Clinical trial results:
A Randomized, Double-Blind, Parallel, Placebo or Amlodipine-Controlled Study of the Effects of Losartan on Proteinuria in Pediatric Patients With or Without Hypertension

Summary

EudraCT number	2006-006415-74
Trial protocol	NO LT HU ES GB DE Outside EU/EEA
Global end of trial date	31 March 2011

Results information

Result version number	v1 (current)
This version publication date	13 April 2016
First version publication date	10 April 2015

Trial information

Trial identification

Sponsor protocol code	0954-326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00568178
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000008-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to study the safety and efficacy of losartan compared to placebo (nonhypertensives) or amlodipine (hypertensives) on reduction of proteinuria in children and adolescents up to 17 years of age with hypertension (if ≥6 years old) and without hypertension (if ≥1 year old).

The study included a 12-week double-blind treatment phase and a 36-month open-label extension phase. Participants who completed or discontinued the initial 12-week phase of the study and who opted to participate in the open label extension phase were randomized to either losartan or enalapril at a dose of the investigator's choosing for the duration of the extension. The open label extension was designed to continue until the 100th participant completed 3 years of follow-up. Thus, participants were in the extension for varying durations based upon the time of their enrollment.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Lithuania: 12
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Colombia: 31
Country: Number of subjects enrolled	India: 25

Country: Number of subjects enrolled	Guatemala: 14
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	Mexico: 47
Country: Number of subjects enrolled	Panama: 9
Country: Number of subjects enrolled	Peru: 37
Country: Number of subjects enrolled	Philippines: 17
Country: Number of subjects enrolled	Puerto Rico: 7
Country: Number of subjects enrolled	Romania: 11
Worldwide total number of subjects	306
EEA total number of subjects	60

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)	13
Children (2-11 years)	154
Adolescents (12-17 years)	139
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

As of March 2011, the study was completed.

Phase III First Patient In: 21Jun07; Last Patient Last Visit (double-blind base study): 16Sep08; and (open-label extension): 31Mar11. The study included 52 centers (USA, Europe, Latin America, and Asia) and participants included children aged 6-17 (hypertensive) or 1-17 (normotensive) with proteinuria.

Pre-assignment

Screening details:

During a 4-week, single-blind run-in participants received losartan placebo (normotensive) or amlodipine (hypertensive) and underwent wash-out of anti-hypertensive agents. To qualify for randomization, participants had to have a mean urine Pr/Cr ratio of ≥0.3 gram/gram (gm/gm) derived from baseline urine samples.

Period 1

Period 1 title	Double Blind Base Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan Double Blind Normotensive

Arm description:

Normotensive participants who were randomized to losartan. Losartan dispensed as tablets or suspension depending on participant weight and ability to swallow tablets.

Losartan suspension dosing: 0.7 milligram/kilograms/day (mg/kg/day) titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Losartan Potassium
Investigational medicinal product code	
Other name	Cozaar®
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Either tablets (25 or 50 mg) or liquid suspension (2.5 mg/mL) were administered. Liquid suspension prepared using losartan 50 mg tablets for participants who weighed less than 25 kilograms (kg) or for those participants unable to swallow tablets.

Losartan Use During the Double-Blind Treatment Phase: Losartan suspension dosing at 0.7 milligram/kilograms/day (mg/kg/day) titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks. Losartan tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks; or losartan placebo.

Losartan Use During the Treatment Extension Phase: Dose modifications of the drug were left up to the discretion of the Investigators based on each participant's level of tolerance.

Arm title	Placebo Double Blind Normotensive

Arm description:

Normotensive participants who were randomized to losartan placebo. Losartan placebo dispensed as tablets or suspension depending on participant weight and ability to swallow tablets.

Losartan placebo suspension dosing: 0.7 mg/kg/day titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan placebo tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Losartan Potassium Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Either placebo tablets (25 or 50 mg) or placebo liquid suspension (2.5 mg/mL) were administered orally for 12 weeks. Placebo liquid suspension prepared using losartan placebo 50 mg tablets for participants who weighed less than 25 kilograms (kg) or for those participants unable to swallow tablets. Participants randomized to losartan placebo had a sham titration at the 2 week visit.

Arm title	Losartan Double Blind Hypertensive

Arm description:

Hypertensive patients who were randomized to receive losartan and amlodipine placebo for 12 weeks. Losartan dispensed as tablets or suspension depending on participant weight and ability to swallow tablets. Amlodipine placebo dispensed as suspension for duration of study.

Losartan suspension dosing: 0.7 milligram/kilograms/day (mg/kg/day) titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Amlodipine placebo suspension dosing: starting dose 0.05 or 0.1 titrated to 0.2 mg/kg/day orally (max 5 mg/day) after 2 weeks if necessary to control blood pressure for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Losartan Potassium
Investigational medicinal product code	
Other name	Cozaar®
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Either tablets (25 or 50 mg) or liquid suspension (2.5 mg/mL) were administered. Liquid suspension prepared using losartan 50 mg tablets for participants who weighed less than 25 kilograms (kg) or for those participants unable to swallow tablets.

Losartan Use During the Double-Blind Treatment Phase: Losartan suspension dosing at 0.7 milligram/kilograms/day (mg/kg/day) titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks. Losartan tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks; or losartan placebo.

Losartan Use During the Treatment Extension Phase: Dose modifications of the drug were left up to the discretion of the Investigators based on each participant's level of tolerance.

Investigational medicinal product name	Amlodipine Besylate Placebo Suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Liquid suspension prepared using amlodipine besylate placebo tablets (1 mg/mL) administered orally for 12 Weeks.

Arm title	Amlodipine Double Blind Hypertensive

Arm description:

Hypertensive patients who were randomized to receive amlodipine and losartan placebo for 12 weeks. Losartan placebo dispensed as tablets or suspension depending on participant weight and ability to swallow tablets.

Losartan placebo suspension dosing: 0.7 mg/kg/day titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan placebo tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Amlodipine suspension dosing: starting dose 0.05 or 0.1 titrated to 0.2 mg/kg/day orally (max 5 mg/day) after 2 weeks if necessary to control blood pressure for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Amlodipine Besylate Suspension
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Liquid suspension prepared using amlodipine besylate 5 mg tablets (1 mg/mL) administered orally. Starting dose 0.05 or 0.1 mg/kg/day and titrated to 0.2 mg/kg/day (5 mg maximum dose) per day for 12 Weeks.

Investigational medicinal product name	Losartan Potassium Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Either placebo tablets (25 or 50 mg) or placebo liquid suspension (2.5 mg/mL) were administered orally for 12 weeks. Placebo liquid suspension prepared using losartan placebo 50 mg tablets for participants who weighed less than 25 kilograms (kg) or for those participants unable to swallow tablets. Participants randomized to losartan placebo had a sham titration at the 2 week visit.

Number of subjects in period 1	Losartan Double Blind Normotensive	Placebo Double Blind Normotensive	Losartan Double Blind Hypertensive
Started	122	124	30
Completed	116	118	29
Not completed	6	6	1
Consent withdrawn by subject	1	1	-
Physician decision	1	1	-
Adverse event, non-fatal	-	2	1
Lost to follow-up	1	-	-
Progressive disease	-	-	-

Protocol deviation	3	2	-

Number of subjects in period 1	Amlodipine Double Blind Hypertensive
Started	30
Completed	25
Not completed	5
Consent withdrawn by subject	-
Physician decision	1
Adverse event, non-fatal	2
Lost to follow-up	1
Progressive disease	1
Protocol deviation	-

Period 2

Period 2 title	Open Label Extension
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan Open Label Extension

Arm description:

All participants who completed the 12-week DB treatment phase (or discontinued early due to increased proteinuria) were invited to participate in the open-label extension and were randomized in a 1:1 ratio to either losartan or enalapril. Dosing of study medication during the extension phase of the study was at the investigator’s discretion. Losartan 25-mg and 50-mg tablets were available for participants able to swallow tablets. For participants unable to swallow tablets, or who weighed <25 kg, losartan suspension (2.5 mg/ml) was prepared.

Arm type	Experimental
Investigational medicinal product name	Losartan Potassium
Investigational medicinal product code	
Other name	Cozaar®
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Either tablets (25 or 50 mg) or liquid suspension (2.5 mg/mL) were administered. Liquid suspension prepared using losartan 50 mg tablets for participants who weighed less than 25 kilograms (kg) or for those participants unable to swallow tablets.

Losartan Use During the Double-Blind Treatment Phase: Losartan suspension dosing at 0.7 milligram/kilograms/day (mg/kg/day) titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks. Losartan tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks; or losartan placebo.

Losartan Use During the Treatment Extension Phase: Dose modifications of the drug were left up to the discretion of the Investigators based on each participant's level of tolerance.

Arm title	Enalapril Open Label Extension

Arm description:

All participants who completed the 12-week DB treatment phase (or discontinued early due to increased proteinuria) were invited to participate in the open-label extension and were randomized in a 1:1 ratio to either losartan or enalapril. Dosing of study medication during the extension phase of the study was at the investigator's discretion. Enalapril 2.5-, 5-, 10-, and 20-mg tablets were available for participants able to swallow tablets. For participants unable to swallow tablets, or who weighed <25 kg, enalapril suspension (1 mg/mL) was prepared.

Arm type	Active comparator
Investigational medicinal product name	Enalapril Maleate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet and powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Enalapril 2.5-, 5-, 10-, and 20-mg tablets or enalapril suspension (1 mg/mL prepared from 20 mg tablet), oral administration, once daily for 36 months.

Number of subjects in period 2[1]	Losartan Open Label Extension	Enalapril Open Label Extension
Started	134	134
Completed	55	54
Not completed	79	80
Consent withdrawn by subject	4	4
Physician decision	9	8
Termination of trial	45	47
Adverse event, non-fatal	11	8
Pregnancy	-	1
Lost to follow-up	6	11
Progressive disease	3	1
Protocol deviation	1	-

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: After completing or discontinuing early from the DB study, participants could join an optional OL losartan versus enalapril extension. Of 306 participants who began the DB study, 268 participants continued in the extension.

Baseline characteristics

Reporting groups

Reporting group title	Double Blind Base Study

Reporting group description: -

Reporting group values	Double Blind Base Study	Total	
Number of subjects	306	306	
Age categorical Units: Subjects			
≤6 Years of Age	75	75	
7-12 Years of Age	114	114	
13-17 Years of Age	117	117	
Age continuous Units: years			
arithmetic mean	10.1		
standard deviation	± 4.7	-	
Gender categorical Units: Subjects			
Female	130	130	
Male	176	176	
Ethnicity (NIH/OMB)			
National Institutes of Health (NIH)/Office of management and Budget (OMB) ethnic categories			
Units: Subjects			
Hispanic or Latino	161	161	
Not Hispanic or Latino	145	145	
Hypertensive			
Sitting systolic blood pressure (SiSBP) or diastolic blood pressure (SiDBP) ≥90th percentile AND participant on medication for proteinuria/hypertension OR SiSBP or SiDBP ≥95th percentile AND participant NOT on medication for proteinuria/hypertension OR documented hypertension and on anti-hypertensive medication, whether or not medicated for proteinuria.			
Units: Subjects			
Yes	60	60	
No	246	246	
Prior Angiotensin Converting Enzyme Inhibitor /Angiotensin II Type I Receptor Blocker (ACE-I/ARB)Use Units: Subjects			
Yes	164	164	
No	142	142	
Race Units: Subjects			
Asian	52	52	
Black	10	10	
Multi-Racial	70	70	
White	162	162	
Other	12	12	
Region Units: Subjects			
United States	25	25	

Outside of United States	281	281	
Tanner Stage			
A scale of physical development. The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, and development of pubic hair. Stages range from I to V with I being the least developed.			
Units: Subjects			
Stage I	147	147	
Stage II	47	47	
Stage III	40	40	
Stage IV	47	47	
Stage V	25	25	
Body Mass Index (BMI)			
Units: kilograms per meter squared (kg/m2)			
arithmetic mean	19.5		
standard deviation	± 4.9	-	
Duration of Hypertension			
Calculated for patients in hypertensive stratum.			
Units: years			
arithmetic mean	5.5		
standard deviation	± 4.5	-	
Height			
Units: centimeters (cm)			
arithmetic mean	133.9		
standard deviation	± 27.9	-	
Protein-to-Creatinine Ratio			
Units: grams/grams			
arithmetic mean	2.5		
standard deviation	± 3.3	-	
Diastolic Blood Pressure			
Units: millimeters of mercury (mm Hg)			
arithmetic mean	67.3		
standard deviation	± 11.2	-	
Sitting Systolic Blood Pressure			
Units: mm Hg			
arithmetic mean	106.6		
standard deviation	± 13.6	-	
Weight			
Units: Kilograms (kg)			
arithmetic mean	38		
standard deviation	± 20.3	-	

Subject analysis sets

Subject analysis set title	Losartan Double Blind
Subject analysis set type	Full analysis

Subject analysis set description:

"Losartan Double Blind" group includes the following: Normotensive participants (1 to 17 years of age) who were randomized to losartan in the double-blind and Hypertensive participants (6 to 17 years of age) who were randomized to losartan & amlodipine placebo in the double-blind. Participants were assigned to a normotensive or hypertensive group based on clinical profile.

Losartan therapy was administered orally, in tablet or suspension form, at an initial dose of approximately 0.7 mg/kg once daily (up to 50 or 100 mg total daily dose, weight-dependent).

Subject analysis set title	Amlodipine/Placebo Double Blind
Subject analysis set type	Full analysis

Subject analysis set description:

"Amlodipine/Placebo Double Blind" group includes the following: Normotensive participants randomized to losartan placebo in the double-blind and Hypertensive participants randomized to amlodipine and losartan placebo in the double-blind. Participants were assigned to a normotensive or hypertensive group based on clinical profile.

Losartan placebo dispensed as tablets or suspension depending on participant weight and ability to swallow tablets. Losartan placebo tablet dosing: 25 mg/day orally titrated to 50 mg/day (patients <50 kg) OR 50 mg/day orally titrated to 100 mg/day (patients ≥50 kg) for 12 weeks. Losartan placebo suspension dosing: 0.7 mg/kg/day titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Amlodipine dispensed as suspension for duration of study. Amlodipine suspension dosing: starting dose 0.05 or 0.1 titrated to 0.2 mg/kg/day orally (max 5 mg/day) after 2 weeks if necessary to control blood pressure for 12 weeks

Reporting group values	Losartan Double Blind	Amlodipine/Placebo Double Blind	
Number of subjects	152	154	
Age categorical Units: Subjects			
≤6 Years of Age	33	42	
7-12 Years of Age	57	57	
13-17 Years of Age	62	55	
Age continuous Units: years			
arithmetic mean	10.4	9.7	
standard deviation	± 4.7	± 4.6	
Gender categorical Units: Subjects			
Female	66	64	
Male	86	90	
Ethnicity (NIH/OMB)			
National Institutes of Health (NIH)/Office of management and Budget (OMB) ethnic categories			
Units: Subjects			
Hispanic or Latino	79	82	
Not Hispanic or Latino	73	72	
Hypertensive			
Sitting systolic blood pressure (SiSBP) or diastolic blood pressure (SiDBP) ≥90th percentile AND participant on medication for proteinuria/hypertension OR SiSBP or SiDBP ≥95th percentile AND participant NOT on medication for proteinuria/hypertension OR documented hypertension and on anti-hypertensive medication, whether or not medicated for proteinuria.			
Units: Subjects			
Yes	30	30	
No	122	124	
Prior Angiotensin Converting Enzyme Inhibitor /Angiotensin II Type I Receptor Blocker (ACE-I/ARB)Use Units: Subjects			
Yes	83	81	
No	69	73	
Race			

Units: Subjects			
Asian	26	26	
Black	5	5	
Multi-Racial	36	34	
White	77	85	
Other	8	4	
Region Units: Subjects			
United States	15	10	
Outside of United States	137	144	
Tanner Stage			
A scale of physical development. The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia, and development of pubic hair. Stages range from I to V with I being the least developed.			
Units: Subjects			
Stage I	69	78	
Stage II	26	21	
Stage III	22	18	
Stage IV	23	24	
Stage V	12	13	
Body Mass Index (BMI) Units: kilograms per meter squared (kg/m2)			
arithmetic mean	19.8	19.2	
standard deviation	± 5.5	± 4.2	
Duration of Hypertension			
Calculated for patients in hypertensive stratum.			
Units: years			
arithmetic mean	4.8	6.1	
standard deviation	± 4.1	± 4.8	
Height Units: centimeters (cm)			
arithmetic mean	135.8	132	
standard deviation	± 27.3	± 28.4	
Protein-to-Creatinine Ratio Units: grams/grams			
arithmetic mean	2.2	2.8	
standard deviation	± 2.6	± 3.8	
Diastolic Blood Pressure Units: millimeters of mercury (mm Hg)			
arithmetic mean	66.8	67.8	
standard deviation	± 10.7	± 11.6	
Sitting Systolic Blood Pressure Units: mm Hg			
arithmetic mean	106	107.2	
standard deviation	± 13.4	± 13.8	
Weight Units: Kilograms (kg)			
arithmetic mean	39.6	36.4	
standard deviation	± 21	± 19.5	

End points

End points reporting groups

Reporting group title	Losartan Double Blind Normotensive

Reporting group description:

Normotensive participants who were randomized to losartan. Losartan dispensed as tablets or suspension depending on participant weight and ability to swallow tablets.

Losartan suspension dosing: 0.7 milligram/kilograms/day (mg/kg/day) titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Reporting group title	Placebo Double Blind Normotensive

Reporting group description:

Normotensive participants who were randomized to losartan placebo. Losartan placebo dispensed as tablets or suspension depending on participant weight and ability to swallow tablets.

Losartan placebo suspension dosing: 0.7 mg/kg/day titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan placebo tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Reporting group title	Losartan Double Blind Hypertensive

Reporting group description:

Hypertensive patients who were randomized to receive losartan and amlodipine placebo for 12 weeks. Losartan dispensed as tablets or suspension depending on participant weight and ability to swallow tablets. Amlodipine placebo dispensed as suspension for duration of study.

Losartan suspension dosing: 0.7 milligram/kilograms/day (mg/kg/day) titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Amlodipine placebo suspension dosing: starting dose 0.05 or 0.1 titrated to 0.2 mg/kg/day orally (max 5 mg/day) after 2 weeks if necessary to control blood pressure for 12 weeks.

Reporting group title	Amlodipine Double Blind Hypertensive

Reporting group description:

Hypertensive patients who were randomized to receive amlodipine and losartan placebo for 12 weeks. Losartan placebo dispensed as tablets or suspension depending on participant weight and ability to swallow tablets.

Losartan placebo suspension dosing: 0.7 mg/kg/day titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Losartan placebo tablet dosing: 25 mg/day orally titrated to 50 mg/day (participants <50 kg) OR 50 mg/day orally titrated to 100 mg/day (participants ≥50 kg) for 12 weeks.

Amlodipine suspension dosing: starting dose 0.05 or 0.1 titrated to 0.2 mg/kg/day orally (max 5 mg/day) after 2 weeks if necessary to control blood pressure for 12 weeks.

Reporting group title	Losartan Open Label Extension

Reporting group description:

All participants who completed the 12-week DB treatment phase (or discontinued early due to increased proteinuria) were invited to participate in the open-label extension and were randomized in a 1:1 ratio to either losartan or enalapril. Dosing of study medication during the extension phase of the study was at the investigator’s discretion. Losartan 25-mg and 50-mg tablets were available for participants able to swallow tablets. For participants unable to swallow tablets, or who weighed <25 kg, losartan suspension (2.5 mg/ml) was prepared.

Reporting group title	Enalapril Open Label Extension

Reporting group description:

All participants who completed the 12-week DB treatment phase (or discontinued early due to increased proteinuria) were invited to participate in the open-label extension and were randomized in a 1:1 ratio to either losartan or enalapril. Dosing of study medication during the extension phase of the study was at the investigator's discretion. Enalapril 2.5-, 5-, 10-, and 20-mg tablets were available for participants able to swallow tablets. For participants unable to swallow tablets, or who weighed <25 kg, enalapril suspension (1 mg/mL) was prepared.

Subject analysis set title	Losartan Double Blind
Subject analysis set type	Full analysis

Subject analysis set description:

"Losartan Double Blind" group includes the following: Normotensive participants (1 to 17 years of age) who were randomized to losartan in the double-blind and Hypertensive participants (6 to 17 years of age) who were randomized to losartan & amlodipine placebo in the double-blind. Participants were assigned to a normotensive or hypertensive group based on clinical profile.

Losartan therapy was administered orally, in tablet or suspension form, at an initial dose of approximately 0.7 mg/kg once daily (up to 50 or 100 mg total daily dose, weight-dependent).

Subject analysis set title	Amlodipine/Placebo Double Blind
Subject analysis set type	Full analysis

Subject analysis set description:

"Amlodipine/Placebo Double Blind" group includes the following: Normotensive participants randomized to losartan placebo in the double-blind and Hypertensive participants randomized to amlodipine and losartan placebo in the double-blind. Participants were assigned to a normotensive or hypertensive group based on clinical profile.

Losartan placebo dispensed as tablets or suspension depending on participant weight and ability to swallow tablets. Losartan placebo tablet dosing: 25 mg/day orally titrated to 50 mg/day (patients <50 kg) OR 50 mg/day orally titrated to 100 mg/day (patients ≥50 kg) for 12 weeks. Losartan placebo suspension dosing: 0.7 mg/kg/day titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Amlodipine dispensed as suspension for duration of study. Amlodipine suspension dosing: starting dose 0.05 or 0.1 titrated to 0.2 mg/kg/day orally (max 5 mg/day) after 2 weeks if necessary to control blood pressure for 12 weeks

Primary: Double-Blind Treatment Phase: Percentage Change From Baseline in Urinary Protein/Creatinine (Pr/Cr) Ratio (gm/gm) at Week 12

End point title	Double-Blind Treatment Phase: Percentage Change From Baseline in Urinary Protein/Creatinine (Pr/Cr) Ratio (gm/gm) at Week 12

End point description:

Change in urinary protein excretion, determined as urinary Pr/Cr ratio compared to baseline (BL), after approximately twelve weeks of treatment. BL was defined as values obtained at Visit 3, Week (-1) during the Single Blind Run-in period.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Losartan Double Blind	Amlodipine/Placebo Double Blind		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	150[1]	152[2]		
Units: percentage change				
geometric mean (confidence interval 95%)	-35.8 (-43.11 to -27.55)	1.37 (-10.27 to 14.51)		

Notes:

[1] - Randomized participants who took ≥1 dose of study drug and had BL and post randomization measurement
[2] - Randomized participants who took ≥1 dose of study drug and had BL and post randomization measurement

Statistical analyses

Statistical analysis title	DB Treatment:Percent Change From BL in Pr/Cr Ratio

Statistical analysis description:

Analyzed using a mixed model for the change from BL in urinary protein excretion (on a logarithmic scale) with fixed effect terms for treatment, stratification factors, time, treatment by time interaction and BL urinary protein excretion (on log scale). A random effect for patient and an unstructured variance-covariance was used. This repeated measurements model for the change from BL in urinary protein excretion included measurements taken at Weeks 4, 8, and 12 (or early discontinuation).

Comparison groups	Amlodipine/Placebo Double Blind v Losartan Double Blind
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≤ 0.001
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.74

Notes:

[3] - Primary hypothesis was addressed based on the ratio of geometric means (obtained after antilog transformation of the difference in LS-means) at week 12, with its 95% confidence interval and associated p-value. Geometric means (obtained after antilog transformation of the LS-means), along with the percent change and its 95% confidence interval in each treatment group were presented.

Primary: Open Label Extension: Percentage Change From Baseline of Urinary Pr/Cr Ratio (gm/gm) at Month 36

End point title	Open Label Extension: Percentage Change From Baseline of Urinary Pr/Cr Ratio (gm/gm) at Month 36

End point description:

Change in urinary protein excretion, determined as urinary Pr/Cr ratio compared to baseline, after approximately three years of treatment. Baseline for efficacy data in the extension was defined as the last value obtained in the double-blind treatment phase.

End point type	Primary

End point timeframe:

Baseline and Month 36

End point values	Losartan Open Label Extension	Enalapril Open Label Extension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[4]	130[5]		
Units: percentage change				
geometric mean (confidence interval 95%)	-30.01 (-44.35 to -11.98)	-40.45 (-52.45 to -25.42)		

Notes:

[4] - Randomized participants who took ≥1 dose of study drug and had BL and post randomization measurement

[5] - Randomized participants who took ≥1 dose of study drug and had BL and post randomization measurement

Statistical analyses

Statistical analysis title	Extension: Percent Change From BL in Pr/Cr Ratio

Statistical analysis description:

Change in urinary protein excretion (on logarithmic scale) analyzed using a mixed model with fixed-effect terms for treatment, time, treatment by time interaction, stratum, and BL urinary protein excretion (on logarithmic scale, with BL defined as the last value observed in double-blind study). A random effect for patient and an unstructured variance-covariance were used.

Comparison groups	Losartan Open Label Extension v Enalapril Open Label Extension
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority[6]
Method	Mixed models analysis
Parameter estimate	Geometric Mean Ratio
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.6

Notes:

[6] - Repeated measurements model for the change from BL in urinary protein excretion included measurements taken at months 6, 12, 18, 24, 30, and 36. Geometric means and the ratio of geometric means (obtained after antilog transformation of the difference in LS-means) with 95% confidence interval at all these time points were presented.

Primary: Open Label Extension: Change From Baseline in Glomerular Filtration Rate (GFR) at Month 36

End point title	Open Label Extension: Change From Baseline in Glomerular Filtration Rate (GFR) at Month 36

End point description:

GFR was measured at months 6, 12, 18, 24, 30 and 36. GFR was based on creatinine clearance (mL/min/1.73 m^2), as determined by the Schwartz formula:

GFR = 0.55 x height (cm) / Serum creatinine (mg/dL) [Note: For male participants, ages 13 to 17 years, 0.70 was used as the multiplier in place of 0.55].

GFR values were compared to the baseline GFR measure. Baseline in regard to the extension was defined as the last value obtained in the double-blind treatment phase.

End point type	Primary

End point timeframe:

Baseline and Month 36

End point values	Losartan Open Label Extension	Enalapril Open Label Extension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[7]	127[8]		
Units: mL/min1.73m^2				
least squares mean (confidence interval 95%)	3.3 (-5.2 to 11.7)	7 (-1.4 to 15.4)		

Notes:

[7] - All participants with ≥1 study dose, 1 BL measurement and a post-randomization measurement.

[8] - All participants with ≥1 study dose, 1 BL measurement and a post-randomization measurement.

Statistical analyses

Statistical analysis title	Extension: Change from BL in GFR at Month 36

Statistical analysis description:

Change in GFR analyzed using a mixed model with fixed-effect terms for treatment, time, treatment by time interaction, stratum, and BL GFR. A random effect for participant and an unstructured variance-covariance were used. This repeated measurements model for the change from BL in GFR included measurements taken at months 6, 12, 18, 24, 30, and 36. LS-means and difference in LS-means with 95% confidence interval at all these timepoints were presented.

Comparison groups	Losartan Open Label Extension v Enalapril Open Label Extension
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Difference in LS Means
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	7.6

Secondary: Double-Blind Treatment Phase: Change From Baseline in Systolic Blood Pressure (SBP) in Hypertensive Participants at Week 12

End point title	Double-Blind Treatment Phase: Change From Baseline in Systolic Blood Pressure (SBP) in Hypertensive Participants at Week 12[9]

End point description:

SBP was measured in hypertensive participants at week 4, week 8 and week 12 (or early discontinuation).

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: A subgroup analysis was performed to study the effect of losartan and amlodipine on blood pressure in pediatric participants with proteinuria and hypertension. As a result, only the DB

hypertensive arms were included in the analysis.

End point values	Losartan Double Blind Hypertensive	Amlodipine Double Blind Hypertensive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[10]	30[11]		
Units: mm Hg				
least squares mean (confidence interval 95%)	-5.5 (-8.6 to -2.4)	-0.1 (-3.3 to 3.1)		

Notes:

[10] - Hypertensive participants randomized to losartan in DB and receiving ≥1 dose of study therapy.

[11] - Hypertensive participants randomized to amlodipine in DB and receiving ≥1 dose of study therapy.

Statistical analyses

Statistical analysis title	Change from BL in SBP at Week 12

Statistical analysis description:

The change from baseline in systolic blood pressure was analyzed using a mixed model similar to the primary endpoint, overall and for normotensive and hypertensive participants separately.

Comparison groups	Losartan Double Blind Hypertensive v Amlodipine Double Blind Hypertensive
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Difference in LS Means
Point estimate	-5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	-1

Secondary: Double-Blind Treatment Phase: Change From Baseline in Diastolic Blood Pressure (DBP) in Hypertensive Participants at Week 12

End point title	Double-Blind Treatment Phase: Change From Baseline in Diastolic Blood Pressure (DBP) in Hypertensive Participants at Week 12[12]

End point description:

DBP was measured in hypertensive participants at week 4, week 8 and week 12 (or early discontinuation).

End point type	Secondary

End point timeframe:

Baseline and Week 12

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: A subgroup analysis was performed to study the effect of losartan and amlodipine on blood pressure in pediatric participants with proteinuria and hypertension. As a result, only the DB

hypertensive arms were included in the analysis.

End point values	Losartan Double Blind Hypertensive	Amlodipine Double Blind Hypertensive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[13]	30[14]		
Units: mm Hg				
least squares mean (confidence interval 95%)	-3.8 (-7 to -0.7)	0.8 (-2.5 to 4.1)		

Notes:

[13] - Hypertensive participants randomized to losartan in DB and receiving ≥1 dose of study therapy.

[14] - Hypertensive participants randomized to amlodipine in DB and receiving ≥1 dose of study therapy.

Statistical analyses

Statistical analysis title	Change from BL in DBP at Week 12

Statistical analysis description:

The change from baseline in diastolic blood pressure was analyzed using a mixed model similar to the primary endpoint, overall and for normotensive and hypertensive participants separately.

Comparison groups	Losartan Double Blind Hypertensive v Amlodipine Double Blind Hypertensive
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Difference in LS Means
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	-0.1

Adverse events information

Timeframe for reporting adverse events:

Double-blind base study: From Day 1 through Week 14 (double-blind treatment phase plus post-study visit)
Open-Label Extension: From end of DB (Week 12) up to 36 months

Adverse event reporting additional description:

All Subjects as Treated, Base and Extension Combined

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Losartan: Double-Blind Base Study

Reporting group description:

"Losartan Double Blind" group includes the following: Normotensive participants (1 to 17 years of age) who were randomized to losartan in the double-blind and Hypertensive participants (6 to 17 years of age) who were randomized to losartan & amlodipine placebo in the double-blind. Participants were assigned to a normotensive or hypertensive group based on clinical profile.

Losartan therapy was administered orally, in tablet or suspension form, at an initial dose of approximately 0.7 mg/kg once daily (up to 50 or 100 mg total daily dose, weight-dependent).

Reporting group title	Amlodipine/Placebo: Double-Blind Base Study

Reporting group description:

"Amlodipine/Placebo Double Blind" group includes the following: Normotensive participants randomized to losartan placebo in the double-blind and Hypertensive participants randomized to amlodipine and losartan placebo in the double-blind. Participants were assigned to a normotensive or hypertensive group based on clinical profile.

Losartan placebo dispensed as tablets or suspension depending on participant weight and ability to swallow tablets. Losartan placebo tablet dosing: 25 mg/day orally titrated to 50 mg/day (patients <50 kg) OR 50 mg/day orally titrated to 100 mg/day (patients ≥50 kg) for 12 weeks. Losartan placebo suspension dosing: 0.7 mg/kg/day titrated at 2 weeks to 1.4 mg/kg/day orally (maximum 50 mg if <50 kg or 100 mg if ≥50 kg) for 12 weeks.

Amlodipine dispensed as suspension for duration of study. Amlodipine suspension dosing: starting dose 0.05 or 0.1 titrated to 0.2 mg/kg/day orally (max 5 mg/day) after 2 weeks if necessary to control blood pressure for 12 weeks

Reporting group title	Losartan: Open-Label Extension

Reporting group description:

All participants who completed the 12-week DB treatment phase (or discontinued early due to increased proteinuria) were invited to participate in the open-label extension and were randomized in a 1:1 ratio to either losartan or enalapril. Dosing of study medication during the extension phase of the study was at the investigator's discretion. Losartan 25-mg and 50-mg tablets were available for participants able to swallow tablets. For participants unable to swallow tablets, or who weighed <25 kg, losartan suspension (2.5 mg/ml) was prepared.

Reporting group title	Enalapril: Open-Label Extension

Reporting group description:

All participants who completed the 12-week DB treatment phase (or discontinued early due to increased proteinuria) were invited to participate in the open-label extension and were randomized in a 1:1 ratio to either losartan or enalapril. Dosing of study medication during the extension phase of the study was at the investigator's discretion. Enalapril 2.5-, 5-, 10-, and 20-mg tablets were available for participants able to swallow tablets. For participants unable to swallow tablets, or who weighed <25 kg, enalapril suspension (1 mg/mL) was prepared.

Serious adverse events	Losartan: Double-Blind Base Study	Amlodipine/Placebo: Double-Blind Base Study	Losartan: Open-Label Extension
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 152 (5.26%)	5 / 154 (3.25%)	27 / 134 (20.15%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastasis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			

subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Somatoform disorder neurologic			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Lipomeningocele			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal hypoplasia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Epilepsy			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thrombocytopenia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	0 / 152 (0.00%)	1 / 154 (0.65%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Glomerulonephritis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerulonephritis membranoproliferative			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lupus nephritis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 152 (0.00%)	1 / 154 (0.65%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal impairment			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arthritis bacterial			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 152 (0.66%)	1 / 154 (0.65%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpangina			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinusitis			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 152 (0.00%)	2 / 154 (1.30%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			

subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Enalapril: Open-Label Extension		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 134 (18.66%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipoma			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphoma			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to lung			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastasis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypovolaemic shock			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Somatoform disorder neurologic			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Blood creatinine increased				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Congenital, familial and genetic disorders			
Lipomeningocele			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal hypoplasia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aphasia			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 134 (1.49%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gingival bleeding			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema			

subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Glomerulonephritis				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Glomerulonephritis membranoproliferative				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lupus nephritis				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrotic syndrome				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proteinuria				

subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	2 / 134 (1.49%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Systemic lupus erythematosus				
subjects affected / exposed	3 / 134 (2.24%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 3			
Infections and infestations				

Appendicitis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis bacterial			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Helicobacter infection			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpangina			
subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritonitis bacterial			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	3 / 134 (2.24%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pyelonephritis				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 134 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	0 / 134 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	1 / 134 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Obesity			
subjects affected / exposed	0 / 134 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Losartan: Double-Blind Base Study	Amlodipine/Placebo: Double-Blind Base Study	Losartan: Open-Label Extension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 152 (46.71%)	66 / 154 (42.86%)	83 / 134 (61.94%)
Investigations			
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	8 / 134 (5.97%)
occurrences (all)	0	0	10
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 152 (3.95%)	3 / 154 (1.95%)	3 / 134 (2.24%)
occurrences (all)	6	3	3
Headache			
subjects affected / exposed	13 / 152 (8.55%)	20 / 154 (12.99%)	7 / 134 (5.22%)
occurrences (all)	24	31	19
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 152 (0.00%)	0 / 154 (0.00%)	11 / 134 (8.21%)
occurrences (all)	0	0	12
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	6 / 152 (3.95%)	2 / 154 (1.30%)	8 / 134 (5.97%)
occurrences (all)	6	2	10
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 152 (5.26%)	7 / 154 (4.55%)	12 / 134 (8.96%)
occurrences (all)	10	7	15
Vomiting			
subjects affected / exposed	6 / 152 (3.95%)	4 / 154 (2.60%)	16 / 134 (11.94%)
occurrences (all)	8	4	22
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 152 (3.29%)	6 / 154 (3.90%)	8 / 134 (5.97%)
occurrences (all)	6	8	9
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 152 (0.00%)	1 / 154 (0.65%)	8 / 134 (5.97%)
occurrences (all)	0	1	9
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 152 (5.92%)	8 / 154 (5.19%)	9 / 134 (6.72%)
occurrences (all)	10	8	13
Gastroenteritis			
subjects affected / exposed	3 / 152 (1.97%)	3 / 154 (1.95%)	9 / 134 (6.72%)
occurrences (all)	3	3	15
Influenza			
subjects affected / exposed	2 / 152 (1.32%)	1 / 154 (0.65%)	3 / 134 (2.24%)
occurrences (all)	2	1	4
Nasopharyngitis			
subjects affected / exposed	24 / 152 (15.79%)	19 / 154 (12.34%)	31 / 134 (23.13%)
occurrences (all)	28	22	40
Pharyngitis			
subjects affected / exposed	6 / 152 (3.95%)	6 / 154 (3.90%)	21 / 134 (15.67%)
occurrences (all)	6	7	43
Pharyngotonsillitis			

subjects affected / exposed	0 / 152 (0.00%)	1 / 154 (0.65%)	8 / 134 (5.97%)
occurrences (all)	0	1	11
Upper respiratory tract infection			
subjects affected / exposed	7 / 152 (4.61%)	9 / 154 (5.84%)	15 / 134 (11.19%)
occurrences (all)	8	13	50
Urinary tract infection			
subjects affected / exposed	2 / 152 (1.32%)	3 / 154 (1.95%)	10 / 134 (7.46%)
occurrences (all)	2	3	14
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 152 (0.66%)	0 / 154 (0.00%)	4 / 134 (2.99%)
occurrences (all)	1	0	5

Non-serious adverse events	Enalapril: Open-Label Extension		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 134 (58.21%)		
Investigations			
Urine protein/creatinine ratio increased			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	10		
Headache			
subjects affected / exposed	12 / 134 (8.96%)		
occurrences (all)	23		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 134 (5.97%)		
occurrences (all)	10		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	9		
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	4 / 134 (2.99%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 134 (8.21%)		
occurrences (all)	13		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	3 / 134 (2.24%)		
occurrences (all)	3		
Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	10		
Gastroenteritis			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	10		
Influenza			
subjects affected / exposed	7 / 134 (5.22%)		
occurrences (all)	9		
Nasopharyngitis			
subjects affected / exposed	20 / 134 (14.93%)		
occurrences (all)	28		
Pharyngitis			
subjects affected / exposed	20 / 134 (14.93%)		
occurrences (all)	31		
Pharyngotonsillitis			
subjects affected / exposed	6 / 134 (4.48%)		
occurrences (all)	6		
Upper respiratory tract infection			
subjects affected / exposed	9 / 134 (6.72%)		
occurrences (all)	20		

Urinary tract infection subjects affected / exposed occurrences (all)	10 / 134 (7.46%) 15		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	9 / 134 (6.72%) 15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2007	Protocol Amendment 1 (-01) added a provision to the protocol by which an investigator could discontinue a patient early (e.g., after Week 4 or 8) from the double-blind portion of the study based on the patient's urine protein-to-creatinine ratio and the investigator's judgment and knowledge of the patient. The patient was then able to directly enter the 2-year, randomized, open-label, enalapril versus losartan extension.
14 April 2008	Extension Amendment 1 (-11) added a provision to the protocol that the extension (originally 2 years for all patients who entered) would continue until 100 patients completed 3 years of follow-up, resulting in patients participating in the extension for varying durations based upon the time of their enrollment.
29 April 2009	Extension Amendment 2 (-12) indicated that a new excipient (Sodium Citrate and Citric Acid Oral Solution USP) would be used in place of Bicitra™ for preparation of the enalapril suspension formulation. This change was necessary because the manufacturer of Bicitra™ discontinued production. After Bicitra™ was used or expired (whichever came first), sites began using Sodium Citrate and Citric Acid Oral Solution USP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported