Clinical trial results:
Acceptability, safety, pharmacokinetics and effects on blood pressure of paediatric formulation of perindopril, S 90052 (0.020 to 0.110 mg/kg/d)/S 90652 (0.025 to 0.135 mg/kg/d), in hypertensive children.
An open, noncomparative, 3-month then 24-month (minimal duration) multicentre study.

Summary

EudraCT number	2005-000474-42
Trial protocol	IT
Global end of trial date	27 April 2010

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CL2-90652-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes Cedex, France, 92284
Public contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier 50 rue Carnot 92284 Suresnes Cedex, +33 155724366, clinicaltrials@servier.com
Scientific contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier 50 rue Carnot 92284 Suresnes Cedex, +33 155724366, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 April 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2010
Global end of trial reached?	Yes
Global end of trial date	27 April 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to assess the acceptability of S 90052/S 90652, the orodispersible formulation of perindopril and to assess the safety of S 90052/S 90652.

Protection of trial subjects:

Temporary discontinuations of the study treatment were allowed during the study if a dose decreasing procedure was decided.
Definitive discontinuations of the study drug were to be decided in case of serious adverse drug reaction(s), or adverse event(s) not compatible with the continuation of the study treatment, or insufficient BP control. In the extension part of the study, the apparition of signs of pubescence in girls was also a reason for definitive discontinuations of the study drug:
A serious adverse reaction was defined as a serious adverse event that the investigator considered might be due to the research.
Adverse events considered as not compatible with the continuation of the study drug were the following angioedema postural hypotension or occurrences of malaises, serum potassium level > 5.5 mEq/L and estimated GFR ≤ 25 mL/min/1.73m².
Insufficient BP control was defined as the occurrence of a threatening hypertension; SBP or DBP equal to or above the 97.5th percentile + 30 mmHg the occurrence of a SBP or a DBP equal to or above the 95th percentile in spite of the administration of the maximal authorised dose of S 90652 in combination with additional antihypertensive agent(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2003
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	48 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	62
EEA total number of subjects	62

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	54
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In all, 20 centres located in Belgium, France and Italy were opened: four centres in Belgium, 15 centres in France and one centre in Italy. Eighteen centres selected at least one patient, and 17 centres included at least one patient.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	62
Number of subjects completed	62

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Subgroup A

Arm description:

Confirmed and untreated arterial hypertension (defined as a systolic blood pressure (SBP) or a diastolic blood pressure (DBP) equal to or above the 97.5th percentile + 10 mmHg).

Arm type	Experimental
Investigational medicinal product name	S 90052 (perindopril tert-butylamine salt)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

0.020 mg/kg/day, oral

Investigational medicinal product name	S 90652 (perindopril arginine salt)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

0.025 mg/kg/day, oral

Arm title	Subgroup B

Arm description:

Arterial hypertension controlled with an ongoing treatment including an angiotensin-converting enzyme inhibitor (ACE-I) or other BP lowering medication(s), when the switch of the ACE-I (if an ACE-I was administered) or the switch of another BP lowering medication (if no ACE-I was administered) by S 90052/ S 90652 could be considered.

Arm type	Experimental

Investigational medicinal product name	S 90652 (perindopril arginine salt)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

0.025 mg/kg/day, 0.050 mg/kg/day or 0.100 mg/kg/day, oral, depending upon the previous antihypertensive treatment.

Investigational medicinal product name	S 90052 (perindopril tert-butylamine salt)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

0.020 mg/kg/day, 0.040 mg/kg/day or 0.080 mg/kg/day, oral

Arm title	Subgroup C

Arm description:

Poorly controlled arterial hypertension treated with medication(s) that did not include any ACE-I, when the addition of S 90052/ S 90652 was expected to improve BP control.

Arm type	Experimental
Investigational medicinal product name	S 90052 (perindopril tert-butylamine salt)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

0.020 mg/kg/day, oral

Investigational medicinal product name	S 90652 (perindopril arginine salt)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Orodispersible tablet
Routes of administration	Oral use

Dosage and administration details:

0.025 mg/kg/day, oral

Number of subjects in period 1	Subgroup A	Subgroup B	Subgroup C
Started	6	51	5
Completed	5	27	4
Not completed	1	24	1
Adverse event, non-fatal	-	6	-
Lost to follow-up	-	1	-
Protocol deviation	1	5	-
Lack of efficacy	-	2	-
non medical reason	-	10	1

Baseline characteristics

Reporting groups	
Reporting group title	Subgroup A
Reporting group description:	
Confirmed and untreated arterial hypertension (defined as a systolic blood pressure (SBP) or a diastolic blood pressure (DBP) equal to or above the 97.5th percentile + 10 mmHg).	
Reporting group title	Subgroup B
Reporting group description:	
Arterial hypertension controlled with an ongoing treatment including an angiotensin-converting enzyme inhibitor (ACE-I) or other BP lowering medication(s), when the switch of the ACE-I (if an ACE-I was administered) or the switch of another BP lowering medication (if no ACE-I was administered) by S 90052/ S 90652 could be considered.	
Reporting group title	Subgroup C
Reporting group description:	
Poorly controlled arterial hypertension treated with medication(s) that did not include any ACE-I, when the addition of S 90052/ S 90652 was expected to improve BP control.	

Reporting group values	Subgroup A	Subgroup B	Subgroup C
Number of subjects	6	51	5
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	3	23	1
Adolescents (12-17 years)	3	28	4
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	4.8	6.8	9.4
standard deviation	± 1.6	± 3.9	± 3.8
Gender categorical Units: Subjects			
Female	3	19	1
Male	3	32	4

Reporting group values	Total		
Number of subjects	62		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		

Children (2-11 years)	27		
Adolescents (12-17 years)	35		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	23		
Male	39		

End points

End points reporting groups

Reporting group title	Subgroup A
Reporting group description:	
Confirmed and untreated arterial hypertension (defined as a systolic blood pressure (SBP) or a diastolic blood pressure (DBP) equal to or above the 97.5th percentile + 10 mmHg).	
Reporting group title	Subgroup B
Reporting group description:	
Arterial hypertension controlled with an ongoing treatment including an angiotensin-converting enzyme inhibitor (ACE-I) or other BP lowering medication(s), when the switch of the ACE-I (if an ACE-I was administered) or the switch of another BP lowering medication (if no ACE-I was administered) by S 90052/ S 90652 could be considered.	
Reporting group title	Subgroup C
Reporting group description:	
Poorly controlled arterial hypertension treated with medication(s) that did not include any ACE-I, when the addition of S 90052/ S 90652 was expected to improve BP control.	

Primary: No primary criterion

End point title	No primary criterion[1]
End point description:	

End point type	Primary
End point timeframe:	
No primary efficacy criterion was defined as the main objective was to study the safety of S 90052/S 90652.	

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 primary efficacy criterion was defined as the main objective was to study the safety of S 90052/S 90652.

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of systolic blood pressure over time until M24

End point title	Evolution of systolic blood pressure over time until M24
End point description:	
Efficacy criteria were systolic blood pressure. No primary efficacy criterion was defined as the main objective was to study the safety of S 90052/S 90652.	
End point type	Secondary
End point timeframe:	
From selection to last visit	

End point values	Subgroup A	Subgroup B	Subgroup C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[2]	51[3]	5[4]	
Units: mmHg				
arithmetic mean (standard deviation)	-7.8 (± 10.7)	0.8 (± 16.4)	-9.6 (± 13)	

Notes:

[2] - FAS

[3] - FAS

[4] - FAS

Attachments (see zip file)	Statistical analysis_SBP/Statistical analysis_SBP.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of diastolic blood pressure over time until M24

End point title	Evolution of diastolic blood pressure over time until M24

End point description:

Efficacy criteria were systolic and diastolic blood pressures. No primary efficacy criterion was defined as the main objective was to study the safety of S 90052/S 90652.

End point type	Secondary

End point timeframe:

From selection to last visit

End point values	Subgroup A	Subgroup B	Subgroup C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5[5]	51[6]	5[7]	
Units: mmHg				
arithmetic mean (standard deviation)	-13.2 (± 12.1)	-1 (± 14.1)	-11 (± 4.8)	

Notes:

[5] - FAS

[6] - FAS

[7] - FAS

Attachments (see zip file)	Statistical analysis_DBP/Statistical analysis_DBP.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Over the course of the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	5.0
Reporting groups	
Reporting group title	Subgroup A
Reporting group description: -	
Reporting group title	Subgroup C
Reporting group description: -	
Reporting group title	Subgroup B
Reporting group description: -	

Serious adverse events	Subgroup A	Subgroup C	Subgroup B
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	5 / 5 (100.00%)	28 / 51 (54.90%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fall			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver transplant rejection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Tonsillar hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenoidal hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Pharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Biopsy kidney			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	6 / 51 (11.76%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transplant evaluation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations NOS			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 51 (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
Joint sprain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Therapeutic agent toxicity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture NOS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 51 (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
Congenital, familial and genetic disorders			
Multiple epiphyseal dysplasia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dyskinesia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive sleep apnoea syndrome			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 51 (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
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Blood and lymphatic system disorders			
Haemolytic anaemia NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	4 / 51 (7.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis NOS			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal polyp			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gingival hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic polyp			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Hepatobiliary disorders			
Cholangitis NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Henoch-Schonlein purpura			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Renal and urinary disorders			
Nephropathy NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vesico-ureteric reflux			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurogenic bladder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
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 aggravated			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
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 operation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenotonsillectomy			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Angioplasty			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder catheter removal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillectomy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enema administration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otorhinolaryngological surgery			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Epiphysiolysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw cyst			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Infections and infestations			
Gastroenteritis viral NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
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 pneumococcal			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpetic stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis enteroviral			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Otitis media serous chronic NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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 mycoplasmal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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 NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	0 / 51 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
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 NOS			

subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition NOS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Subgroup A	Subgroup C	Subgroup B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	5 / 5 (100.00%)	45 / 51 (88.24%)
Investigations			
Biopsy kidney			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	6 / 51 (11.76%)
occurrences (all)	0	2	7
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)	1 / 5 (20.00%)	8 / 51 (15.69%)
occurrences (all)	2	1	12
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	4 / 51 (7.84%)
occurrences (all)	0	5	4
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	4 / 51 (7.84%)
occurrences (all)	0	1	4
Blood and lymphatic system disorders			
Anaemia NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	4 / 51 (7.84%)
occurrences (all)	0	1	4
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	3 / 51 (5.88%)
occurrences (all)	1	0	4

Gastrointestinal disorders			
Gastroenteritis NOS			
subjects affected / exposed	3 / 6 (50.00%)	2 / 5 (40.00%)	13 / 51 (25.49%)
occurrences (all)	6	3	19
Diarrhoea NOS			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	7 / 51 (13.73%)
occurrences (all)	2	1	11
Abdominal pain upper			
subjects affected / exposed	2 / 6 (33.33%)	2 / 5 (40.00%)	4 / 51 (7.84%)
occurrences (all)	2	3	6
Gingival hypertrophy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	4 / 51 (7.84%)
occurrences (all)	0	1	4
Respiratory, thoracic and mediastinal disorders			
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)	3 / 5 (60.00%)	11 / 51 (21.57%)
occurrences (all)	2	4	13
Pharyngitis			
subjects affected / exposed	2 / 6 (33.33%)	1 / 5 (20.00%)	9 / 51 (17.65%)
occurrences (all)	2	1	9
Cough			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	7 / 51 (13.73%)
occurrences (all)	0	2	7
Rhinitis allergic NOS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 5 (0.00%)	3 / 51 (5.88%)
occurrences (all)	1	0	7
Skin and subcutaneous tissue disorders			
Ingrowing nail			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	3 / 51 (5.88%)
occurrences (all)	0	1	4
Rash NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	3 / 51 (5.88%)
occurrences (all)	0	2	3
Renal and urinary disorders			
Nephropathy NOS			

subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	3 / 51 (5.88%)
occurrences (all)	0	1	3
Infections and infestations			
Urinary tract infection NOS			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	9 / 51 (17.65%)
occurrences (all)	0	7	15
Bronchitis acute NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	9 / 51 (17.65%)
occurrences (all)	0	1	12
Rhinitis NOS			
subjects affected / exposed	2 / 6 (33.33%)	1 / 5 (20.00%)	7 / 51 (13.73%)
occurrences (all)	2	1	10
Respiratory tract infection NOS			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	7 / 51 (13.73%)
occurrences (all)	0	8	13
Ear infection NOS			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	5 / 51 (9.80%)
occurrences (all)	2	2	10
Bronchitis NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	6 / 51 (11.76%)
occurrences (all)	0	1	7
Upper respiratory tract infection NOS			
subjects affected / exposed	0 / 6 (0.00%)	2 / 5 (40.00%)	4 / 51 (7.84%)
occurrences (all)	0	6	5
Viral infection NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	4 / 51 (7.84%)
occurrences (all)	0	1	5
Herpes simplex			
subjects affected / exposed	0 / 6 (0.00%)	0 / 5 (0.00%)	5 / 51 (9.80%)
occurrences (all)	0	0	5
Gastroenteritis viral NOS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 5 (20.00%)	3 / 51 (5.88%)
occurrences (all)	0	3	4
Influenza			
subjects affected / exposed	1 / 6 (16.67%)	1 / 5 (20.00%)	2 / 51 (3.92%)
occurrences (all)	1	1	2

Varicella subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 5 (20.00%) 1	3 / 51 (5.88%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2003	The number of centres, the duration of the study, the study drug new formulation, the dosages and the assay centre for perindopril and perindoprilat assays. The protocol code changed from CL2-90052-002 to CL2-90652-001: - Due to the rate of inclusion lower than expected, the total number of centres was increased from 8 to 20. - For the same reason, the duration of the recruitment (12 months) was extended to 18 months and the duration of the study from 16 months to 22 months. - Perindopril tert-butylamine salt was replaced by arginine salt. The doses were modified to take into account the different molecular weights of the two salts; the packaging and the information/informed consent forms were modified. Upon approval of the amendment, the patients to be enrolled in the study received S 90652. Ongoing patients at the time of the implementation of the amendment completed D120 visit with S 90052. - Due to the small volume of blood collected from children, the assay centre AAI (Applied Analytical Industries), located in Germany, experienced difficulties to extract sufficient amounts of perindopril and perindoprilat from the small volume samples (0.2 mL). Therefore, the decision was made to have perindopril and perindoprilat assays performed by Technologie SERVIER (TES) in France, where the method had been validated.
24 September 2004	Included the following changes: - The study initially planned in French paediatric centres was extended to European paediatric centres. The total number of centres was increased to 20. - The duration of the recruitment (18 months) was extended to 36 months and the duration of the study from 22 months to 40 months. - The upper age limit was raised to 16 years old in boys. The information/informed consent form was modified accordingly.
11 September 2008	This amendment allowed to obtain echocardiographic data from exams performed within the usual medical follow-up of the patients but outside the study. Exams performed before study treatment initiation and after at least two years of study treatment were concerned, and allowed to assess cardiac function and structure parameters in hypertensive children. Concerning ongoing patients, if there was no echocardiographic data available (under study treatment) after at least two years of study treatment, an echocardiography was to be performed at one of the follow up visits. Each participant (if capable) and his/her parents were asked to sign an additional consent form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took these decisions to be compliant with the existing ICH E3 Clinical Study Report.

Notes: