Clinical trial results:
Clinical efficacy and mechanistic evaluation of Eplerenone for Central serous chorio-retinopathy – the VICI randomised trial.

Summary

EudraCT number	2016-000113-70
Trial protocol	GB
Global end of trial date	03 June 2019

Results information

Result version number	v1 (current)
This version publication date	12 July 2020
First version publication date	12 July 2020

Trial information

Trial identification

Sponsor protocol code	NA

Additional study identifiers

ISRCTN number	ISRCTN92746680
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust
Sponsor organisation address	SGH - Level E, Laboratory and Pathology Block, SCBR - MP 138, Southampton, United Kingdom, SO16 6YD
Public contact	CTEU Bristol, CTEU Bristol, 0117 342 2374, vici-trial@bristol.ac.uk
Scientific contact	CTEU Bristol, CTEU Bristol, 0117 342 2374, vici-trial@bristol.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2019
Global end of trial reached?	Yes
Global end of trial date	03 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether vision following eplerenone therapy alongside usual care is superior to placebo with usual care in eyes with chronic Central serous chorio-retinopathy.

Protection of trial subjects:

All potential participants were sent or given an invitation letter and patient information sheet (PIS) (approved by the local Research Ethics Committee,(REC)) describing the study. The patient had time to read the PIS and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wished. Full informed consent was obtained for every trial participant. The patient's GP was informed of their participation in the trial. All members of the direct healthcare team are contractually bound to abide by standard NHS conditions of confidentiality and the need to access medical records will be explained to each patient during the process of obtaining consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 114
Worldwide total number of subjects	114
EEA total number of subjects	114

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	114
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 223 patients initially eligible, 114 gave written informed consent and were randomised.

Pre-assignment

Screening details:

Between December 2016 and February 2018, 402 patients were screened. During the initial eligibility screening stage 97 patients were found to be ineligible. Eighty-two initially eligible patients were not approached for consent. Of patients who were eligible and given a PIL, 44 declined to consent.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Assessor

Blinding implementation details:

Masking was implemented by over-encapsulation of the eplerenone/placebo to produce identical capsules. Capsules were supplied in bottles with identical labelling except for a unique bottle number. Bottle numbers were assigned against an allocation list. Only personnel at the manufacturing pharmacy and the trial database manager had access to the allocation list for the purposes of producing and managing the IMP.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo with usual care

Arm description:

Placebo tablet, manufactured to match the Eplerenone tablets, with usual care.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Same regimen as for intervention

Arm title	Eplerenone with usual care

Arm description:

Eplerenone 25 mg/day increased to 50 mg/day after 1 week (as per manufacturer’s recommendations for dose initiation) in addition to usual care. Treatment will be continued until there is evidence of complete resolution of sub-retinal fluid.

Arm type	Experimental
Investigational medicinal product name	Eplerenone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Eplerenone 25 mg/day increased to 50 mg/day after 1 week (as per manufacturer’s recommendations for dose initiation) in addition to usual care. Treatment will be continued until there is evidence of complete resolution of SRF. The 25mg and 50mg doses will be achieved using 25mg and 50mg strength tablets respectively.

Number of subjects in period 1	Placebo with usual care	Eplerenone with usual care
Started	57	57
Completed	57	57

Baseline characteristics

Reporting groups	
Reporting group title	Placebo with usual care
Reporting group description:	
Placebo tablet, manufactured to match the Eplerenone tablets, with usual care.	
Reporting group title	Eplerenone with usual care
Reporting group description:	
Eplerenone 25 mg/day increased to 50 mg/day after 1 week (as per manufacturer's recommendations for dose initiation) in addition to usual care. Treatment will be continued until there is evidence of complete resolution of sub-retinal fluid.	

Reporting group values	Placebo with usual care	Eplerenone with usual care	Total
Number of subjects	57	57	114
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	49.9	47.4	
standard deviation	± 7.9	± 7.1	-
Gender categorical Units: Subjects			
Female	14	15	29
Male	43	42	85
Ethnicity Units: Subjects			
White	53	46	99
Asian	4	9	13
Mixed	0	1	1
Other	0	1	1
Smoking Units: Subjects			
Current	10	12	22
Ex	16	25	41
Never	31	20	51
Heart failure Units: Subjects			
Yes	0	0	0
No	57	57	114

Myocardial infarction Units: Subjects			
Yes	1	0	1
No	56	57	113
History of angina Units: Subjects			
Yes	0	0	0
No	57	57	114
CCS class Units: Subjects			
No angina	57	57	114
NYHA class Units: Subjects			
Class 0	56	57	113
Class I	1	0	1
Transient ischemic attack Units: Subjects			
Yes	0	0	0
No	57	57	114
Stroke Units: Subjects			
Yes	1	0	1
No	56	57	113
DVT Units: Subjects			
Yes	0	1	1
No	57	56	113
PE Units: Subjects			
Yes	0	1	1
No	57	56	113
Claudication Units: Subjects			
Yes	0	0	0
No	57	57	114
Diabetes Units: Subjects			
None	55	54	109
Oral	1	2	3
Non-insulin injections	1	1	2
BCVA score Units: Subjects			
Low (54-67)	7	7	14
High (68-85)	50	50	100
Family history of CSCR Units: Subjects			
Yes	1	0	1
No	56	57	113
Pupils abnormal Units: Subjects			
Yes	0	0	0

No	57	57	114
Cornea abnormal Units: Subjects			
Yes	3	0	3
No	54	57	111
Anterior chamber cells present Units: Subjects			
Yes	0	0	0
No	57	57	114
Anterior chamber flare present Units: Subjects			
Yes	0	1	1
No	57	56	113
Lens status Units: Subjects			
Phakic	57	55	112
Pseudophakic	0	2	2
Nuclear sclerosis (NUC) Units: Subjects			
Grade NUC-0	47	51	98
Grade NUC-1	9	4	13
Grade NUC-2	1	0	1
Unrecorded	0	2	2
Cortical (COR) Units: Subjects			
Grade COR-0	56	55	111
Grade COR-1	1	0	1
Unrecorded	0	2	2
Central Optical Involvement (CEN) Units: Subjects			
Yes	2	2	4
No	55	53	108
Unrecorded	0	2	2
Posterior subcapsular (PSC) Units: Subjects			
Grade PSC-0	57	55	112
Unrecorded	0	2	2
Disc abnormal Units: Subjects			
Yes	0	0	0
No	57	57	114
Cataract surgery Units: Subjects			
Yes	0	2	2
No	57	55	112
Macular atrophy of RPE Units: Subjects			
Yes	3	2	5
No	52	54	106
Unrecorded	2	1	3

Systolic blood pressure Units: mmHg			
median	132	129	
inter-quartile range (Q1-Q3)	125 to 146	121 to 141	-
Diastolic blood pressure Units: mmHg			
median	80	80	
inter-quartile range (Q1-Q3)	75 to 88	72.5 to 88.5	-
Heart rate Units: bpm			
median	68	73	
inter-quartile range (Q1-Q3)	60 to 76	66 to 80	-
TSH/thyrotropin Units: mIU/L			
median	2	2	
inter-quartile range (Q1-Q3)	1.1 to 2.2	1.2 to 2.2	-
Thyroxine Units: pmol/L			
median	14	14	
inter-quartile range (Q1-Q3)	13 to 17	13 to 16	-
Triiodothyronine Units: nmol/L			
median	4.5	4.6	
inter-quartile range (Q1-Q3)	4.4 to 4.8	4.3 to 4.8	-
HbA1c Units: mmol/mol			
median	35	36	
inter-quartile range (Q1-Q3)	33.5 to 37	33 to 39	-
Haematocrit (Hct) Units: L/L			
arithmetic mean	0.4	0.4	
standard deviation	± 0.0	± 0.0	-
Platelets Units: x10^9/L			
median	250	259	
inter-quartile range (Q1-Q3)	222.5 to 287.5	221 to 290	-
WBC Units: x10^9/L			
median	7	7	
inter-quartile range (Q1-Q3)	5 to 8	5.6 to 7.7	-
Serum creatinine Units: µmol/L			
arithmetic mean	78	79	
standard deviation	± 14.9	± 13.2	-
Urea Units: mmol/L			
arithmetic mean	5	5	
standard deviation	± 1.2	± 1.2	-
Potassium Units: mmol/L			
arithmetic mean	4	4	
standard deviation	± 0.3	± 0.4	-

Sodium			
Units: mmol/L			
median	140	141	
inter-quartile range (Q1-Q3)	139 to 141	139 to 142	-
Chloride			
Units: mmol/L			
arithmetic mean	102	102	
standard deviation	± 2.7	± 2.6	-
Bicarbonate			
Units: mmol/L			
arithmetic mean	27	25	
standard deviation	± 3.3	± 2.2	-
eGFR			
Units: ml/min			
median	82	84	
inter-quartile range (Q1-Q3)	60 to 90	71 to 90	-
Bilirubin			
Units: µmol/L			
median	8	8	
inter-quartile range (Q1-Q3)	7 to 12	6 to 11	-
ALT			
Units: units/L			
median	22	28	
inter-quartile range (Q1-Q3)	19 to 29	21 to 39	-
Albumin			
Units: g/L			
median	45	45	
inter-quartile range (Q1-Q3)	41 to 47	41 to 47	-
Protein			
Units: g/L			
median	73	72	
inter-quartile range (Q1-Q3)	70 to 76	69 to 76	-
CSCR duration			
Units: Months			
median	9	8	
inter-quartile range (Q1-Q3)	6 to 18	6 to 22	-
IOP measurement			
Units: mmHg			
median	15	15	
inter-quartile range (Q1-Q3)	14 to 18	13 to 17	-
Cup disc ratio			
Units: Ratio			
median	0.3	0.3	
inter-quartile range (Q1-Q3)	0.2 to 0.3	0.2 to 0.3	-
BCVA			
Units: EDTRS letters read			
median	78	77	
inter-quartile range (Q1-Q3)	73 to 82	73 to 80	-
Low luminance VA			
Units: ETDRS letters read			
median	64	57	
inter-quartile range (Q1-Q3)	57 to 67	50 to 64	-

Choroidal thickness			
Units: µm			
median	461	447	
inter-quartile range (Q1-Q3)	381.5 to 534.5	398 to 509	-
SRFT			
Units: µm			
median	119	147	
inter-quartile range (Q1-Q3)	88 to 178	93 to 196	-
Central subfield retinal thickness			
Units: µm			
median	322	360	
inter-quartile range (Q1-Q3)	280 to 394	290 to 406	-

End points

End points reporting groups	
Reporting group title	Placebo with usual care
Reporting group description:	
Placebo tablet, manufactured to match the Eplerenone tablets, with usual care.	
Reporting group title	Eplerenone with usual care
Reporting group description:	
Eplerenone 25 mg/day increased to 50 mg/day after 1 week (as per manufacturer's recommendations for dose initiation) in addition to usual care. Treatment will be continued until there is evidence of complete resolution of sub-retinal fluid.	

Primary: BCVA at 12 months	
End point title	BCVA at 12 months
End point description:	
End point type	Primary
End point timeframe:	
Baseline to 12 months	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: ETDRS letters read				
median (inter-quartile range (Q1-Q3))				
Baseline	78 (73 to 82)	77 (73 to 80)		
4 weeks	80 (73 to 84)	79 (75 to 83)		
3 months	80 (74 to 85)	79 (76 to 83.5)		
6 months	81 (74 to 86)	80 (74 to 84)		
9 months	81 (74.5 to 86.5)	80 (74 to 85)		
12 months	82 (74 to 87)	81 (77 to 85)		

Statistical analyses

Statistical analysis title	BCVA
Comparison groups	Eplerenone with usual care v Placebo with usual care

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.236
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	4.57
Variability estimate	Standard error of the mean
Dispersion value	1.45

Secondary: Low luminance VA at 12 months

End point title	Low luminance VA at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: ETDRS letters read				
median (inter-quartile range (Q1-Q3))				
Baseline	64 (57 to 67)	57 (50 to 64)		
4 weeks	63 (55 to 67)	63 (54 to 67.5)		
3 months	62 (58 to 69)	63 (57 to 68)		
6 months	66 (59 to 71)	62 (56 to 71.5)		
9 months	65 (59.5 to 73)	65 (58 to 70)		
12 months	65 (60 to 75)	66 (57 to 71)		

Statistical analyses

Statistical analysis title	Low luminance VA at 12 months
Comparison groups	Eplerenone with usual care v Placebo with usual care

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.785
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.79
upper limit	5.02
Variability estimate	Standard error of the mean
Dispersion value	2.25

Secondary: Central subfield retinal thickness (CSRT) at 12 months

End point title	Central subfield retinal thickness (CSRT) at 12 months

End point description:

End point type	Secondary

End point timeframe:

Baseline to 12 months post-randomisation

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: µm				
median (inter-quartile range (Q1-Q3))				
Baseline	322 (280 to 394)	360 (290 to 406)		
4 weeks	330 (272 to 386)	328 (248.5 to 393.5)		
3 months	285 (250 to 341)	295 (240.5 to 383)		
6 months	270 (247 to 313)	290 (226 to 366)		
9 months	268 (230 to 322)	273 (220 to 366)		
12 months	253 (232 to 303)	272 (229 to 368)		

Statistical analyses

Statistical analysis title	CSRT at 12 months
Comparison groups	Placebo with usual care v Eplerenone with usual care

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	24.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.86
upper limit	56.56
Variability estimate	Standard error of the mean
Dispersion value	16.44

Secondary: Sub-retinal fluid thickness (SRFT) at 12 months

End point title	Sub-retinal fluid thickness (SRFT) at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and 12 months	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: µm				
median (inter-quartile range (Q1-Q3))				
Baseline	119 (88 to 178)	147 (93 to 196)		
12 months	61 (0 to 111)	89 (23 to 196)		

Statistical analyses

Statistical analysis title	SRFT at 12 months
Statistical analysis description:	
Multiple imputation used to account for missing data.	
Comparison groups	Placebo with usual care v Eplerenone with usual care

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	48.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.43
upper limit	82.73
Variability estimate	Standard error of the mean
Dispersion value	17.68

Secondary: Macular atrophy of the RPE at 12 months

End point title	Macular atrophy of the RPE at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	49		
Units: Subjects				
Yes	3	4		
No	50	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Area change in macular RPE hypoautofluorescence at 12 months

End point title	Area change in macular RPE hypoautofluorescence at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and 12 months	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: µm				
median (inter-quartile range (Q1-Q3))	0.03 (0.03 to 0.04)	0.72 (-0.73 to 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Choroidal thickness at 12 months

End point title	Choroidal thickness at 12 months

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: µm				
median (inter-quartile range (Q1-Q3))				
Baseline	460.5 (381.5 to 534.5)	447 (398 to 509)		
12 months	444 (375 to 524)	495.5 (423 to 534)		

Statistical analyses

Statistical analysis title	Choroidal thickness at 12 months

Statistical analysis description:

Multiple imputation used to account for missing data

Comparison groups	Placebo with usual care v Eplerenone with usual care

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	38.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.31
upper limit	64.74
Variability estimate	Standard error of the mean
Dispersion value	13.38

Secondary: Reduced choroidal permeability at 12 months

End point title	Reduced choroidal permeability at 12 months

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	49		
Units: Subjects				
Yes	3	1		
No	51	48		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 overall composite score at 12 months

End point title	VFQ-25 overall composite score at 12 months

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	87 (80.3 to 91.3)	89 (81.2 to 92)		
12 months	92 (86.1 to 94.6)	89 (83.7 to 93.3)		

Statistical analyses

Statistical analysis title	VFQ-25 overall composite score at 12 months
Comparison groups	Placebo with usual care v Eplerenone with usual care
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.127
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.45
upper limit	0.68
Variability estimate	Standard error of the mean
Dispersion value	1.56

Notes:

[1] - Multiple imputation used to account for missing data

Secondary: Time to resolution of SRF	
End point title	Time to resolution of SRF
End point description:	
End point type	Secondary
End point timeframe:	
12 month follow-up period	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Days				
median (confidence interval 95%)	458.2 (214.1 to 702.3)	603.3 (313.1 to 893.5)		

Statistical analyses

Statistical analysis title	Time to complete resolution of SRF
Comparison groups	Placebo with usual care v Eplerenone with usual care
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.463
Method	Interval-censored regression
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.51
Variability estimate	Standard error of the mean
Dispersion value	0.26

Secondary: Time to complete or partial resolution

End point title	Time to complete or partial resolution
End point description:	
End point type	Secondary
End point timeframe:	
12 month follow-up period	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: days				
median (confidence interval 95%)	184.2 (122.3 to 246)	141.1 (57.9 to 224.4)		

Statistical analyses

Statistical analysis title	Time to complete or partial resolution of SRF
Comparison groups	Placebo with usual care v Eplerenone with usual care
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.418
Method	Interval-censored regression
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.01
Variability estimate	Standard error of the mean
Dispersion value	0.31

Secondary: Time to recurrence of SRF

End point title	Time to recurrence of SRF
End point description:	

End point type	Secondary
End point timeframe:	
12 month follow-up period	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: days				
median (confidence interval 95%)	192.1 (136.6 to 247.6)	182.5 (117.7 to 247.3)		

Statistical analyses

Statistical analysis title	Time to recurrence of SRF
Comparison groups	Placebo with usual care v Eplerenone with usual care

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.836
Method	Interval-censored regression
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	2.66
Variability estimate	Standard error of the mean
Dispersion value	0.48

Secondary: New CSCR in fellow eye

End point title	New CSCR in fellow eye
End point description:	
End point type	Secondary
End point timeframe:	
12 month follow-up period	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Subjects				
Yes	4	5		
No	53	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Any CSCR in fellow eye

End point title	Any CSCR in fellow eye
End point description:	
End point type	Secondary
End point timeframe:	
12 month follow-up period	

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Subjects				
Yes	8	8		
No	49	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Response (complete or partial)

End point title	Response (complete or partial)

End point description:

End point type	Secondary

End point timeframe:

12 month follow-up period

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	52		
Units: Subjects				
3 months	19	25		
6 months	27	33		
12 months	38	38		
Never	16	14		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 near vision

End point title	VFQ-25 near vision

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	75 (66.7 to 83.3)	83 (66.7 to 91.7)		
12 months	83 (75 to 100)	83 (66.7 to 91.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 distance vision

End point title	VFQ-25 distance vision

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	92 (83.3 to 100.0)	100 (83.3 to 100)		
12 months	92 (83.3 to 100)	100 (83.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 general health

End point title	VFQ-25 general health

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	75 (50 to 75)	75 (50 to 75)		
12 months	75 (50 to 75)	75 (50 to 75)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 general vision

End point title	VFQ-25 general vision

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	70 (60 to 80)	60 (60 to 80)		
12 months	80 (60 to 80)	80 (60 to 80)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 driving

End point title	VFQ-25 driving

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	54		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	92 (83.3 to 100)	92 (83.3 to 100)		
12 months	92 (83.3 to 100)	92 (83.3 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 peripheral vision

End point title	VFQ-25 peripheral vision

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	100 (75 to 100)	100 (75 to 100)		
12 months	100 (100 to 100)	100 (75 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 colour vision

End point title	VFQ-25 colour vision

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	100 (100 to 100)	100 (100 to 100)		
12 months	100 (100 to 100)	100 (100 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 ocular pain

End point title	VFQ-25 ocular pain

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	88 (75 to 100)	100 (75 to 100)		
12 months	100 (75 to 100)	100 (75 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 role difficulties

End point title	VFQ-25 role difficulties

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	88 (75 to 100)	88 (62.5 to 100)		
12 months	100 (75 to 100)	88 (62.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 dependency

End point title	VFQ-25 dependency

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	100 (91.7 to 100)	100 (91.7 to 100)		
12 months	100 (100 to 100)	100 (100 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 social functioning

End point title	VFQ-25 social functioning

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	100 (100 to 100)	100 (100 to 100)		
12 months	100 (100 to 100)	100 (100 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: VFQ-25 mental health

End point title	VFQ-25 mental health

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Score				
median (inter-quartile range (Q1-Q3))				
Baseline	75 (56.3 to 87.5)	75 (62.5 to 87.5)		
12 months	88 (75 to 93.8)	81 (75 to 87.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of SRF and classification

End point title	Resolution of SRF and classification

End point description:

End point type	Secondary

End point timeframe:

4 weeks, 3 months, 6 months, 9 months and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	56		
Units: Subjects				
4 weeks - complete resolution	2	4		
4 weeks - partial resolution	4	8		
4 weeks - non-responder	48	44		
3 months - complete resolution	6	5		
3 months - partial resolution	12	15		
3 months - non-responder	36	32		
6 months - complete resolution	11	8		
6 months - partial resolution	10	16		
6 months - non-responder	33	28		
9 months - complete resolution	13	9		
9 months - partial resolution	10	14		
9 months - non-responder	29	28		
12 months - complete resolution	16	8		
12 months - partial resolution	13	14		
12 months - non-responder	25	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Study eye FFA phenotype

End point title	Study eye FFA phenotype

End point description:

End point type	Secondary

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: Subjects				
Baseline - smoke stack	1	4		
Baseline - ink-blot	37	35		
Baseline - chronic epitheliopathy	19	18		
12 months - smoke stack	2	0		
12 months - ink-blot	17	26		
12 months - chronic epitheliopathy	27	15		
12 months - no early or late leakage visible	8	9		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Choroidal thickness in fellow eye

End point title	Choroidal thickness in fellow eye

End point description:

End point type	Post-hoc

End point timeframe:

Baseline and 12 months

End point values	Placebo with usual care	Eplerenone with usual care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	54		
Units: µm				
median (inter-quartile range (Q1-Q3))				
Baseline	429 (365.5 to 486)	386 (328 to 477)		

12 months	466 (416 to 554)	475 (390 to 525)		

Statistical analyses

Statistical analysis title	Choroidal thickness in fellow eye
Comparison groups	Placebo with usual care v Eplerenone with usual care
Number of subjects included in analysis	104
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	= 0.056
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	30.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	60.58
Variability estimate	Standard error of the mean
Dispersion value	15.57

Notes:

[2] - Multiple imputation used to account for missing data

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 12 months post-randomisation

Adverse event reporting additional description:

All expected and unexpected adverse events reported using MedDRA dictionary.
For all events, 'non-serious adverse events' includes ALL events (serious and non-serious). This is consistent with the trial publication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo with usual care

Reporting group description:

Placebo tablet, manufactured to match the Eplerenone tablets, with usual care.

Reporting group title	Eplerenone with usual care

Reporting group description:

Eplerenone 25 mg/day increased to 50 mg/day after 1 week (as per manufacturer's recommendations for dose initiation) in addition to usual care. Treatment will be continued until there is evidence of complete resolution of sub-retinal fluid.

Serious adverse events	Placebo with usual care	Eplerenone with usual care	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 57 (5.26%)	0 / 57 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Metabolic surgery			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			

subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo with usual care	Eplerenone with usual care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 57 (54.39%)	30 / 57 (52.63%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Withdrawal hypertension			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Circumcision			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Hernia repair			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Metabolic surgery			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Tonsillectomy			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Malaise			

subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Chills			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 57 (3.51%)	3 / 57 (5.26%)	
occurrences (all)	2	3	
Oropharyngeal pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	

Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	1 / 57 (1.75%)	3 / 57 (5.26%)	
occurrences (all)	1	5	
Palpitations			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 57 (5.26%)	4 / 57 (7.02%)	
occurrences (all)	3	4	
Headache			
subjects affected / exposed	6 / 57 (10.53%)	3 / 57 (5.26%)	
occurrences (all)	7	5	
Burning sensation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Eye disorders			
Decrease in visual acuity ≥15 letters (non-study eye)			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Incident choroidal neovascularisation (non-study eye)			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Blepharospasm (study eye)			

subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Hordeolum (study eye)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction (study eye)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Vision blurred (study eye)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Dry eye (non-study eye)			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Retinal tear (non-study eye)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Angle closure glaucoma (both eyes)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Blepharitis (both eyes)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Dry eye (both eyes)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Ocular hypertension (both eyes)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Visual impairment (both eyes)			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Eye contusion			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)	2 / 57 (3.51%)	
occurrences (all)	3	2	
Flatulence			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	5 / 57 (8.77%)	4 / 57 (7.02%)	
occurrences (all)	7	7	
Vomiting			
subjects affected / exposed	0 / 57 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	8	
Abdominal pain			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Tongue coated			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pruritus			

subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Rash			
subjects affected / exposed	1 / 57 (1.75%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Alopecia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 57 (3.51%)	3 / 57 (5.26%)	
occurrences (all)	3	3	
Muscle spasms			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	5 / 57 (8.77%)	7 / 57 (12.28%)	
occurrences (all)	5	7	
Sjogren's syndrome			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infection			
subjects affected / exposed	3 / 57 (5.26%)	8 / 57 (14.04%)	
occurrences (all)	4	10	
Diverticulitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			

subjects affected / exposed	8 / 57 (14.04%)	8 / 57 (14.04%)	
occurrences (all)	8	8	
Diabetes mellitus			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2016	The trial schema and data collection table have been updated due to inconsistencies in the previous version of the protocol. Time frames for study visits have been added. Coordinating centre will also have code lists for unmasking. OCT images will only be graded by an independent reading centre at baseline and 12 months. Updated exclusion criteria, only patients receiving a combination of an ACE inhibitor and an ARB are excluded. The following exclusion criteria has been added due to guidance in the SmPC 'Patients receiving high doses of Aspirin (>75mg).' Randomisation must take place within one month of taking screening blood tests. Otherwise screening tests must be repeated
05 October 2016	Detail added to say that optometrists are allowed logs of previous refractions when carrying out visual function assessments. The following inclusion criterion has been added: 'Investigator believes that there is sufficient evidence from patient history, case note documentation or appearance of the macula that CSCR has been present for at least 4 months.' Patients with BCVA scores of up to 85 are now eligible for inclusion. Conconmittant medication list has been updated. Lists of primary and secondary outcomes have been edited. OCT A is to performed where equipment is available at screening and 12 months. Unmasking requires approval from CI/Co-Lead. Analyses section has been updated based on feedback from DMSC meeting.
26 January 2017	Correction to say that VICI is a phase 3 trial not a phase 2 trial Fundus photography has been added to the trial schema and data collection table. This procedure will be carried out twice (screening & 12 month follow up visit) and takes around 5 minutes. This had been omitted in error from previous versions of the protocol. We are not measuring fasting blood glucose. This had been removed from the trial schema before the protocol was submitted for approval but in error not removed from section 9.2 of the study protocol.
20 March 2018	Section 4.7. Updated minor text error in sample size justification. Sections 5.3, 6.2 and Table 1. Updated to include OCT-A at baseline or an interim time-point and at 12 months. Section 8.1. Updated reference safety information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31982075