Clinical trial results:
A randomised controlled trial of Losartan as an anti-fibrotic agent in non-alcoholic steatohepatitis (FELINE).

Summary

EudraCT number	2009-015166-62
Trial protocol	GB
Global end of trial date	31 December 2014

Results information

Result version number	v1 (current)
This version publication date	04 August 2016
First version publication date	04 August 2016

Trial information

Trial identification

Sponsor protocol code	EME-08/43/15

Additional study identifiers

ISRCTN number	ISRCTN57849521
ClinicalTrials.gov id (NCT number)	NCT01051219
WHO universal trial number (UTN)	-
Other trial identifiers	REC Ref: 10/H0904/8, NIHR CSP: 37194

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Joint Research Office, Level 1, Regent Point, Regent Farm Road, Gosforth, Newcastle upon Tyne , United Kingdom, NE3 3HD
Public contact	Professor Christopher Paul Day , Newcastle University, 0191 2227043, c.p.day@ncl.ac.uk
Scientific contact	Professor Christopher Paul Day , Newcastle University, 0191 2227043, c.p.day@ncl.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	06 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2014
Global end of trial reached?	Yes
Global end of trial date	31 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question/objective is to determine whether Losartan, taken as a tablet (50mg once a day) versus a dummy pill (which will look exactly the same as the real medication) is effective at slowing down, halting or reversing liver fibrosis (scar tissue) in patients with non-alcoholic steatohepatitis.

Protection of trial subjects:

Losartan is already a licensed medication used to treat patients with raised blood pressure, renal disease, diabetes and chronic heart failure. The medication is not currently licensed as an antifibrotic agent, but it is known to be safe. Based on previous studies and patients already taking Losartan, we know that the most common adverse reactions are dizziness, vertigo, hypotension, fatigue, low blood sugar and raised blood potassium levels. Patients will be assessed at regular intervals throughout the study and as patients with NASH are likely to have raised blood pressure, it is not expected that low blood pressure will be a major concern. Any expected drug reactions will be included in the patient information leaflet and, everything will be explained to the patient verbally.

Patients will be advised by their doctor to report any unusual symptoms or reactions. Patients will be provided with a contact number on which they may contact a member of the study team to obtain advice and express any concerns, throughout the duration of the study. This information will be included in the patient information leaflet.

Background therapy:

Participants were not prevented from interventions or procedures considered as part of routine care while participating in FELINE

Evidence for comparator:

N/A

Actual start date of recruitment	01 May 2011
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: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	39
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were identified by research staff, considered by the PI or Co-Investigator for inclusion and then if eligible approached to see whether they were interested. Interested patients were provided with the PIS to take away and read. Those then wishing to participate were made an appointment to return to the clinic to sign the ICF.

Pre-assignment

Screening details:

Visit 1 was the screening visit and took place directly after the participant had consented – a full screening assessment was then undertaken to ensure participants were definitely eligible to take part and met the eligibility criteria.

Pre-assignment period milestones

Number of subjects started	49[1]
Number of subjects completed	45

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen fail (after consented): 4

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Potentially eligible patients were consented prior to a full screening assessment being undertaken. 49 patients were consented and screened, of these 45 were eligible to take part in the study. The other 4 patients failed screening and did not meet the eligibility criteria for the study - they did not therefore participate in the study.

Period 1

Period 1 title	Visit 2 - Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan

Arm description:

Active Drug

Arm type	Experimental
Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one 50mg capsule taken daily

Arm title	Placebo

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

Dosage and administration details:

one capsule taken daily

Number of subjects in period 1	Losartan	Placebo
Started	24	21
Completed	24	21

Period 2

Period 2 title	Visit 3 - 1 week
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan

Arm description:

Active drug

Arm type	Experimental
Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one 50mg capsule taken daily

Arm title	Placebo

Arm description:	
Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
one capsule taken daily	

Number of subjects in period 2	Losartan	Placebo
Started	24	21
Completed	24	21

Period 3	
Period 3 title	Visit 4 - 4 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor
Blinding implementation details:	
Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.	

Arms	
Are arms mutually exclusive?	Yes
Arm title	Losartan
Arm description:	
active drug	
Arm type	Experimental
Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
one 50mg capsule taken daily	
Arm title	Placebo

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

Dosage and administration details:

one capsule taken daily

Number of subjects in period 3	Losartan	Placebo
Started	24	21
Completed	23	21
Not completed	1	0
lost to follow-up	1	-

Period 4

Period 4 title	Visit 5 - 24 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan

Arm description:	
active drug	
Arm type	Experimental
Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one 50mg capsule taken daily

Arm title	Placebo

Arm description:	
placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
one capsule taken daily	

Number of subjects in period 4	Losartan	Placebo
Started	23	21
Completed	23	21

Period 5	
Period 5 title	Visit 6 - 48 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor
Blinding implementation details:	
Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.	

Arms	
Are arms mutually exclusive?	Yes
Arm title	Losartan
Arm description:	
active drug	
Arm type	Experimental
Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
one 50mg capsule taken daily	
Arm title	Placebo

Arm description:	
placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one capsule taken daily

Number of subjects in period 5	Losartan	Placebo
Started	23	21
Completed	20	19
Not completed	3	2
Consent withdrawn by subject	1	2
lost to follow-up	2	-

Period 6

Period 6 title	Visit 7 - 72 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan

Arm description:

active drug

Arm type	Experimental
Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one 50mg capsule taken daily

Arm title	Placebo
Arm description: placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one capsule taken daily

Number of subjects in period 6	Losartan	Placebo
Started	20	19
Completed	19	19
Not completed	1	0
lost to follow-up	1	-

Period 7

Period 7 title	Visit 8 - 96 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan

Arm description:

active drug

Arm type	Experimental
Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

one 50mg capsule taken daily

Arm title	Placebo

Arm description:

placebo

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

Dosage and administration details:

one capsule taken daily

Number of subjects in period 7	Losartan	Placebo
Started	19	19
Completed	20	21

Joined	1	2
withdrawals who still completed end of study visit	1	2

Period 8

Period 8 title	Visit 9 - 108 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Randomisation was administered centrally via Newcastle Clinical Trials Unit, using a system to ensure concealment of allocation. A blocked allocation system was used to allocate patients to the 2 groups, with centre as a stratifying factor. Randomisation generated a treatment number for each participant that linked to the corresponding allocated study drug (blinded), in accordance with block size and strata. A code-break list was provided to each site pharmacy at participating hospitals.

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan

Arm description:

active drug

Arm type	Experimental

Investigational medicinal product name	Losartan
Investigational medicinal product code	
Other name	Cozaar
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
one 50mg capsule taken daily

Arm title	Placebo

Arm description:
placebo

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

Dosage and administration details:
one capsule taken daily

Number of subjects in period 8[2]	Losartan	Placebo
Started	19	19
Completed	16	18
Not completed	3	1
lost to follow-up	3	1

Notes:
[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Three participants wished to withdraw from the study after completing visit 5 – they did however still complete an end of study visit and this is why the figures show a slight increase in numbers at visit 8

Baseline characteristics

Reporting groups	
Reporting group title	Losartan
Reporting group description: Active Drug	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Losartan	Placebo	Total
Number of subjects	24	21	45
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	20	39
From 65-84 years	5	1	6
85 years and over	0	0	0
Age continuous Units: years			
median	58	45	
full range (min-max)	25 to 75	21 to 76	-
Gender categorical Units: Subjects			
Female	11	9	20
Male	13	12	25
ethnic group Units: Subjects			
White	21	19	40
other mixed background	1	0	1
Asian - Indian	1	0	1
Asian - Pakistani	1	1	2
Chinese	0	1	1
units of alcohol consumed Units: Subjects			
none	13	9	22
1-5 units	7	7	14
6-9 units	0	1	1
10-15 units	3	2	5
16-19 units	1	0	1
20-27 units	0	1	1
≥ 28 units	0	1	1

ECG abnormal			
ECG abnormal from screening			
Units: Subjects			
Yes	5	4	9
No	19	17	36
ultrasound abnormal			
number of patients with an abnormal ultrasound			
Units: Subjects			
Yes	13	6	19
No	5	4	9
missing	4	7	11
did not have ultrasound	2	4	6
stratum			
diabetes			
Units: Subjects			
yes	15	12	27
no	9	9	18
CNS			
physical examination of CNS			
Units: Subjects			
Normal	22	19	41
Abnormal	1	0	1
Not examined	0	1	1
Missing	1	1	2
Neck			
physical examination of neck			
Units: Subjects			
Normal	22	20	42
Abnormal	0	0	0
Not examined	1	0	1
Missing	1	1	2
HEENT			
Physical Examination of HEENT			
Units: Subjects			
Normal	19	19	38
Abnormal	0	0	0
Not examined	4	1	5
Missing	1	1	2
Respiratory			
Physical examination of respiratory			
Units: Subjects			
Normal	23	20	43
Abnormal	0	0	0
Not examined	0	0	0
Missing	1	1	2
Cardiovascular			
physical examination of cardiovascular			
Units: Subjects			
Normal	23	20	43
Abnormal	0	0	0
Not examined	0	0	0

Missing	1	1	2
Gastrointestinal			
physical examination of gastrointestinal			
Units: Subjects			
Normal	23	18	41
Abnormal	0	2	2
Not examined	0	0	0
Missing	1	1	2
Abdomen			
physical examination of Abdomen			
Units: Subjects			
Normal	21	18	39
Abnormal	2	2	4
Not examined	0	0	0
Missing	1	1	2
Musculoskeletal			
physical examination of Musculoskeletal			
Units: Subjects			
Normal	21	19	40
Abnormal	0	0	0
Not examined	2	1	3
Missing	1	1	2
endocrine and metabolic			
physical examination of endocrine and metabolic			
Units: Subjects			
Normal	22	19	41
Abnormal	0	0	0
Not examined	1	1	2
Missing	1	1	2
Hematopoietic/Lymphatic			
physical examination of Hematopoietic/Lymphatic			
Units: Subjects			
Normal	20	19	39
Abnormal	0	0	0
Not examined	3	1	4
Missing	1	1	2
Neurological			
physical examination of neurological			
Units: Subjects			
Normal	21	20	41
Abnormal	1	0	1
Not examined	1	0	1
missing	1	1	2
dermatological			
physical examination of dermatological			
Units: Subjects			
Normal	19	19	38
Abnormal	2	1	3
Not examined	2	0	2
Missing	1	1	2
psychiatric/psychological			

physical examination of psychiatric/psychological			
Units: Subjects			
Normal	19	18	37
Abnormal	0	0	0
Not examined	4	2	6
Missing	1	1	2
Weight			
Weight in KG			
Units: kg			
median	85.1	96.7	
full range (min-max)	74.2 to 121	61.6 to 132.5	-
Height			
Height (taken at screening) in cm			
Units: cm			
median	167	171.3	
full range (min-max)	152 to 183	152 to 194	-
BMI			
Body mass index			
Units: kg/m2			
median	32.8	34.11	
full range (min-max)	26.11 to 43.39	26.46 to 45.18	-
Waist			
waist measurement in cm			
Units: cm			
median	105.85	111.4	
full range (min-max)	96 to 126	88 to 136	-
systolic blood pressure			
Units: mm Hg			
median	133.5	127	
full range (min-max)	109 to 165	115 to 180	-
diastolic blood pressure			
Units: mm Hg			
median	78.5	81	
full range (min-max)	67 to 95	70 to 100	-
sitting heart rate			
Units: bpm			
median	75	77	
full range (min-max)	59 to 100	59 to 88	-
fibroscan liver stiffness			
Units: kpa			
median	8.15	6.05	
full range (min-max)	5.2 to 17.3	3 to 11.9	-
fibroscan stiffness (E) median			
Units: kpa			
median	8.9	7.95	
full range (min-max)	1.6 to 26.6	7.1 to 8.8	-
ELF test result			
ELF test result from screening			
Units: score			
median	8.84	7.96	
full range (min-max)	6.54 to 11.83	6.43 to 10.28	-

sodium			
Units: mmol/L			
median	139.5	141	
full range (min-max)	135 to 143	136 to 145	-
potassium			
Units: mmol/L			
median	4.35	4.3	
full range (min-max)	3.8 to 4.8	3.7 to 4.8	-
Urea			
Units: mmol/L			
median	4.9	5	
full range (min-max)	3.2 to 7.9	3.3 to 6.9	-
Glucose			
Units: mmol/L			
median	5.95	6.2	
full range (min-max)	4.44 to 17.1	3.6 to 15.9	-
AST			
Units: U/L			
median	35	46	
full range (min-max)	14 to 102	30 to 70	-
ALT			
Units: U/L			
median	52.5	65	
full range (min-max)	21 to 136	33 to 135	-
ALP			
Alkaline Phosphatase			
Units: U/L			
median	89.5	72	
full range (min-max)	44 to 173	49 to 116	-
Creatinine			
Units: umol/L			
median	75.5	72	
full range (min-max)	48 to 105	5 to 97	-
Total bilirubin			
Units: umol/L			
median	10	10	
full range (min-max)	5 to 25	4 to 45	-
Albumin			
Units: g/L			
median	44.5	46	
full range (min-max)	34 to 50	35 to 75	-
Triglyceride			
Units: mmol/L			
median	1.7	2	
full range (min-max)	0.9 to 7.9	0.4 to 4.4	-
HDL cholesterol			
Units: mmol/L			
median	1.1	1.1	
full range (min-max)	0.7 to 2.8	0.8 to 3.5	-
total cholesterol			
Units: mmol/L			
median	4.3	4.6	

full range (min-max)	2.1 to 7.5	1 to 6.5	-
LDL cholesterol Units: mmol/L			
median	2.5	3.2	
full range (min-max)	0.8 to 3.8	1.2 to 4.4	-
Gamma GT Units: U/L			
median	70	62	
full range (min-max)	18 to 355	23 to 256	-
haemaglobin Units: g/dL			
median	14.6	14.9	
full range (min-max)	12.3 to 142	13.2 to 18	-
Leukocytes (WBC) Units: x10(9)/L			
median	7.2	7.3	
full range (min-max)	4.3 to 13.1	4.4 to 12.3	-
Platelets Units: x10(9)/L			
median	224	224	
full range (min-max)	137 to 360	158 to 404	-
MCV Units: fL			
median	89.55	87.3	
full range (min-max)	76.9 to 99	80.2 to 94.3	-
HBA1C Units: mmol/mol			
median	53.5	42	
full range (min-max)	34 to 81	31 to 81	-
Prothrombus time Units: seconds			
median	11	11	
full range (min-max)	1 to 15	10 to 22	-
Apolopoproteins Units: µg/L			
median	1.35	1.35	
full range (min-max)	1 to 2	1 to 1.7	-
Alpha-2-macroglobulin Units: mg/100ml			
median	1.4	1.9	
full range (min-max)	0 to 2.5	1.2 to 4.2	-
haptoglobins Units: n/a			
median	1.9	2	
full range (min-max)	0.6 to 797	0.7 to 1651	-
IgG Units: g/L			
median	10.4	10.8	
full range (min-max)	6.7 to 15.1	6.6 to 15	-
IgA Units: g/L			
median	2.9	2.64	

full range (min-max)	0.87 to 5.08	1 to 6.3	-
IgM			
Units: g/L			
median	1.09	1.02	
full range (min-max)	0.26 to 2.75	0.25 to 7	-
insulin			
Units: U/g			
median	22.2	23.8	
full range (min-max)	9.7 to 81.4	4.4 to 57.6	-
C-peptide			
Units: n/a			
median	2.31	2.22	
full range (min-max)	0.68 to 4138	0.16 to 3054	-

End points

End points reporting groups

Reporting group title	Losartan
Reporting group description: Active Drug	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Losartan
Reporting group description: Active drug	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Losartan
Reporting group description: active drug	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Losartan
Reporting group description: active drug	
Reporting group title	Placebo
Reporting group description: placebo	
Reporting group title	Losartan
Reporting group description: active drug	
Reporting group title	Placebo
Reporting group description: placebo	
Reporting group title	Losartan
Reporting group description: active drug	
Reporting group title	Placebo
Reporting group description: placebo	
Reporting group title	Losartan
Reporting group description: active drug	
Reporting group title	Placebo
Reporting group description: placebo	
Reporting group title	Losartan
Reporting group description: active drug	
Reporting group title	Placebo

Reporting group description:

placebo

Primary: Kleiner fibrosis score

End point title	Kleiner fibrosis score[1]

End point description:

Change in Kleiner fibrosis stage from baseline to 96 weeks (Visit 8).

The primary outcome will be change in Kleiner fibrosis score based on histological fibrosis stage (as judged by two independent blinded histopathologists, from liver biopsies), from pre-treatment to end-of-study defined as 24 month score minus baseline score

End point type	Primary

End point timeframe:

24 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No inferential statistical testing carried out as study closed to recruitment early

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-1 to 1)	0 (-1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Length

End point title	Length

End point description:

Change in biopsy length from BL to 24 months defined as 24 months length minus BL length
Length is defined as total length of liver tissue core(s)

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: mm				
median (full range (min-max))	-1.91 (-31.2 to 12.4)	-3.36 (-28.2 to 20.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Diagnostic Category

End point title	Diagnostic Category

End point description:

Change in diagnostic category from BL to 24 months defined as 24 months diagnostic category minus BL diagnostic category

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: category				
median (full range (min-max))	0 (-1 to 1)	0 (-1 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Grade of Steatosis

End point title	Grade of Steatosis

End point description:

Change in grade of steatosis from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: percentage				
median (full range (min-max))	0 (-2 to 1)	0 (-2 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: % Steatotic Hepatocytes

End point title	% Steatotic Hepatocytes
End point description:	
Change in % steatotic hepatocytes from BL to 24 months defined as 24 months value minus BL value	
End point type	Secondary
End point timeframe:	
Baseline and 24 months	

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: percentage				
median (full range (min-max))	-10 (-60 to 50)	-20 (-70 to 20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatocyte ballooning

End point title	Hepatocyte ballooning
End point description:	
Change in Hepatocyte ballooning from BL to 24 months defined as 24 months value minus BL value	
End point type	Secondary
End point timeframe:	
baseline and 24 months	

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-1 to 1)	0 (-1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lobular Inflammation

End point title	Lobular Inflammation
End point description: Change in lobular inflammation from BL to 24 months defined as 24 months value minus BL value	
End point type	Secondary
End point timeframe: baseline and 24 months	

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-1 to 1)	0 (-2 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: SAF lobular inflammation

End point title	SAF lobular inflammation
End point description: Change in SAF lobular inflammation from BL to 24 months defined as 24 months value minus BL value	
End point type	Secondary
End point timeframe: baseline and 24 months	

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-1 to 1)	0 (-1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: NAFLD score (NAS)

End point title	NAFLD score (NAS)

End point description:

Change in NAS from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-3 to 3)	-1 (-4 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: FLIP Activity Score

End point title	FLIP Activity Score

End point description:

Change in FLIP activity score from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-2 to 1)	-1 (-2 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Global grade - Brunt 1999

End point title	Global grade - Brunt 1999

End point description:

Change in Global Grade from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: grade				
median (full range (min-max))	-1 (-1 to 1)	-1 (-2 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sinusoidal/pericellular fibrosis

End point title	Sinusoidal/pericellular fibrosis

End point description:

Change in Sinusoidal/pericellular fibrosis from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-1 to 2)	0 (-2 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: 7 tier staging system

End point title	7 tier staging system

End point description:

Change in 7 tier staging system fibrosis from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: staging system				
median (full range (min-max))	0 (-2 to 2)	0 (-2 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Portal inflammation

End point title	Portal inflammation

End point description:

Change in portal inflammation from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-1 to 2)	0 (-1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apopotic bodies

End point title	Apopotic bodies

End point description:

Change in apoptotic bodies from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

Baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	0 (-1 to 1)	0 (-1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mallory-Denk bodies

End point title	Mallory-Denk bodies

End point description:

Change in Mallory-Denk bodies from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14[2]	17		
Units: score				
median (full range (min-max))	0 (-1 to 0)	0 (-2 to 1)		

Notes:

[2] - one biopsy has a missing score

Statistical analyses

No statistical analyses for this end point

Secondary: SF36 PCS

End point title	SF36 PCS

End point description:

Change in SF36 physical component summary (PCS) from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: score				
median (full range (min-max))	-1.47 (-14.19 to 4.28)	-2.9 (-15.36 to 28.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF36 MCS

End point title	SF36 MCS

End point description:

Change in SF36 (mental component summary) MCS from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: score				
median (full range (min-max))	1.1 (-30.05 to 16.38)	-0.12 (-20.95 to 21.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF36 - PCS oblique

End point title	SF36 - PCS oblique

End point description:

Change in SF36 (physical component summary) PCS calculated using the oblique method from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: score				
median (full range (min-max))	-1.75 (-20.6 to 5.83)	-2.83 (-11.87 to 21.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: SF36-MCS oblique

End point title	SF36-MCS oblique

End point description:

Change in SF36 (mental component summary) MCS calculated using the oblique method from BL to 24 months defined as 24 months value minus BL value

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: score				
median (full range (min-max))	-0.22 (-32.4 to 14.7)	-0.55 (-12.61 to 17.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLDQ AS

End point title	CLDQ AS

End point description:

Change in CLDQ abdominal symptoms (AS) from BL to 24 months defined as 24 months value minus BL value
If one element in domain missing then domain set to missing

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	19		
Units: score				
median (full range (min-max))	0 (-3.67 to 2)	0 (-2.33 to 3.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLDQ SS

End point title	CLDQ SS

End point description:

Change in CLDQ systemic symptoms (SS) from BL to 24 months defined as 24 months value minus BL value
If one element in domain missing then domain set to missing

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: score				
median (full range (min-max))	-0.5 (-1.6 to 0.4)	-0.3 (-1.4 to 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLDQ FA

End point title	CLDQ FA

End point description:

Change in CLDQ fatigue (FA) from BL to 24 months defined as 24 months value minus BL value
If one element in domain missing then domain set to missing

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	20		
Units: score				
median (full range (min-max))	-0.6 (-1.8 to 0.4)	-0.2 (-1.6 to 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLDQ AC

End point title	CLDQ AC

End point description:

Change in CLDQ activity (AC) from BL to 24 months defined as 24 months value minus BL value
If one element in domain missing then domain set to missing

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: score				
median (full range (min-max))	-0.33 (-3.33 to 2.33)	-0.33 (-3 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLDQ EF

End point title	CLDQ EF

End point description:

Change in CLDQ emotional function (EF) from BL to 24 months defined as 24 months value minus BL value
If one element in domain missing then domain set to missing

End point type	Secondary

End point timeframe:

baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	18		
Units: score				
median (full range (min-max))	0 (-3.63 to 1.13)	-0.13 (-1.75 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLDQ WO

End point title	CLDQ WO

End point description:

Change in CLDQ worry (WO) from BL to 24 months defined as 24 months value minus BL value
If one element in domain missing then domain set to missing

End point type	Secondary

End point timeframe:
baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: score				
median (full range (min-max))	0 (-3.6 to 1.2)	0.1 (-2.2 to 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: CLDQ overall

End point title	CLDQ overall

End point description:

Change in CLDQ Overall from BL to 24 months defined as 24 months value minus BL value
If one element in domain missing then domain set to missing

End point type	Secondary

End point timeframe:
baseline and 24 months

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	17		
Units: score				
median (full range (min-max))	-0.17 (-2.28 to 0.38)	-0.1 (-1.07 to 0.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fibroscan

End point title	Fibroscan

End point description:

liver stiffness

End point type	Secondary

End point timeframe:
Visit 8

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: kpa				
median (full range (min-max))	5.05 (3.4 to 15.4)	5.95 (3.6 to 20.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fibroscan

End point title	Fibroscan

End point description:
Liver stiffness (E) median

only received results for those in the losartan reporting arm - none received for the placebo arm and therefore no analysis conducted within this arm.

End point type	Secondary

End point timeframe:
Visit 8

End point values	Losartan			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: kpa				
median (full range (min-max))	9.5 (0 to 14)			

Statistical analyses

No statistical analyses for this end point

Secondary: ELF

End point title	ELF

End point description:
ELF score

End point type	Secondary

End point timeframe:
Visit 8

End point values	Losartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	16		
Units: score				
median (full range (min-max))	9.45 (7.91 to 11.03)	8.97 (7.31 to 10.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events were collected from Visit 2 (Baseline) through to Visit 9 (108 weeks)	
Assessment type	Systematic
Dictionary used	
Dictionary name	as reported
Dictionary version	1.0
Reporting groups	
Reporting group title	Losartan
Reporting group description: active drug	
Reporting group title	Placebo
Reporting group description: placebo	

Serious adverse events	Losartan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	1 / 21 (4.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Epistaxis	Additional description: nose bleeds		
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
2nd right rib fracture	Additional description: fell over whilst walking dogs		
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dislocation of left 1st metacarpal	Additional description: knocked down by bike		
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fracture of left 1st metacarpal	Additional description: knocked down by bike		

subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (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	Losartan	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 24 (87.50%)	16 / 21 (76.19%)	
General disorders and administration site conditions			
ankle swelling			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
anxiety			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
axilla abscess			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
back pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
cervical spondylosis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
colonoscopy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
constipation			

subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
cough			
subjects affected / exposed	3 / 24 (12.50%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	2 / 24 (8.33%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
diarrhoea and vomiting			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
dislocated left knee cap			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
dizzyness			
subjects affected / exposed	4 / 24 (16.67%)	6 / 21 (28.57%)	
occurrences (all)	5	6	
dorsal capsulotomy of mcp (metacapophalangeal) joints in right hand			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
dry mouth			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
dyslipidaemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
dysmenorrhoea			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
dyspepsia			
subjects affected / exposed	2 / 24 (8.33%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Dysphagia			

subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
dysuria			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
elective removal of screw from left ankle			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
elective surgery for cystoscopy and bladder biopsy			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
eructation			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
excision scalp lipoma			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
extreme coldness in extremities- especially hand and feet.			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
falls			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
fatigue			
subjects affected / exposed	1 / 24 (4.17%)	2 / 21 (9.52%)	
occurrences (all)	2	3	
Fibromyalgia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
generalized stabbing pain and ache from left ankle up to the left hip.			

subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
gout			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
headaches			
subjects affected / exposed	2 / 24 (8.33%)	6 / 21 (28.57%)	
occurrences (all)	2	14	
herniated lumbar disc			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
hot and cold sweats			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	1 / 24 (4.17%)	4 / 21 (19.05%)	
occurrences (all)	1	6	
hypertension			
subjects affected / exposed	2 / 24 (8.33%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Influenza			
subjects affected / exposed	0 / 24 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
insomnia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
left ankle pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
left knee pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
left lower leg - hot tender and tight			

at night			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
left shoulder pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
leg cramps			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
leg pain			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
light headed			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	4	
loin pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
lower respiratory tract infection			
subjects affected / exposed	3 / 24 (12.50%)	4 / 21 (19.05%)	
occurrences (all)	4	5	
Malaise			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
memory impairment			
subjects affected / exposed	2 / 24 (8.33%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Migraine			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
muscle spasm			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
myalgia			
subjects affected / exposed	2 / 24 (8.33%)	2 / 21 (9.52%)	
occurrences (all)	2	2	

nausea			
subjects affected / exposed	2 / 24 (8.33%)	3 / 21 (14.29%)	
occurrences (all)	3	6	
oesteoarthritis both knees			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
pain in left ankle			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
pain in tongue when eating or drinking since taking 1 week of antibiotics.			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
painful eye after laser eye treatment			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
painful wisdom tooth			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
palella ligament injury			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
palpitations			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
parasthesia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
post liver biopsy pain			
subjects affected / exposed	2 / 24 (8.33%)	1 / 21 (4.76%)	
occurrences (all)	4	2	
Pruritus			
subjects affected / exposed	3 / 24 (12.50%)	0 / 21 (0.00%)	
occurrences (all)	6	0	
rectal polyps removed			

subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
right knee pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
severe trigonitis			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
shoulder pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
sleep apnoea			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
sore throat			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
tonsilitis			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
toothache and subsequent tooth extraction			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
viral illness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
viral upper respiratory infection			
subjects affected / exposed	4 / 24 (16.67%)	3 / 21 (14.29%)	
occurrences (all)	5	6	
vitamin d deficiency			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
vomiting			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	2	1	

whiplash following rta subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0	
whiplash/back pain subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1	
Social circumstances depression subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0	
Eye disorders scratch on left cornea subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 21 (4.76%) 2	
Reproductive system and breast disorders Hysterectomy subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0	
Gastrointestinal disorders Irritable bowel syndrome subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	1 / 21 (4.76%) 1	
Respiratory, thoracic and mediastinal disorders asthma subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1	
Skin and subcutaneous tissue disorders skin erthema subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0	
skin rash subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1	
soft tissue facial injuries subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0	
Renal and urinary disorders			

kidney stone			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Renal colic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
ear infection			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
skin infection			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 December 2010	Updated in line with feedback from the MHRA: - Description of concomitant medications to be avoided by participants and potential drug interactions added - Biochemistry profile has been expanded to include urea and electrolytes - The dose of Losartan has been justified as being a standard dose and the dose which has been used in previous studies - extra visit (visit three) added to the study schedule in which participants will revisit the clinic/research centre for measurement of urea, electrolytes, blood pressure and waist circumference - electrolyte disturbance included as an exclusion criteria
25 November 2011	- Amendment to study schedule to remove and add assessments - Clarification of number of tablets/capsules in each bottle - Correction of visit numbers throughout the protocol (to coincide with information in earlier amendment).
20 December 2011	- Amendment to protocol and study schedule to add assessments (GSK biomarker analysis) - Patients to be fasted prior to all visits, apart from visit three (week one) - Clarification re Fibroscan and patient's BMI - Review of compliance of medication added to schedule at visit three (week one) - "Tablets" amended to "Capsules" in the protocol for accuracy - Code break list to be used instead of code break envelopes - Updated web address for online randomisation - Change in fax number for reporting SAEs - Co-Investigator added to protocol contacts - Membership of Trial Management Group amended - Addition of three new sites (and Principal Investigator details)
14 May 2012	- Exclusion criteria (HBA1C >15.0 and amendment to diabetes treatment) - Ultrasound may be carried out +/- 1 month from screening visit date - Amendment to number of centres participating
14 August 2012	- Clarification of when local serum samples and samples for GSK Biomarker analysis are to be taken. - The serum sample for assessment of GSK Biomarkers no longer be collected at both screening and baseline visits, only at the baseline visit. - Clarification that patients may opt out of having samples taken for GSK Biomarker analysis, but continue in the main part of the study. - Clarification that Fibroscan to be carried out when facilities are available. - Amendment to number of centres participating. More sites are currently being invited to participate.
18 February 2013	Protocol amended in order to reflect changes in the funding arrangements and the changes in statistical analysis due to the reduced recruitment figures.
09 July 2013	Amendment made to the assessments carried out if patients withdraw early from the study as a liver biopsy for those who wish to withdraw early from the study would not help to assess a change in fibrosis of the liver. Therefore for those who wished to withdraw early a liver biopsy would not be requested. All other tests remained the same.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported