EU Clinical Trials Register

Clinical trial results:

Reducing pathology in Alzheimer's Disease through Angiotensin taRgeting. The RADAR Trial. A phase II, two arm, double-blind, placebo-controlled, randomised trial to evaluate the effect of losartan on brain tissue changes in patients diagnosed with Alzheimer's disease.

Summary

EudraCT number	2012-003641-15
Trial protocol	GB
Global end of trial date	31 May 2019

Results information

Result version number	v1 (current)
This version publication date	21 August 2021
First version publication date	21 August 2021

Trial information

Trial identification

Sponsor protocol code	2625

Additional study identifiers

ISRCTN number	ISRCTN93682878
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	North Bristol NHS Research and Innovation
Sponsor organisation address	Southmead Hospital, Southmead Road, Bristol, United Kingdom,
Public contact	Clinical Trials Manager, North Bristol NHS Trust, +44 (0117) 32 38602, helen.lewis@nbt.nhs.uk
Scientific contact	Clinical Trials Manager, North Bristol NHS Trust, +44 (0117) 32 38602, helen.lewis@nbt.nhs.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	01 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2019
Global end of trial reached?	Yes
Global end of trial date	31 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To what extent does angiotensin II signalling blockade by losartan reduce MRI-based measures of brain atrophy (wasting) in Alzheimer's Disease?

Angiotensin II is a small molecule that is already well known for being responsible for the contraction of blood vessels which in turn increases blood pressure. More recent evidence over the last decades has come to light of how angiotensin II is also very promiscuous in biochemical terms. Angiotensin II (or Ang II) is very involved in processes that increase inflammation; it inhibits the release of the chemical acetylcholine which is vital for memory formation in the brain; it is heavily involved with how cells regulate calcium levels which in turn can impact on levels of cell death and the activation of other mechanisms that also damage cells. All of these facets are characteristics of the detrimental processes that are all very active in the brain of patients with Alzheimer's disease.

Protection of trial subjects:

An open label phase of the trial was conducted to ensure participant drug toloerability. Safety bloods were taken during the trial to monitor participant safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2013
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: 211
Worldwide total number of subjects	211
EEA total number of subjects	211

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)	37
From 65 to 84 years	168
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Participants were identified from AD clinic lists, primary care and from the 'Join Dementia Research' portal. Potential participants were sent; letter of invitation, Patient Information Sheet, Companion Information sheet and a reply slip. Response dependent participants were phoned for eligibility check and to make consenting/screening appointment

Pre-assignment

Screening details:

Pre-screening phase: early eligibility assessment (medication records, brief telephone assessment)
Screening visit: eligibility assessment (MMSE, blood tests)
Open label phase (including washout period): drug tolerabity (BP, blood for safety tests, record AEs)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention - Losartan

Arm description:

We used a maximum dose of over-encapsulated 100mg of losartan which was titrated directly from over-encapsulated 25 mg losartan that was initially given for 7 days and, reflecting standard clinical practice

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

Dosage and administration details:

Following randomisation, patients followed the same titration pattern as was followed in the open label phase of 25mg for 7 days then 100mg as a maintenance dosage with a 14-day monitoring and dispensing follow-up visit within the randomised phase

Arm title	Control - placebo

Arm description:

The placebo used in this study was similarly over-encapsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK

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:

The placebo used in this study was similarly capsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK.

Number of subjects in period 1	Intervention - Losartan	Control - placebo
Started	105	106
Completed	105	106

Period 2

Period 2 title	3 month
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention - Losartan

Arm description: -

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

Dosage and administration details:

Following randomisation, patients followed the same titration pattern as was followed in the open label phase of 25mg for 7 days then 100mg as a maintenance dosage with a 14-day monitoring and dispensing follow-up visit within the randomised phase

Arm title	Control - placebo

Arm description: -

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

Dosage and administration details:

The placebo used in this study was similarly capsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK.

Number of subjects in period 2	Intervention - Losartan	Control - placebo
Started	105	106
Completed	105	106

Period 3

Period 3 title	6 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention - Losartan

Arm description: -

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

Dosage and administration details:

Following randomisation, patients followed the same titration pattern as was followed in the open label phase of 25mg for 7 days then 100mg as a maintenance dosage with a 14-day monitoring and dispensing follow-up visit within the randomised phase

Arm title	Control - placebo

Arm description: -

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:

The placebo used in this study was similarly capsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK.

Number of subjects in period 3	Intervention - Losartan	Control - placebo
Started	105	106
Completed	105	106

Period 4

Period 4 title	9 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention - Losartan

Arm description: -

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

Dosage and administration details:

Following randomisation, patients followed the same titration pattern as was followed in the open label phase of 25mg for 7 days then 100mg as a maintenance dosage with a 14-day monitoring and dispensing follow-up visit within the randomised phase

Arm title	Control - placebo

Arm description: -

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:

The placebo used in this study was similarly capsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK.

Number of subjects in period 4	Intervention - Losartan	Control - placebo
Started	105	106
Completed	105	106

Period 5

Period 5 title	12 months
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention - Losartan

Arm description: -

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

Dosage and administration details:

Following randomisation, patients followed the same titration pattern as was followed in the open label phase of 25mg for 7 days then 100mg as a maintenance dosage with a 14-day monitoring and dispensing follow-up visit within the randomised phase

Arm title	Control - placebo

Arm description: -

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:

The placebo used in this study was similarly capsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK.

Number of subjects in period 5	Intervention - Losartan	Control - placebo
Started	105	106
Completed	105	106

Period 6

Period 6 title	12 months hypertension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention - hypertensive

Arm description: -

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

Dosage and administration details:

Following randomisation, patients followed the same titration pattern as was followed in the open label phase of 25mg for 7 days then 100mg as a maintenance dosage with a 14-day monitoring and dispensing follow-up visit within the randomised phase

Arm title	Intervention - normatensive

Arm description: -

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

Dosage and administration details:

Following randomisation, patients followed the same titration pattern as was followed in the open label phase of 25mg for 7 days then 100mg as a maintenance dosage with a 14-day monitoring and dispensing follow-up visit within the randomised phase

Arm title	Control - hypertensive

Arm description: -

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:

The placebo used in this study was similarly capsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK.

Arm title	Control - normatensive

Arm description: -

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:

The placebo used in this study was similarly capsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK.

Number of subjects in period 6[1]	Intervention - hypertensive	Intervention - normatensive	Control - hypertensive
Started	37	47	43
Completed	37	47	43

Number of subjects in period 6[1]	Control - normatensive
Started	44
Completed	44

Notes:

[1] - 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: The numbers reflect subgroups within arms rather than preceding periods

Baseline characteristics

Reporting groups

Reporting group title	Intervention - Losartan
Reporting group description:	
We used a maximum dose of over-encapsulated 100mg of losartan which was titrated directly from over-encapsulated 25 mg losartan that was initially given for 7 days and, reflecting standard clinical practice	
Reporting group title	Control - placebo
Reporting group description:	
The placebo used in this study was similarly over-encapsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK	

Reporting group values	Intervention - Losartan	Control - placebo	Total
Number of subjects	105	106	211
Age categorical			
Units: Subjects			
<70	39	39	78
70-79	39	42	81
>79	27	25	52
Gender categorical			
Units: Subjects			
Female	45	39	84
Male	60	67	127
Ethnicity			
Units: Subjects			
White	104	106	210
Other	1	0	1
Hypertensive			
Units: Subjects			
Yes	47	50	97
No	58	56	114
Taking anti-dementia drug			
Units: Subjects			
Yes	100	102	202
No	5	4	9
Schelten's score			
Units: Subjects			
Absent/Low	62	62	124
Moderate/Sever	43	44	87
Years of education			
Units: years			
median	12	12	
inter-quartile range (Q1-Q3)	10 to 16	11 to 16	-
Time since diagnosis			
Units: years			
median	1.38	1.10	
inter-quartile range (Q1-Q3)	0.64 to 2.29	0.69 to 2.43	-
Total brain volume			

Units: ml			
arithmetic mean	1022	1036	
standard deviation	± 99	± 111	-

Total intracranial volume			
Units: ml			
arithmetic mean	1440	1459	
standard deviation	± 140	± 146	-

Lateral ventricular volume			
Units: ml			
median	48	47	
inter-quartile range (Q1-Q3)	35 to 69	35 to 64	-

Total hippocampal volume			
Units: ml			
arithmetic mean	5.2	5.0	
standard deviation	± 0.9	± 1.0	-

Left hippocampal volume			
Units: ml			
arithmetic mean	2.5	2.5	
standard deviation	± 0.5	± 0.5	-

Right hippocampal volume			
Units: ml			
arithmetic mean	2.6	2.6	
standard deviation	± 0.5	± 0.5	-

NPI			
Units: instrument score			
median	8	6	
inter-quartile range (Q1-Q3)	3 to 18	2 to 15	-

BADLS			
Units: instrument score			
median	7	5	
inter-quartile range (Q1-Q3)	2 to 13	2 to 9	-

DEMQOL			
Units: instrument score			
median	96	96	
inter-quartile range (Q1-Q3)	87 to 102	85 to 102	-

DEMQOL-PROXY			
Units: instrument score			
median	91	92	
inter-quartile range (Q1-Q3)	82 to 100	83 to 99	-

Sitting systolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±	±	-

Sitting diastolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±	±	-

Standing systolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±	±	-

| Mean Systolic BP | | | |

Units: mmHG			
arithmetic mean			
standard deviation	±	±	-
Standing diastolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±	±	-
Mean Diastolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±	±	-
ADAS-COG			
Units: instrument score			
arithmetic mean			
standard deviation	±	±	-
MMSE			
Units: instrument score			
arithmetic mean		22	
standard deviation	±	± 3	-

Subject analysis sets

Subject analysis set title	Reduced N BL BP 1 - Intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
Incomplete N of baseline blood pressure measures	
Subject analysis set title	Reduced N BL BP 1 - Control
Subject analysis set type	Full analysis
Subject analysis set description:	
Incomplete set of baseline blood pressure measures	
Subject analysis set title	Reduced N BL BP 2 - Intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
incomplete baseline BP measures	
Subject analysis set title	Reduced N BL BP 2 - Control
Subject analysis set type	Full analysis
Subject analysis set description:	
incomplete set of baseline blood pressure measures	
Subject analysis set title	Reduced N BL ADAS - Intervention
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
incomplete baseline adas-cog instrument	
Subject analysis set title	Reduced N BL ADAS - Control
Subject analysis set type	Full analysis
Subject analysis set description:	
incomplete baseline adas-cog instrument	
Subject analysis set title	Reduced N BL MMSE - Intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
incomplete baseline MMSE instrument	

Reporting group values	Reduced N BL BP 1 - Intervention	Reduced N BL BP 1 - Control	Reduced N BL BP 2 - Intervention
Number of subjects	85	85	83
Age categorical			
Units: Subjects			
<70			
70-79			
>79			
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
White			
Other			
Hypertensive			
Units: Subjects			
Yes			
No			
Taking anti-dementia drug			
Units: Subjects			
Yes			
No			
Schelten's score			
Units: Subjects			
Absent/Low			
Moderate/Sever			
Years of education			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Time since diagnosis			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Total brain volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±
Total intracranial volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±
Lateral ventricular volume			
Units: ml			
median			
inter-quartile range (Q1-Q3)			
Total hippocampal volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±

Left hippocampal volume
Units: ml
    arithmetic mean
    standard deviation
	
	±
		
		±
			
			±

Right hippocampal volume
Units: ml
    arithmetic mean
    standard deviation
	
	±
		
		±
			
			±

NPI
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

BADLS
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

DEMQOL
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

DEMQOL-PROXY
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

Sitting systolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	138
	± 14
		
		138
		± 15
			
			±

Sitting diastolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	77
	± 9
		
		78
		± 9
			
			±

Standing systolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±
		
		±
			
			137
			± 17

Mean Systolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±
		
		±
			
			138
			± 13

Standing diastolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±
		
		±
			
			80
			± 12

Mean Diastolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±
		
		±
			
			79
			± 9

ADAS-COG
Units: instrument score
    arithmetic mean
    standard deviation
	
	±
		
		±
			
			±

MMSE			
Units: instrument score			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Reduced N BL BP 2 - Control	Reduced N BL ADAS - Intervention	Reduced N BL ADAS - Control
Number of subjects	84	103	104
Age categorical			
Units: Subjects			
<70			
70-79			
>79			
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
White			
Other			
Hypertensive			
Units: Subjects			
Yes			
No			
Taking anti-dementia drug			
Units: Subjects			
Yes			
No			
Schelten's score			
Units: Subjects			
Absent/Low			
Moderate/Sever			
Years of education			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Time since diagnosis			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Total brain volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±
Total intracranial volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±
Lateral ventricular volume			
Units: ml			
median			

inter-quartile range (Q1-Q3)			
Total hippocampal volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±
Left hippocampal volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±
Right hippocampal volume			
Units: ml			
arithmetic mean			
standard deviation	±	±	±
NPI			
Units: instrument score			
median			
inter-quartile range (Q1-Q3)			
BADLS			
Units: instrument score			
median			
inter-quartile range (Q1-Q3)			
DEMQOL			
Units: instrument score			
median			
inter-quartile range (Q1-Q3)			
DEMQOL-PROXY			
Units: instrument score			
median			
inter-quartile range (Q1-Q3)			
Sitting systolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±	±	±
Sitting diastolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±	±	±
Standing systolic BP			
Units: mmHG			
arithmetic mean	134		
standard deviation	± 17	±	±
Mean Systolic BP			
Units: mmHG			
arithmetic mean	136		
standard deviation	± 15	±	±
Standing diastolic BP			
Units: mmHG			
arithmetic mean	79		
standard deviation	± 9	±	±
Mean Diastolic BP			
Units: mmHG			
arithmetic mean	78		

standard deviation	± 8	±	±
ADAS-COG			
Units: instrument score			
arithmetic mean		20	19
standard deviation	±	± 8	± 7
MMSE			
Units: instrument score			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Reduced N BL MMSE - Intervention		
Number of subjects	103		
Age categorical			
Units: Subjects			
<70			
70-79			
>79			
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity			
Units: Subjects			
White			
Other			
Hypertensive			
Units: Subjects			
Yes			
No			
Taking anti-dementia drug			
Units: Subjects			
Yes			
No			
Schelten's score			
Units: Subjects			
Absent/Low			
Moderate/Sever			
Years of education			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Time since diagnosis			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Total brain volume			
Units: ml			
arithmetic mean			
standard deviation	±		
Total intracranial volume			
Units: ml			

arithmetic mean			
standard deviation	±		

Lateral ventricular volume
Units: ml
    median
    inter-quartile range (Q1-Q3)			

Total hippocampal volume
Units: ml
    arithmetic mean
    standard deviation
	
	±		

Left hippocampal volume
Units: ml
    arithmetic mean
    standard deviation
	
	±		

Right hippocampal volume
Units: ml
    arithmetic mean
    standard deviation
	
	±		

NPI
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

BADLS
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

DEMQOL
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

DEMQOL-PROXY
Units: instrument score
    median
    inter-quartile range (Q1-Q3)			

Sitting systolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±		

Sitting diastolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±		

Standing systolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±		

Mean Systolic BP
Units: mmHG
    arithmetic mean
    standard deviation
	
	±		

Standing diastolic BP Units: mmHG			

arithmetic mean			
standard deviation	±		
Mean Diastolic BP			
Units: mmHG			
arithmetic mean			
standard deviation	±		
ADAS-COG			
Units: instrument score			
arithmetic mean			
standard deviation	±		
MMSE			
Units: instrument score			
arithmetic mean	22		
standard deviation	± 4		

End points

End points reporting groups

Reporting group title	Intervention - Losartan
Reporting group description:	
We used a maximum dose of over-encapsulated 100mg of losartan which was titrated directly from over-encapsulated 25 mg losartan that was initially given for 7 days and, reflecting standard clinical practice	
Reporting group title	Control - placebo
Reporting group description:	
The placebo used in this study was similarly over-encapsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK	
Reporting group title	Intervention - Losartan
Reporting group description: -	
Reporting group title	Control - placebo
Reporting group description: -	
Reporting group title	Intervention - Losartan
Reporting group description: -	
Reporting group title	Control - placebo
Reporting group description: -	
Reporting group title	Intervention - Losartan
Reporting group description: -	
Reporting group title	Control - placebo
Reporting group description: -	
Reporting group title	Intervention - Losartan
Reporting group description: -	
Reporting group title	Control - placebo
Reporting group description: -	
Reporting group title	Intervention - hypertensive
Reporting group description: -	
Reporting group title	Intervention - normatensive
Reporting group description: -	
Reporting group title	Control - hypertensive
Reporting group description: -	
Reporting group title	Control - normatensive
Reporting group description: -	
Subject analysis set title	Reduced N BL BP 1 - Intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
Incomplete N of baseline blood pressure measures	
Subject analysis set title	Reduced N BL BP 1 - Control
Subject analysis set type	Full analysis
Subject analysis set description:	
Incomplete set of baseline blood pressure measures	
Subject analysis set title	Reduced N BL BP 2 - Intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
incomplete baseline BP measures	
Subject analysis set title	Reduced N BL BP 2 - Control
Subject analysis set type	Full analysis

Subject analysis set description:	
incomplete set of baseline blood pressure measures	
Subject analysis set title	Reduced N BL ADAS - Intervention
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
incomplete baseline adas-cog instrument	
Subject analysis set title	Reduced N BL ADAS - Control
Subject analysis set type	Full analysis
Subject analysis set description:	
incomplete baseline adas-cog instrument	
Subject analysis set title	Reduced N BL MMSE - Intervention
Subject analysis set type	Full analysis
Subject analysis set description:	
incomplete baseline MMSE instrument	

Primary: Mean brain volume at 12 months

End point title	Mean brain volume at 12 months
End point description:	
End point type	Primary
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
arithmetic mean (standard deviation)	1002 (± 98)	1018 (± 111)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean brain volume at 12m
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.46
upper limit	0.89

Secondary: 12 month BSI

End point title	12 month BSI
End point description:	
brain volume change from baseline to 12 months as measured by the boundary shift interval	
End point type	Secondary
End point timeframe:	
baseline to 12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
arithmetic mean (standard deviation)	20.0 (± 10.8)	19.1 (± 10.3)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean BSI
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.411
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.72
upper limit	4.19

Secondary: Mean MMSE at 12 months

End point title	Mean MMSE at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	97		
Units: instrument score				
arithmetic mean (standard deviation)	19 (± 6)	19 (± 6)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean MMSE at 12m
Comparison groups	Control - placebo v Intervention - Losartan
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	0.78

Secondary: NPI at 12 months

End point title	NPI at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	99		
Units: instrument score				
median (inter-quartile range (Q1-Q3))	8 (3 to 18)	8 (3 to 17)		

Statistical analyses

Statistical analysis title	Adjusted ratio of geometric mean NPI 12 months
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Regression, Linear
Parameter estimate	ratio of geometric means
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.13

Secondary: BADLS at 12 months

End point title	BADLS at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	100		
Units: instrument score				
median (inter-quartile range (Q1-Q3))	10 (3 to 17)	7 (3 to 14)		

Statistical analyses

Statistical analysis title	Adjusted ratio of BADLS 12 month geometric means
Comparison groups	Intervention - Losartan v Control - placebo

Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Regression, Linear
Parameter estimate	ratio of geometric means
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.21

Secondary: DEMQOL at 12 months

End point title	DEMQOL at 12 months
End point description:	
End point type	Secondary
End point timeframe:	

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	95		
Units: instrument score				
median (inter-quartile range (Q1-Q3))	96 (87 to 105)	94 (85 to 101)		

Statistical analyses

Statistical analysis title	Adjusted ratio of 12 month DEMQOL geometric means
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Regression, Linear
Parameter estimate	ratio of geometric means
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.09

Secondary: DEMQOL-PROXY at 12 months

End point title	DEMQOL-PROXY at 12 months
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	98		
Units: instrument score				
median (inter-quartile range (Q1-Q3))	93 (83 to 99)	93 (82 to 100)		

Statistical analyses

Statistical analysis title	Adjusted difference of 12m DEMQOL-PROXY means
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	4.28

Secondary: 12 month ADAS-COG

End point title	12 month ADAS-COG
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	92		
Units: instrument score				
arithmetic mean (standard deviation)	23 (± 12)	24 (± 12)		

Statistical analyses

Statistical analysis title	Adjusted difference in 12 m ADAS-COG mean
Comparison groups	Control - placebo v Intervention - Losartan
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.71
upper limit	1.66

Secondary: White Matter Hyperintensity at 12 months

End point title	White Matter Hyperintensity at 12 months
End point description:	

End point type	Secondary
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: ml				
median (inter-quartile range (Q1-Q3))	11992 (2548 to 24039)	9793 (4788 to 20263)		

Statistical analyses

Statistical analysis title	Ratio of geometric means of 12 month WMH
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.697
Method	Regression, Linear
Parameter estimate	ratio of geometric means
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.05

Other pre-specified: Compliance sensitivity analysis

End point title	Compliance sensitivity analysis
End point description:	
End point type	Other pre-specified
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	87		
Units: ml				
arithmetic mean (standard deviation)	1002 (± 100)	1019 (± 113)		

Statistical analyses

Statistical analysis title	CACE analysis
Statistical analysis description:	
CACE analysis based on treatment compliance status	
Comparison groups	Intervention - Losartan v Control - placebo

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106
Method	2SLS IV regression
Parameter estimate	Mean difference (net)
Point estimate	-3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.14
upper limit	0.69

Other pre-specified: 12m brain volume by hypertensive status

End point title	12m brain volume by hypertensive status

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Intervention - hypertensive	Intervention - normatensive	Control - hypertensive	Control - normatensive
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	47	43	44
Units: ml				
arithmetic mean (standard deviation)	998 (± 101)	1044 (± 97)	1009 (± 114)	1029 (± 112)

Statistical analyses

Statistical analysis title	Treatment effect moderation of hypertensive status

Statistical analysis description:

primary analysis repeated including an interaction between treatment allocation and hypertensive status

Comparison groups	Intervention - hypertensive v Intervention - normatensive v Control - hypertensive v Control - normatensive
Number of subjects included in analysis	171
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.509
Method	Regression, Linear
Parameter estimate	difference in adjusted mean difference
Point estimate	-2.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.43
upper limit	5.19

Other pre-specified: MI sensitivity analysis of primary outcome (brain volume)

End point title	MI sensitivity analysis of primary outcome (brain volume)

End point description:

End point type	Other pre-specified

End point timeframe:

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	106		
Units: ml				
arithmetic mean (standard error)	1003 (± 10)	1017 (± 10)		

Statistical analyses

Statistical analysis title	repeat primary analysis on multiply imputed data
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.77
upper limit	3.25

Post-hoc: 12 month lateral ventricular volume

End point title	12 month lateral ventricular volume

End point description:

End point type	Post-hoc

End point timeframe:

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
median (inter-quartile range (Q1-Q3))	51 (40 to 78)	50 (40 to 67)		

Statistical analyses

Statistical analysis title	Ratio of geometric means of 12m LVV
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	171
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.443
Method	Regression, Linear
Parameter estimate	ratio of geometric means
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.01

Post-hoc: LVV BSI

End point title	LVV BSI

End point description:

End point type	Post-hoc

End point timeframe:

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	86		
Units: ml				
median (inter-quartile range (Q1-Q3))	5 (3 to 8)	5 (3 to 7)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean LVV BSI
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	169
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.38
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	0.56

Post-hoc: 12m left hippocampal volume

End point title	12m left hippocampal volume
End point description:	

End point type	Post-hoc
End point timeframe:	

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
arithmetic mean (standard deviation)	2.5 (± 0.5)	2.4 (± 0.5)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean 12m LHV
Comparison groups	Control - placebo v Intervention - Losartan
Number of subjects included in analysis	171
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.337
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.03

Post-hoc: LHV BSI

End point title	LHV BSI
End point description:	

End point type	Post-hoc
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
arithmetic mean (standard deviation)	0.11 (± 0.08)	0.11 (± 0.06)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean LHV BSI
Comparison groups	Control - placebo v Intervention - Losartan
Number of subjects included in analysis	171
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.385
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.01

Post-hoc: 12m right hippocampal volume

End point title	12m right hippocampal volume
End point description:	

End point type	Post-hoc

End point timeframe:

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
arithmetic mean (standard deviation)	2.6 (± 0.5)	2.5 (± 0.5)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean 12m RHV
Comparison groups	Control - placebo v Intervention - Losartan
Number of subjects included in analysis	171
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.112
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.03

Post-hoc: RHV BSI

End point title	RHV BSI

End point description:

End point type	Post-hoc

End point timeframe:

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
arithmetic mean (standard deviation)	0.11 (± 0.08)	0.12 (± 0.06)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean RHV BSI
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	171
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.231
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.01

Post-hoc: 12m total hippocampal volume

End point title	12m total hippocampal volume

End point description:

End point type	Post-hoc

End point timeframe:

12 months

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	87		
Units: ml				
arithmetic mean (standard deviation)	5.0 (± 0.9)	4.9 (± 0.9)		

Statistical analyses

Statistical analysis title	Adjusted difference in mean 12m THV
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	171
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.144
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.05

Post-hoc: 12m Schelten's

End point title	12m Schelten's
End point description:	
End point type	Post-hoc
End point timeframe:	
12 months	

End point values	Intervention - Losartan	Control - placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	98		
Units: number of people				
no atrophy	14	9		
only widening of choroid fissure	36	28		
also widening of temporal horn of lateral ventricl	21	43		
moderate loss of hippocampal volume	19	18		
severe volume loss of hippocampus	1	0		

Statistical analyses

Statistical analysis title	Difference in 12m Schelten's score
Comparison groups	Intervention - Losartan v Control - placebo
Number of subjects included in analysis	189
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.004
Method	ordinal logistic regression
Parameter estimate	proportional odds ratio
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.68

Adverse events

Adverse events information

Timeframe for reporting adverse events:

baseline to 12 months

Assessment type	Systematic

Dictionary used

Dictionary name	NA
Dictionary version	NA

Reporting groups

Reporting group title	Intervention - Losartan

Reporting group description:

We used a maximum dose of over-encapsulated 100mg of losartan which was titrated directly from over-encapsulated 25 mg losartan that was initially given for 7 days and, reflecting standard clinical practice

Reporting group title	Control - placebo

Reporting group description:

The placebo used in this study was similarly over-encapsulated and made to match both doses and sourced from St. Mary's Pharmaceutical Unit [SMPU], Cardiff, UK

Serious adverse events	Intervention - Losartan	Control - placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 105 (20.95%)	20 / 106 (18.87%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Elective surgery (throat biopsy)			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Ankle swelling (oedema)			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Persistent nausea, dizziness and headache			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mobility problems and unable to get out of bath				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Overdose of dementia medication				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Food poisoning				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Collapse				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Collapse without loss of consciousness				
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Psychiatric disorders				
Found slumped on sofa unable to sit up, visual hallucinations				
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vivid delusions and aggressive outburst				
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Investigations				
Temp admission to Dementia Assessment Unit				

subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

Injury, poisoning and procedural complications

fall

subjects affected / exposed	2 / 105 (1.90%)	2 / 106 (1.89%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		

fainting

subjects affected / exposed	1 / 105 (0.95%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Participant died. Admitted with femur fracture, dehydration and anaemia. Unrelated to trial

subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		

Cardiac disorders

prolonged syncopal episode

subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

fainting and bradycardia

subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Nervous system disorders

seizure

subjects affected / exposed	1 / 105 (0.95%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Brain pathology

subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Admission 3 days Right sided chest pain. Discharged with anticoagulant meds.			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation and prolapse			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomach pain and breathing difficulty			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention and diarrhoea and vomiting			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Collapse Raised ALT 100 (0-55)			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grossly raised AST serum level			

subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Safety bloods results outside of the safety range			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash around armpits and right side of the abdomen			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
development of diabetes			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Participant died pancreatic cancer			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Hospital admission knee pain. Arthritis			
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hospital admission. Sepsis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis left leg			

subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Cellulitis left leg flare up				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Recurrent bronchitis				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dizzy spell, tremor and cold hands. Discharged with antibiotics.				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Chest infection				
subjects affected / exposed	0 / 105 (0.00%)	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lower respiratory tract infection				
subjects affected / exposed	1 / 105 (0.95%)	0 / 106 (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	Intervention - Losartan	Control - placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 105 (76.19%)	84 / 106 (79.25%)	
General disorders and administration site conditions			
AE			
subjects affected / exposed	80 / 105 (76.19%)	84 / 106 (79.25%)	
occurrences (all)	80	84	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2013	Revisions for clarity, consistency with SOPs and MRE recommendations
18 July 2013	Addition of information pertaining to pilot imaging procedures
28 November 2013	Change to minimisation details and eligibility criteria
07 October 2014	Remove severe hippocampal atrophy as exclusion criteria
03 December 2015	Change to MMSE inclusion criteria
03 March 2016	Inclusion of an embedded qualitative component
27 July 2017	Inclusion of additional pre-screening tools, and clarification to consent wording
11 October 2017	Amendment to the blood pressure range exclusion criteria

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.

This study may still be underpowered, or the intervention may have been given too late or for an insufficient amount of time in the disease process to influence the outcomes or may not have crossed the blood brain barrier as much as expected.

Notes: