	p-value
BCVA	Baseline				
	4 weeks			MD/GMR	
	3 months			MD/GMR	
	6 months			MD/GMR	
	9 months			MD/GMR	
	12 months			MD/GMR	
Test for treatment*time interaction					
Overall treatment effect estimate				MD/GMR	

Notes:
Data are presented as median (IQR) or mean (SD).
SD=standard deviation, CI=confidence interval, MD=mean difference, GMR=geometric mean ratio

Figure F4 Change in BCVA over time

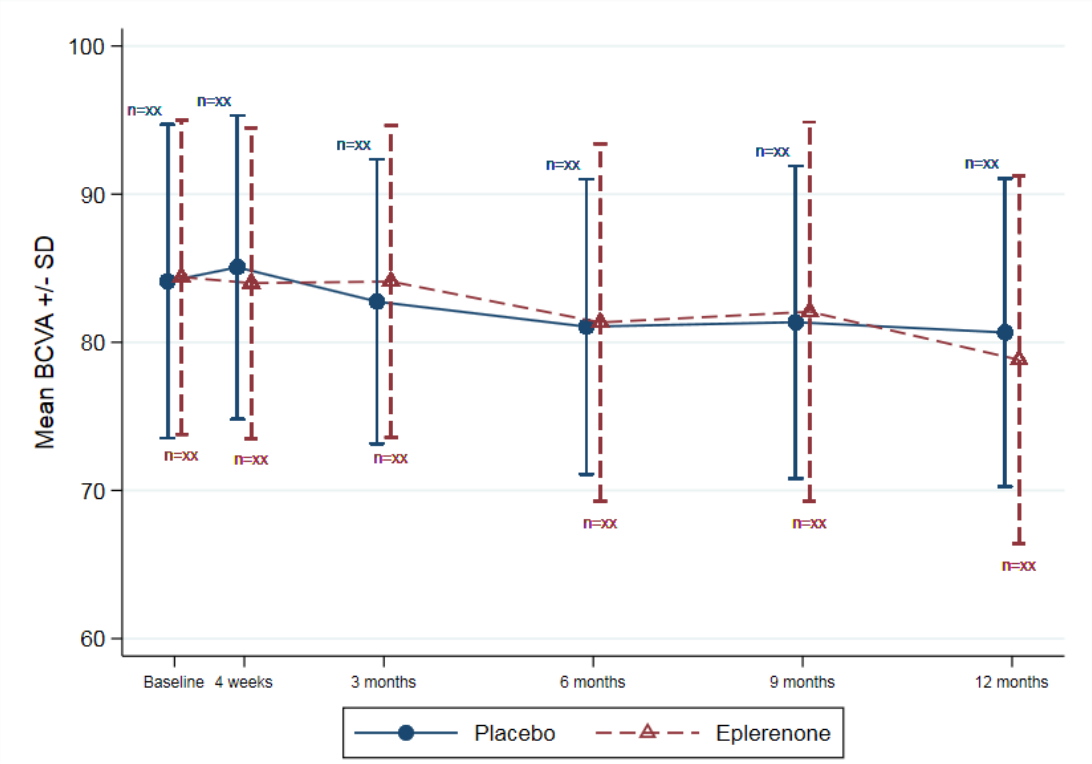


Table T17 Secondary outcomes

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Effect (95% CI)	p-value
Change in maximal sub-retinal fluid thickness				
Sub-retinal fluid thickness – baseline				
Sub-retinal fluid thickness – 12 months			MD/GMR	
Area change in macular RPE hypoautofluorescence				
Area of macular RPE hypoautofluorescence – baseline				
Area of macular RPE hypoautofluorescence – 12 months			MD/GMR	
Choroidal thickness – baseline				
Choroidal thickness – 12 months			MD/GMR	
Proportion of patients with foveal involving macular atrophy of the RPE			OR	
Proportion of patients with reduced choroidal permeability at 12 months			OR	
Any CSCR in fellow eye				
New CSCR in fellow eye			HR/TR/OR	
Resolution of SRF				
Time to resolution of SRF			HR/TR/OR	
Recurrence of SRF				
Time to recurrence of SRF			HR/TR/OR	

Time to complete or partial resolution of sub-foveal SRF	HR/TR/OR
Proportion responded by 3 months	
Proportion responded by 6 months	
Proportion responded by 12 months	

Notes:
Data are presented as median (IQR), mean (SD) or n (%).
CI=confidence interval, MD=mean difference, GMR=geometric mean ratio, OR=odds ratio, HR=hazard ratio, TR=time ratio

Table T18 Secondary outcomes measured at multiple time-points

		Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Effect (95% CI)	p-value
Low luminance BCVA	Baseline				
	4 weeks			MD/GMR	
	3 months			MD/GMR	
	6 months			MD/GMR	
	9 months			MD/GMR	
	12 months			MD/GMR	
Test for treatment*time interaction					
Overall treatment effect estimate				MD/GMR	
CSRT	Baseline				
	4 weeks			MD/GMR	
	3 months			MD/GMR	
	6 months			MD/GMR	
	9 months			MD/GMR	
	12 months			MD/GMR	
Test for treatment*time interaction					
Overall treatment effect estimate				MD/GMR	

Notes:
Data are presented as median (IQR) or mean (SD).
SD=standard deviation, CI=confidence interval, MD=mean difference, GMR=geometric mean ratio.

Table T19 VFQ-25 total and subscale scores

Subscale/Total score	Visit	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Effect (95% CI)	p-value
Total score	Baseline				
	12 months			GMR (95% CI)	
Near vision	Baseline				
	12 months				
Distance vision	Baseline				
	12 months				
General health	Baseline				
	12 months				
General vision	Baseline				
	12 months				
Driving	Baseline				
	12 months				
Peripheral vision	Baseline				
	12 months				
Colour vision	Baseline				
	12 months				
Ocular pain	Baseline				
	12 months				
Vision specific					
Role difficulties	Baseline				
	12 months				
Dependency	Baseline				
	12 months				
Social functioning	Baseline				
	12 months				
Mental health	Baseline				
	12 months				

Notes:
Data are presented as median (IQR) or mean (SD).
SD=standard deviation, CI=confidence interval, GMR=geometric mean ratio

Figure F5 Secondary outcomes

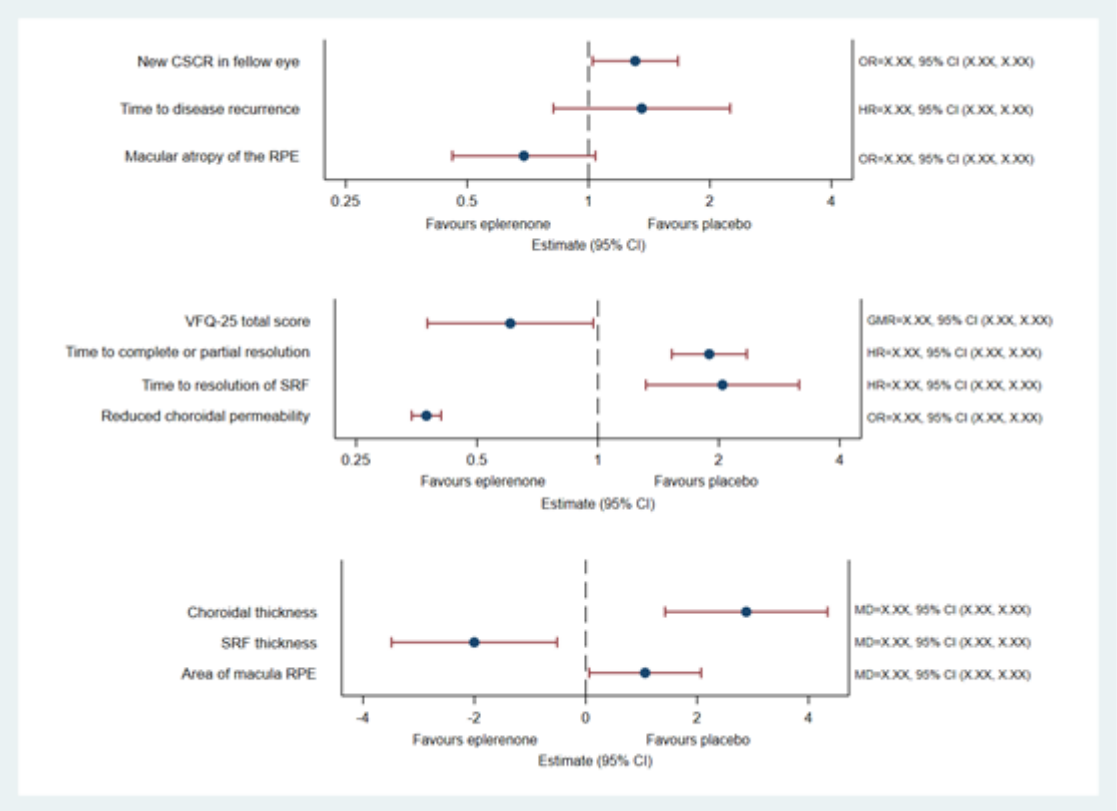


Figure F6 Change in low luminance VA over time

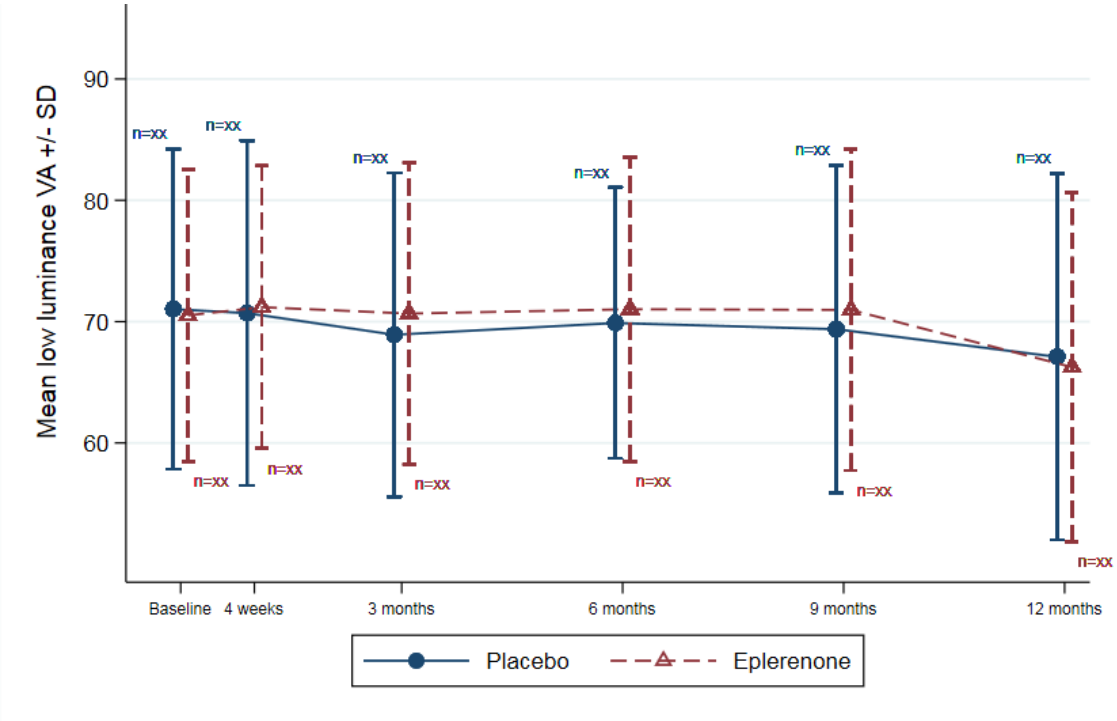
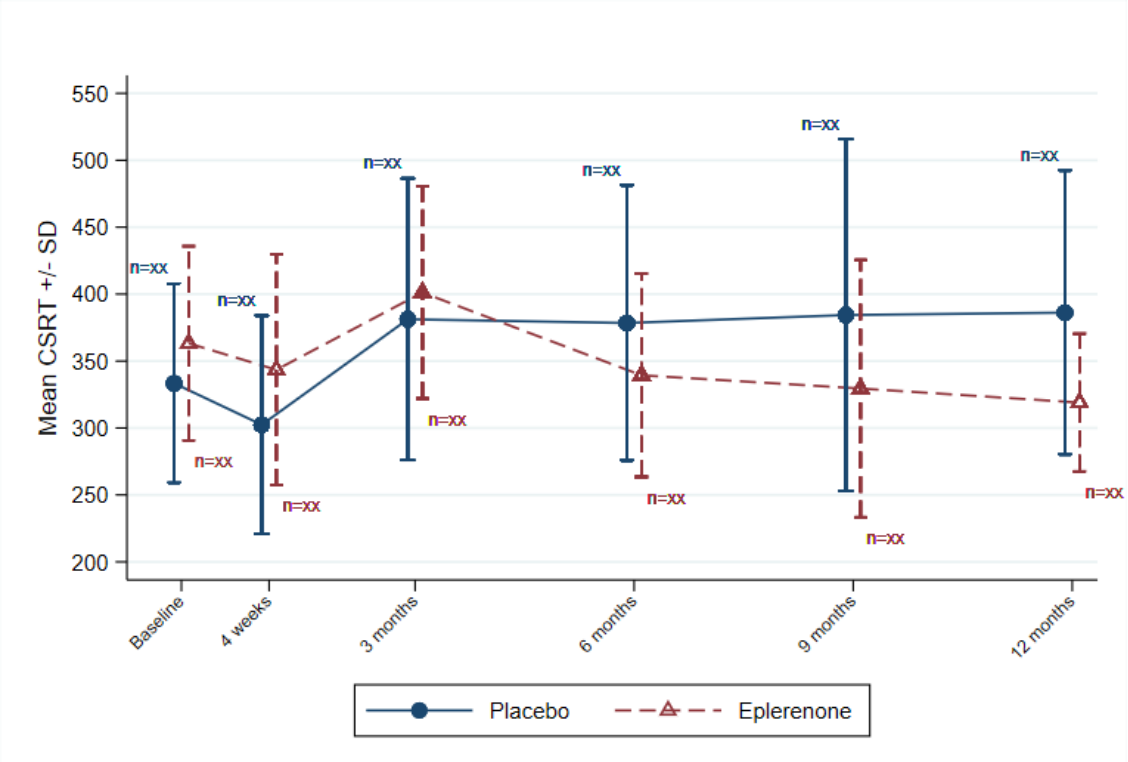


Figure F7 Change in central subfield retinal thickness over time



Notes:
Number of patients on treatment (placebo, eplerenone): X patients on treatment at 4 weeks (x, x); X patients on treatment at 3 months (x, x); X patients on treatment at 6 months (x, x), X patients on treatment at 9 months (x, x); X patients on treatment at 12 months (x, x).

Table T20 Descriptive secondary outcomes

Outcome	Visit		Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)
Study eye FFA phenotype	Baseline	Smoke stack		
		Ink-blot		
		Chronic epitheliopathy		
	12 months	Smoke stack		
		Ink-blot		
		Chronic epitheliopathy		
Resolution of SRF in study eye	4 weeks	Complete resolution		
		Partial resolution		
		No resolution		
	3 months	Complete resolution		
		Partial resolution		
		No resolution		
	6 months	Complete resolution		
		Partial resolution		
		No resolution		
	9 months	Complete resolution		
		Partial resolution		
		No resolution		

	12 months	Complete resolution
		Partial resolution
		No resolution

Notes:
Data are presented as n (%).

Figure F8 Exploratory analyses of overall trial cohort

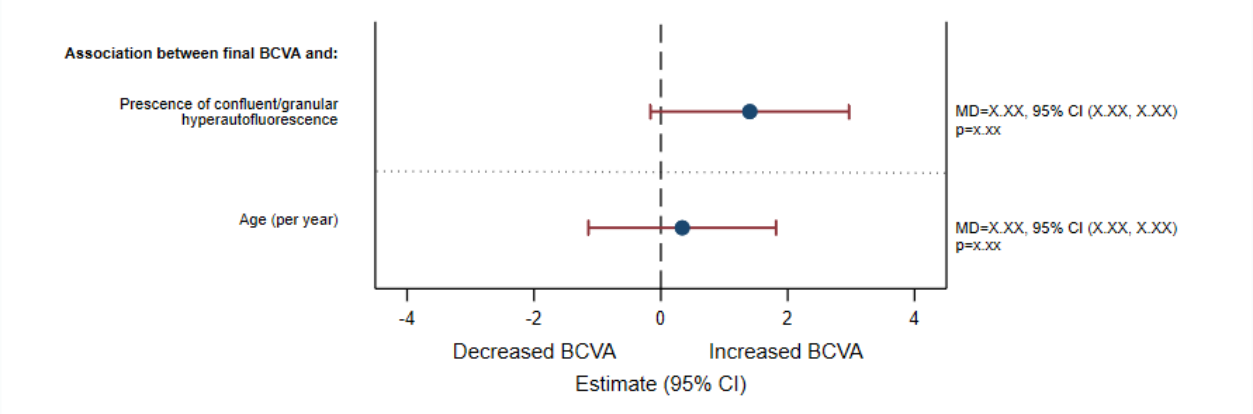


Table T21 Adverse events and serious adverse events

Event (expected or unexpected)	Randomised to placebo (n=XX)				Randomised to eplerenone (n=XX)			
	All events		SAEs		All events		SAEs	
	Events/ patients	%	Events/ patients	%	Events/ patients	%	Events/ patients	%
Study eye events								
Incident choroidal neovascularisation								
Decrease in visual acuity of ≥15 letters								
Other								
Non-study eye events								
Incident choroidal neovascularisation								
Decrease in visual acuity of ≥15 letters								
Other								
Events in both eyes								
Other								
Non-ocular events								
Infections and infestations								
Infection								
Pyelonephritis								
Pharyngitis								
Blood and lymphatic system disorders								
Eosinophilia								

Endocrine disorders
Hypothyroidism
Metabolism and nutrition disorders
Hyperkalaemia
Hyponatraemia
Dehydration
Hypercholesterolaemia
Hypertriglyceridemia
Psychiatric disorders
Insomnia
Nervous system disorders
Dizziness
Syncope
Headache
Hypoesthesia
Cardiac disorders
Myocardial infarction
Left ventricular failure
Atrial fibrillation
Tachycardia
Vascular disorders
Hypotension
Arterial thrombosis limb
Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders
Cough
Gastrointestinal disorders
Diarrhoea
Nausea
Constipation
Vomiting
Flatulence
Skin and subcutaneous tissue disorders
Rash
Pruritus
Hyperhidrosis

Angioedema	
Musculoskeletal and connective tissue disorders	
Muscle spasms	
Musculoskeletal pain	
Back pain	
Renal and urinary disorders	
Renal impairment	
Hepatobiliary disorders	
Cholecystitis	
Reproductive system and breast disorders	
Gynaecomastia	
General disorders and administration site conditions	
Asthenia	
Malaise	
Investigations	
Blood urea increased	
Blood creatinine increase	
Epidermal growth factor receptor decreased	
Blood glucose increased	
Other	
Any event	

Notes:
Any events experienced in patients who were not on treatment will be in documented footnotes

Table T22 Details of expected serious adverse events

Event	Maximum intensity	Relatedness	Group

Table T23 Details of unexpected serious adverse events

Event	Maximum intensity	Relatedness	Group

Table T24 Exploratory analysis of primary outcome assessing association between treatment and adherence

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Effect (95% CI)	p-value for interaction
On treatment and adhered			MD/GMR	
On treatment and did not adhere			MD/GMR	
Not on treatment (disease resolution)			MD/GMR	
Not on treatment (other reason)			MD/GMR	

Notes:
Data are presented as mean (SD) or median (IQR)

Table T25 Adherence to study treatment by prescription (imputed)

Prescription	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)
Baseline		
1 week		
4 week		
3 month		
6 month		
9 month		
Restarting		
Restarting 1 week		
Restarting 4 week		

Notes:
Data are presented as n (%).
For bottles confirmed as lost, multiple imputation was used to impute the number of pills remaining.

Table T26 Sensitivity analysis of exploratory analysis for BCVA, imputing pill count for bottles confirmed as lost

	Randomised to placebo (n=XX)	Randomised to eplerenone (n=XX)	Effect (95% CI)	p-value for interaction
On treatment and adhered			MD/GMR	
On treatment and did not adhere			MD/GMR	
Not on treatment (disease resolution)			MD/GMR	
Not on treatment (other reason)			MD/GMR	

Notes:
Data are presented as mean (SD) or median (IQR)