Clinical trial results:
A Phase III, Randomized, Open-Label, Parallel-Group, Dose-Ranging Clinical Trial to Study the Safety and Efficacy of MK-0954/Losartan Potassium in Pediatric Patients With Hypertension

Summary

EudraCT number	2008-004732-20
Trial protocol	HU LT GB ES Outside EU/EEA
Global end of trial date	14 August 2012

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	15 July 2015

Trial information

Trial identification

Sponsor protocol code	0954-337

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00756938
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., ClinicalTrialsDiscosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDiscosure@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	14 August 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

(1) To define a dose-response relationship for losartan in hypertensive children aged 6 months to 6 years, after a 21-day open-label treatment period (response assessed by change from baseline in mean trough systolic blood pressure [SBP]).

(2) To investigate the safety and tolerability of losartan at doses up to 1.4 mg/kg/day in hypertensive children aged 6 months to 6 years after 12 weeks of treatment.

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	10 June 2008
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	Norway: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Lithuania: 15
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	Philippines: 10
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Guatemala: 22
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	101
EEA total number of subjects	22

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)	27
Children (2-11 years)	74
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants met 1 of the following: 6 months to < 1 year old - mean SBP ≥ 95th percentile ; ≥ 1 year old -mean systolic and/or diastolic blood pressure (DBP) ≥ 95th percentile; had co-morbidities with: mean SBP ≥ 90th percentile (6 months to < 1 year old) or mean SBP and/or DBP ≥ 90th percentile (≥ 1 year old).

Period 1

Period 1 title	12-week Base Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Losartan potassium 0.1 to 1.4 mg/kg

Arm description:

Open-label losartan at starting dose of 0.1 mg/kg/day with uptitration at Weeks 3, 6 or 9 to the next highest dose level if blood pressure goal not achieved

Arm type	Experimental
Investigational medicinal product name	losartan potassium
Investigational medicinal product code	
Other name	MK-0954, Cozaar®
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

losartan potassium, dry powder, to be suspended in liquid and given orally, once daily; doses will start at 0.1 mg/kg and can be escalated up to 1.4 mg/kg (maximum dose 100 mg) until target blood pressure is reached.

Arm title	Losartan potassium 0.3 to 1.4 mg/kg

Arm description:

Open-label losartan at starting dose of 0.3 mg/kg/day with uptitration at Week 3, 6, or 9 to the next highest dose level if blood pressure goal not achieved.

Arm type	Experimental
Investigational medicinal product name	losartan potassium
Investigational medicinal product code	
Other name	MK-0954, Cozaar®
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

losartan potassium, dry powder, to be suspended in liquid and given orally, once daily; doses will start at 0.3 mg/kg and can be escalated up to 1.4 mg/kg (maximum dose 100 mg) until target blood pressure is reached.

Arm title	Losartan potassium 0.7 to 1.4 mg/kg

Arm description:

Open-label losartan at starting dose of 0.7 mg/kg/day with uptitration at Week 3, 6, or 9 to the next highest dose level if blood pressure goal not achieved

Arm type	Experimental

Investigational medicinal product name	losartan potassium
Investigational medicinal product code	
Other name	MK-0954, Cozaar®
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

losartan potassium, dry powder, to be suspended in liquid and given orally, once daily; doses will start at 0.7 mg/kg and can be escalated up to 1.4 mg/kg (maximum dose 100 mg) until target blood pressure is reached.

Number of subjects in period 1	Losartan potassium 0.1 to 1.4 mg/kg	Losartan potassium 0.3 to 1.4 mg/kg	Losartan potassium 0.7 to 1.4 mg/kg
Started	33	34	34
Completed	31	34	32
Not completed	2	0	2
Protocol-specific Criteria Met	1	-	1
Lost to follow-up	1	-	-
Protocol deviation	-	-	1

Period 2

Period 2 title	Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Losartan potassium-Extension

Arm description:

Participants who elected to enter extension; dose level of Losartan was that which was being administered at end of base study.

Arm type	Experimental
Investigational medicinal product name	losartan potassium
Investigational medicinal product code	
Other name	MK-0954, Cozaar®
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

losartan potassium, dry powder, to be suspended in liquid and given orally, once daily; doses will start at 0.1 mg/kg, 0.3 mg/kg, and 0.7 mg/kg, respectively, in the three study arms and can be escalated up to 1.4 mg/kg (maximum dose 100 mg) until target blood pressure is reached.

Number of subjects in period 2[1]	Losartan potassium-Extension
Started	90
Completed	53
Not completed	37
Physician decision	3
Consent withdrawn by subject	10
End of Study	11
Adverse event, non-fatal	1
Protocol-specific Criteria Met	9
Lost to follow-up	1
Lack of efficacy	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: Not all participants who completed the base study elected to enter extension study.

Baseline characteristics

Reporting groups	
Reporting group title	Losartan potassium 0.1 to 1.4 mg/kg
Reporting group description:	
Open-label losartan at starting dose of 0.1 mg/kg/day with uptitration at Weeks 3, 6 or 9 to the next highest dose level if blood pressure goal not achieved	
Reporting group title	Losartan potassium 0.3 to 1.4 mg/kg
Reporting group description:	
Open-label losartan at starting dose of 0.3 mg/kg/day with uptitration at Week 3, 6, or 9 to the next highest dose level if blood pressure goal not achieved.	
Reporting group title	Losartan potassium 0.7 to 1.4 mg/kg
Reporting group description:	
Open-label losartan at starting dose of 0.7 mg/kg/day with uptitration at Week 3, 6, or 9 to the next highest dose level if blood pressure goal not achieved	

Reporting group values	Losartan potassium 0.1 to 1.4 mg/kg	Losartan potassium 0.3 to 1.4 mg/kg	Losartan potassium 0.7 to 1.4 mg/kg
Number of subjects	33	34	34
Age categorical			
Units: Subjects			
Age continuous			
Units: months			
arithmetic mean	40.2	45	40.6
standard deviation	± 24.4	± 21.5	± 21.2
Gender categorical			
Units: Subjects			
Female	13	16	14
Male	20	18	20

Reporting group values	Total		
Number of subjects	101		
Age categorical			
Units: Subjects			
Age continuous			
Units: months			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	43		
Male	58		

End points

End points reporting groups

Reporting group title	Losartan potassium 0.1 to 1.4 mg/kg
Reporting group description:	
Open-label losartan at starting dose of 0.1 mg/kg/day with uptitration at Weeks 3, 6 or 9 to the next highest dose level if blood pressure goal not achieved	
Reporting group title	Losartan potassium 0.3 to 1.4 mg/kg
Reporting group description:	
Open-label losartan at starting dose of 0.3 mg/kg/day with uptitration at Week 3, 6, or 9 to the next highest dose level if blood pressure goal not achieved.	
Reporting group title	Losartan potassium 0.7 to 1.4 mg/kg
Reporting group description:	
Open-label losartan at starting dose of 0.7 mg/kg/day with uptitration at Week 3, 6, or 9 to the next highest dose level if blood pressure goal not achieved	
Reporting group title	Losartan potassium-Extension
Reporting group description:	
Participants who elected to enter extension; dose level of Losartan was that which was being administered at end of base study.	
Subject analysis set title	Base Study-Losartan potassium 0.1 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Patients as Treated Population, which consisted of all randomized participants who received at least 1 dose of study drug. Adverse events for the base study were reported by the dose taken at the time of the event and not the study group to which they were randomly assigned. Adverse events for the study extension were reported as 1 arm.	
Subject analysis set title	Base Study-Losartan potassium 0.3 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Patients as Treated Population, which consisted of all randomized participants who received at least 1 dose of study drug. Adverse events for the base study were reported by the dose taken at the time of the event and not the study group to which they were randomly assigned. Adverse events for the study extension were reported as 1 arm.	
Subject analysis set title	Base Study-Losartan potassium 0.7 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Patients as Treated Population, which consisted of all randomized participants who received at least 1 dose of study drug. Adverse events for the base study were reported by the dose taken at the time of the event and not the study group to which they were randomly assigned. Adverse events for the study extension were reported as 1 arm.	
Subject analysis set title	Base Study-Losartan potassium 1.4 mg/kg
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Patients as Treated Population, which consisted of all randomized participants who received at least 1 dose of study drug. Adverse events for the base study were reported by the dose taken at the time of the event and not the study group to which they were randomly assigned. Adverse events for the study extension were reported as 1 arm.	
Subject analysis set title	Extension-Losartan potassium
Subject analysis set type	Safety analysis
Subject analysis set description:	
All Patients as Treated Population, which consisted of all randomized participants who received at least 1 dose of study drug. Adverse events for the base study were reported by the dose taken at the time of the event and not the study group to which they were randomly assigned. Adverse events for the study extension were reported as 1 arm.	

Primary: Mean Change from Baseline in Systolic Blood Pressure (SBP)

End point title	Mean Change from Baseline in Systolic Blood Pressure (SBP)

End point description:

Sitting blood pressure ([BP] or supine if child could not sit) was measured after the participant had been seated for 5 minutes with back supported, feet on the floor and right arm (or left arm if it was the customary side for BP measurement for the participant) supported at heart level. Systolic BP was determined by averaging 3 replicate measurements obtained at least 1 minute apart.

End point type	Primary

End point timeframe:

Baseline and Day 21

End point values	Losartan potassium 0.1 to 1.4 mg/kg	Losartan potassium 0.3 to 1.4 mg/kg	Losartan potassium 0.7 to 1.4 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	34	33	
Units: mmHg				
arithmetic mean (standard deviation)	-7.31 (± 12.53)	-7.65 (± 7.49)	-6.67 (± 7.86)	

Statistical analyses

Statistical analysis title	Comparsion of Change from Baseline

Statistical analysis description:

The slope of change in SBP after 21 days treatment as compared to baseline as a function of dose was assessed using an analysis of covariance (ANCOVA) model with terms for dose (as a continuous covariate: 0.1, 0.3 or 0.7 mg/kg/day), weight (as a continuous covariate) and presence of co-morbidities/end organ damage (yes/no). The primary hypothesis was assessed by testing whether the slope for dose in the above regression model was zero or not.

Comparison groups	Losartan potassium 0.3 to 1.4 mg/kg v Losartan potassium 0.7 to 1.4 mg/kg v Losartan potassium 0.1 to 1.4 mg/kg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.753
Method	ANCOVA
Parameter estimate	Slope
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.45
upper limit	8.9

Primary: Number of Participants Who Reported 1 or more Clinical and/or Laboratory Adverse Event(s)

End point title	Number of Participants Who Reported 1 or more Clinical and/or

	Laboratory Adverse Event(s)[1]

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drug, whether or not considered related to the use of the drug. Any worsening of a preexisting condition which is temporally associated with the use of the study drug is also an AE.

End point type	Primary

End point timeframe:

up to 12 weeks (Base Study); up to 24 months (Extension)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Base Study-Losartan potassium 0.1 mg/kg	Base Study-Losartan potassium 0.3 mg/kg	Base Study-Losartan potassium 0.7 mg/kg	Base Study-Losartan potassium 1.4 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	54	63	33
Units: Participants				
Clinical Adverse Event	21	30	36	22
Laboratory Adverse Event	1	1	0	0

End point values	Extension-Losartan potassium			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: Participants				
Clinical Adverse Event	75			
Laboratory Adverse Event	5			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Were Discontinued From Study Due to a Clinical and/or Laboratory Adverse Event

End point title	Number of Participants Who Were Discontinued From Study Due to a Clinical and/or Laboratory Adverse Event[2]

End point description:

An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drug, whether or not considered related to the use of the drug. Any worsening of a preexisting condition which is temporally associated with the use of the study drug is also an AE. The number of participants who were discontinued from the study due to an AE regardless of relatedness to the study drug were recorded.

End point type	Primary

End point timeframe:

up to 12 weeks (Base Study); up to 24 months (Extension)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	Base Study-Losartan potassium 0.1 mg/kg	Base Study-Losartan potassium 0.3 mg/kg	Base Study-Losartan potassium 0.7 mg/kg	Base Study-Losartan potassium 1.4 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	34	54	63	33
Units: Participants				
Clinical Adverse Events	0	0	0	0
Laboratory Adverse Events	0	0	0	0

End point values	Extension-Losartan potassium			
Subject group type	Subject analysis set			
Number of subjects analysed	90			
Units: Participants				
Clinical Adverse Events	1			
Laboratory Adverse Events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Diastolic Blood Pressure

End point title	Mean Change from Baseline in Diastolic Blood Pressure

End point description:

Sitting BP (or supine if child could not sit) was measured after the participant had been seated for 5 minutes with back supported, feet on the floor and right arm (or left arm if it was the customary side for BP measurement for the patient) supported at heart level. Diastolic BP was determined by averaging 3 replicate measurements obtained at least 1 minute apart.

End point type	Secondary

End point timeframe:

Baseline and Day 21

End point values	Losartan potassium 0.1 to 1.4 mg/kg	Losartan potassium 0.3 to 1.4 mg/kg	Losartan potassium 0.7 to 1.4 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	34	33	
Units: mmHg				
arithmetic mean (standard deviation)	-8.25 (± 11.76)	-5.15 (± 8.06)	-6.73 (± 8.59)	

Statistical analyses

Statistical analysis title	Comparison of Change from Baseline

Statistical analysis description:

The slope of change in DBP after 21 days treatment as compared to baseline as a function of dose was assessed using an analysis of covariance (ANCOVA) model with terms for dose (as a continuous covariate: 0.1, 0.3 or 0.7 mg/kg/day), weight (as a continuous covariate) and presence of co-morbidities/end organ damage (yes/no). The primary hypothesis was assessed by testing whether the slope for dose in the above regression model was zero or not.

Comparison groups	Losartan potassium 0.1 to 1.4 mg/kg v Losartan potassium 0.3 to 1.4 mg/kg v Losartan potassium 0.7 to 1.4 mg/kg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.643
Method	ANCOVA
Parameter estimate	Slope
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	9.51

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 12 weeks (Base Study); up to 24 months (Extension)

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of study drug. Adverse events are reported by the dose taken at the time of the event and not the study group to which they were randomized. A participant may have reported an adverse event when taking different dose levels and therefore may have been counted more than once.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Base Study-Losartan potassium 0.1 mg/kg
Reporting group description:	
Participants who received 0.1 mg/kg losartan during base study.	
Reporting group title	Base Study-Losartan potassium 0.3 mg/kg
Reporting group description:	
Participants who received 0.3 mg/kg losartan during base study	
Reporting group title	Base Study-Losartan potassium 0.7 mg/kg
Reporting group description:	
Participants who received 0.7 mg/kg losartan during base study	
Reporting group title	Base Study-Losartan potassium 1.4 mg/kg
Reporting group description:	
Participants who received 1.4 mg/kg losartan during base study.	
Reporting group title	Extension Study-Losartan potassium 0.1 mg/kg
Reporting group description:	
Participants who received 0.1 mg/kg losartan during extension study	
Reporting group title	Extension Study-Losartan potassium 0.3 mg/kg
Reporting group description:	
Participants who received 0.3 mg/kg losartan during extension study	
Reporting group title	Extension Study-Losartan potassium 0.7 mg/kg
Reporting group description:	
Participants who received 0.7 mg/kg losartan during extension study	
Reporting group title	Extension Study-Losartan potassium 1.4 mg/kg
Reporting group description:	
Participants who received 1.4 mg/kg losartan during extension study	

Serious adverse events	Base Study-Losartan potassium 0.1 mg/kg	Base Study-Losartan potassium 0.3 mg/kg	Base Study-Losartan potassium 0.7 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 34 (8.82%)	2 / 54 (3.70%)	2 / 63 (3.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nephroblastoma			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 34 (2.94%)	0 / 54 (0.00%)	0 / 63 (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
Toxicity to various agents			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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			
Asthenia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 54 (0.00%)	0 / 63 (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
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Gastritis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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			
Pleural effusion			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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			

Psychomotor retardation			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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 and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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 impairment			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Ureteric stenosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Infections and infestations			
Adenoiditis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Bronchopneumonia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis bacterial			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Gastroenteritis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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

Laryngitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Pneumonia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Pyelonephritis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Pyelonephritis acute			
subjects affected / exposed	1 / 34 (2.94%)	0 / 54 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Sinusitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Upper respiratory tract infection			

subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Urinary tract infection			
subjects affected / exposed	1 / 34 (2.94%)	1 / 54 (1.85%)	0 / 63 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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
Metabolic acidosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (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

Serious adverse events	Base Study-Losartan potassium 1.4 mg/kg	Extension Study-Losartan potassium 0.1 mg/kg	Extension Study-Losartan potassium 0.3 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	3 / 15 (20.00%)	5 / 28 (17.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nephroblastoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
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			
Thermal burn			

subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Toxicity to various agents			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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			
Asthenia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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			
Enteritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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			
Psychomotor retardation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
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 and urinary disorders			
Renal failure acute			

subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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 impairment			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Adenoiditis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Bronchopneumonia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Conjunctivitis bacterial			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	2 / 28 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Pyelonephritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Salmonellosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Sinusitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Upper respiratory tract infection bacterial			

subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
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	Extension Study-Losartan potassium 0.7 mg/kg	Extension Study-Losartan potassium 1.4 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 31 (6.45%)	5 / 42 (11.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nephroblastoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 31 (3.23%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychomotor retardation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adenoiditis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis bacterial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 31 (3.23%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 31 (3.23%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Base Study-Losartan potassium 0.1 mg/kg	Base Study-Losartan potassium 0.3 mg/kg	Base Study-Losartan potassium 0.7 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 34 (47.06%)	26 / 54 (48.15%)	26 / 63 (41.27%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip and/or oral cavity cancer stage III			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	1 / 63 (1.59%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 34 (8.82%)	4 / 54 (7.41%)	3 / 63 (4.76%)
occurrences (all)	3	6	3
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 34 (5.88%)	2 / 54 (3.70%)	2 / 63 (3.17%)
occurrences (all)	2	3	2
Rhinitis allergic			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Investigations			
Protein urine present			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
White blood cells urine positive			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Ligament rupture			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	1 / 63 (1.59%)
occurrences (all)	0	1	1
Eye disorders			

Conjunctivitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 54 (3.70%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 34 (5.88%)	1 / 54 (1.85%)	0 / 63 (0.00%)
occurrences (all)	2	1	0
Constipation			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	2 / 34 (5.88%)	3 / 54 (5.56%)	4 / 63 (6.35%)
occurrences (all)	2	3	4
Vomiting			
subjects affected / exposed	1 / 34 (2.94%)	1 / 54 (1.85%)	1 / 63 (1.59%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 34 (0.00%)	2 / 54 (3.70%)	1 / 63 (1.59%)
occurrences (all)	0	2	1
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Nephrocalcinosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Acute tonsillitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 54 (3.70%)	0 / 63 (0.00%)
occurrences (all)	0	2	0

Ear infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 54 (0.00%)	1 / 63 (1.59%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Impetigo			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	7 / 54 (12.96%)	3 / 63 (4.76%)
occurrences (all)	2	7	3
Oral herpes			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0
Otitis media acute			
subjects affected / exposed	0 / 34 (0.00%)	1 / 54 (1.85%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	3 / 34 (8.82%)	2 / 54 (3.70%)	1 / 63 (1.59%)
occurrences (all)	3	2	1
Respiratory tract infection			
subjects affected / exposed	2 / 34 (5.88%)	1 / 54 (1.85%)	5 / 63 (7.94%)
occurrences (all)	2	1	6
Rhinitis			
subjects affected / exposed	1 / 34 (2.94%)	3 / 54 (5.56%)	0 / 63 (0.00%)
occurrences (all)	2	3	0

Sinusitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 34 (2.94%)	3 / 54 (5.56%)	2 / 63 (3.17%)
occurrences (all)	1	3	3
Urinary tract infection			
subjects affected / exposed	2 / 34 (5.88%)	2 / 54 (3.70%)	4 / 63 (6.35%)
occurrences (all)	3	2	4
Viral infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 54 (0.00%)	0 / 63 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Base Study-Losartan potassium 1.4 mg/kg	Extension Study-Losartan potassium 0.1 mg/kg	Extension Study-Losartan potassium 0.3 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 33 (60.61%)	12 / 15 (80.00%)	20 / 28 (71.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip and/or oral cavity cancer stage III			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 15 (6.67%)	4 / 28 (14.29%)
occurrences (all)	1	1	5
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 33 (15.15%)	1 / 15 (6.67%)	1 / 28 (3.57%)
occurrences (all)	5	1	1
Rhinitis allergic			
subjects affected / exposed	1 / 33 (3.03%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	1	1	0
Investigations			
Protein urine present			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
Red blood cell count decreased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Urine leukocyte esterase positive			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Ligament rupture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 33 (3.03%)	0 / 15 (0.00%)	3 / 28 (10.71%)
occurrences (all)	1	0	3
Eye disorders			

Conjunctivitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 15 (13.33%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)	3 / 15 (20.00%)	3 / 28 (10.71%)
occurrences (all)	2	4	5
Vomiting			
subjects affected / exposed	1 / 33 (3.03%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences (all)	1	0	7
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 33 (6.06%)	2 / 15 (13.33%)	1 / 28 (3.57%)
occurrences (all)	5	2	1
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Nephrocalcinosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Acute tonsillitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 15 (13.33%)	1 / 28 (3.57%)
occurrences (all)	0	2	1
Bronchitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 15 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	3

Ear infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Impetigo			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 15 (13.33%)	4 / 28 (14.29%)
occurrences (all)	3	3	6
Oral herpes			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Otitis media acute			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Pharyngitis			
subjects affected / exposed	1 / 33 (3.03%)	4 / 15 (26.67%)	1 / 28 (3.57%)
occurrences (all)	1	5	1
Respiratory tract infection			
subjects affected / exposed	3 / 33 (9.09%)	2 / 15 (13.33%)	3 / 28 (10.71%)
occurrences (all)	3	2	3
Rhinitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	0	4

Sinusitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 15 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	1 / 33 (3.03%)	2 / 15 (13.33%)	1 / 28 (3.57%)
occurrences (all)	1	2	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 15 (6.67%)	4 / 28 (14.29%)
occurrences (all)	0	1	4
Urinary tract infection			
subjects affected / exposed	4 / 33 (12.12%)	0 / 15 (0.00%)	1 / 28 (3.57%)
occurrences (all)	4	0	1
Viral infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 15 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	2

Non-serious adverse events	Extension Study-Losartan potassium 0.7 mg/kg	Extension Study-Losartan potassium 1.4 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 31 (64.52%)	28 / 42 (66.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip and/or oral cavity cancer stage III			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Hypotension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 31 (6.45%)	4 / 42 (9.52%)	
occurrences (all)	2	10	
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 31 (9.68%)	5 / 42 (11.90%)	
occurrences (all)	3	9	
Rhinitis allergic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Investigations			
Protein urine present			
subjects affected / exposed	2 / 31 (6.45%)	1 / 42 (2.38%)	
occurrences (all)	2	1	
Red blood cell count decreased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Urine leukocyte esterase positive			
subjects affected / exposed	2 / 31 (6.45%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
White blood cells urine positive			
subjects affected / exposed	2 / 31 (6.45%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 31 (3.23%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Ligament rupture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Eye disorders			

Conjunctivitis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 42 (2.38%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	5 / 31 (16.13%)	6 / 42 (14.29%)	
occurrences (all)	5	8	
Vomiting			
subjects affected / exposed	2 / 31 (6.45%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 31 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	4	
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Nephrocalcinosis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Acute tonsillitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 42 (4.76%)	
occurrences (all)	0	2	

Ear infection			
subjects affected / exposed	1 / 31 (3.23%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Gastroenteritis viral			
subjects affected / exposed	0 / 31 (0.00%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Impetigo			
subjects affected / exposed	2 / 31 (6.45%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Laryngitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	5 / 31 (16.13%)	2 / 42 (4.76%)	
occurrences (all)	6	2	
Oral herpes			
subjects affected / exposed	1 / 31 (3.23%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Otitis media acute			
subjects affected / exposed	2 / 31 (6.45%)	2 / 42 (4.76%)	
occurrences (all)	2	3	
Pharyngitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	3 / 31 (9.68%)	5 / 42 (11.90%)	
occurrences (all)	6	13	
Rhinitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 42 (0.00%)	
occurrences (all)	1	0	

Sinusitis			
subjects affected / exposed	2 / 31 (6.45%)	5 / 42 (11.90%)	
occurrences (all)	2	6	
Tonsillitis			
subjects affected / exposed	1 / 31 (3.23%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Upper respiratory tract infection			
subjects affected / exposed	3 / 31 (9.68%)	4 / 42 (9.52%)	
occurrences (all)	8	4	
Urinary tract infection			
subjects affected / exposed	3 / 31 (9.68%)	7 / 42 (16.67%)	
occurrences (all)	12	13	
Viral infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2009	AM1: The primary reason for protocol amendment 337-01 was to remove the COZAAR™ (losartan potassium) Worldwide Product Circular and replace with the COZAAR® (losartan potassium) United States Product Circular
17 June 2010	AM2: The primary reason for protocol amendment was to add language clarifying that Visit 1 screening procedures could be completed over more than 1 day if needed.
20 May 2011	AM3: The primary reason for protocol amendment was to clarify the duration of follow-up in the open-label extension.
21 March 2012	AM5: The primary reason for protocol amendment was to revert the lower age limit for inclusion into the study from 3 months to 6 months of age. The eligibility of children as young as 3 months was proposed in protocol amendment 337-04 but was not implemented due to regulatory concerns.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported