I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**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, non-comparative, 3-month then 24-month (minimal duration) multicentre study.**
Study drug	**S 90052/S 90652**
Studied indication	**Arterial Hypertension**
Development phase	**Phase II**
Protocol code	**CL2-90052-002/003_90652-001/002**
Study initiation date	**16 July 2003 (date of first visit)**
Study completion date	**27 April 2010**
Main coordinator	[redacted]
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **6 place des Pleiades** **92415 Courbevoie Cedex – France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 21 October 2010**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: 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, non-comparative, 3-month then 24-month (minimal duration) multicentre study.
Protocols No's: CL2-90052-002 amended to CL2-90652-001 and CL2-90052-003 amended to CL2-90652-002.

International coordinator: [redacted]

Study centres:
Multicentre study involving 20 centres opened in Belgium, France and Italy. Among them, 17 centres included at least one patient: Belgium – 4 centres – 11 patients included, France – 12 centres – 43 patients included and Italy – 1 centre – 8 patients included.

Publication (reference): Not applicable

Studied period: Initiation date: 16 July 2003 (first visit) Completion date: 27 April 2010	**Phase of development of the study:** II

Objectives:
Primary objectives
- To assess the acceptability of S 90052/S 90652, the orodispersible formulation of perindopril.
- To assess the safety of S 90052/S 90652.

Secondary objectives
- To assess the pharmacokinetic (PK) parameters of perindopril and perindoprilat after repeated administrations of S 90052/S 90652.
- To assess the effects of S 90052/S 90652 on Blood Pressure (BP).
- To define the ranges of weight-adjusted doses likely to obtain or maintain BP control.

To assess the effect of repeated administrations of S 90052/S 90652 on plasmatic ACE activity in hypertensive children between 2 and 11 years old (extended to 16 years for boys, as per Amendment No. 2 to Protocol No. CL2-90652-001).

Methodology:
International, open, non-comparative, multicentre phase II study.

Number of patients:
Planned: 60
Included: 62

Diagnosis and main criteria for inclusion:
Children (males or females) between 2 and 11 (girls)/16 (boys) years old at the date of the selection visit with:
- 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) (Subgroup A) ***or***
- 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 (subgroup B) ***or***
- 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 (subgroup C).
- Estimated GFR ≥ 30 mL/min/1.73m² (modified Schwartz formula).
- No contraindication to treatment with an Angiotensin Converting Enzyme Inhibitor.

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Study drug:

S 90052 (perindopril *tert*-butylamine salt): orodispersible tablets of 0.125 mg, 0.250 mg, 0.500 mg, 1.000 mg and 2.000 mg.

S 90652 (perindopril arginine salt): orodispersible tablets of 0.150 mg, 0.300 mg, 0.6250 mg, 1.250 mg and 2.500 mg.

The study drug was to be taken orally in the morning, before breakfast.

In subgroups A and C: S 90052 starting dose: 0.020 mg/kg/day; S 90652 starting dose: 0.025 mg/kg/day.

In subgroup B: S 90052 starting dose: 0.020 mg/kg/day, 0.040 mg/kg/day or 0.080 mg/kg/day; S 90652 starting dose: 0.025 mg/kg/day, 0.050 mg/kg/day or 0.100 mg/kg/day, depending upon the previous antihypertensive treatment.

The dose could be escalated during the dose-finding period then had to be maintained. The maximal dose was 0.110 mg/kg/day for S 90052 and 0.135 mg/kg/day for S 90652.

Batch No:

S 90052: L01606-L09552-L07530 (0.125 mg), L01607-L09553-L07531 (0.250 mg), L01683-L09554-L05606 (0.500 mg), L01684-L10553-L05607 (1 mg), L07532 (2 mg).

S 90652: L0000263-L0003466-L0009553-L0017999 (0.150 mg), L0000278-L0003467-L0008421-L0018002 (0.300 mg), L0000296-L0003468-L0009556-L0015163-L0022643 (0.625 mg), L0000305-L0003469-L0008427-L0015166-L0022636 (1.250 mg), L0002108-L0003566-L0008430-L0015169-L0021422 (2.5 mg)

Reference product: Not applicable

Duration of treatment:

- Short-term period:
  - Dose finding period: 30 days (inclusion to D30).
  - Maintenance treatment period: 3 months (D30 to D120).
- Extension period: at least 24 months.

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Criteria for evaluation:

Efficacy criteria: resting SBP and DBP measured at each visit using oscillometric automatic devices (Dynamap). Blood pressures were categorised by abacus in 8 classes (H1 to H8, H1 corresponding to the most severe hypertension) and in 4 categories:

- [H1-H2] SBP and/or DBP values equal to or above the 97.5th percentile + 10 mmHg, *i.e.* confirmed hypertension.
- [H3-H8]: SBP and/or DBP values below the 97.5th percentile + 10 mmHg.
- [H1-H4] SBP and/or DBP values equal to or above the 95th percentile.
- [H5-H8] SBP and/or DBP values below the 95th percentile.

Considering abacus, improvement refers to the transition from [H1-H2] category to [H3-H8] category and from [H1-H4] category to [H5-H8] category.

Acceptability and safety criteria: primary criteria of the study were acceptability, adverse events, biochemistry parameters (serum potassium, creatinine and glomerular filtration rate (GFR)), and BP measured at the PK visit (before dosing and 3.5 hours after dosing).

- Acceptability (from selection to last visit): Description of withdrawal due to refusal of orodispersible tablets.
- Adverse events at each visit.
- Complete laboratory tests (at inclusion visit, D120 and every year during the extension period), simplified laboratory tests (serum creatinine, potassium and GFR) at each other visits.
- BP measured at the PK visit (D60) measured before dosing and 3.5 hours after dosing.
- ECG at inclusion and D120.
- Echocardiography at baseline and after at least 2 years of study treatment.
- Clinical examination at each visit, weight and height at inclusion, D30, D60, D120 and every six months during the extension period.

Pharmacokinetic measurements: Blood samples were obtained at inclusion for reference assay, and at the PK visit performed at D60 (D90 or D120 if not done at D60), prior to dosing (at trough) and at 1, 3.5, 5.5 and 7.5 hours post-dose. Perindopril and perindoprilat were assayed using solid-phase extraction followed by liquid chromatography with tandem mass spectrometry detection. ACE activity was measured using a radioenzymatic method. The objectives of the PK and pharmacokinetic/pharmacodynamic (PK/PD) analyses were:

- To describe perindopril and perindoprilat plasma concentrations in paediatric patients and compare them with those in adults.
- To develop a population PK model for perindoprilat and to identify the relevant covariates for perindoprilat PK in order to support dose adjustment in paediatric patients.
- To evaluate the PK/PD relationship between serum ACE activity and perindoprilat plasma concentrations in paediatric patients.

Statistical methods:

Efficacy analysis: descriptive statistics of SBP and DBP values at each visit and changes over time; descriptive analysis of abacus categories. Efficacy analyses were performed in the Full Analysis Set (FAS) defined as included patients having taken at least one dose of the study drug with at least one BP measurement under treatment and in the FAS-24 (defined as patients from the FAS exposed to treatment at least 24 months). The abacus classification was analysed according to 4 categories [H1-H2] / [H3-H8] and [H1-H4] / [H5-H8].

Safety analysis: descriptive statistics were provided in the Safety Set (defined as included patients having taken at least one dose of the study drug). Some analyses were also performed in the SS-24 (included patients exposed to treatment at least 24 months).

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 62 hypertensive children were included in the study. Of them, 3 withdrew during the short-term period and 5 did not wish to continue in the extension period. Among the 54 patients who entered in the extension period, 17 patients withdrew and one patient was lost to follow-up. At the end of the study, 36 patients completed the extension period, *i.e.* were followed at least 24 months (mean study treatment duration of 44 months, approximately).

A total of 20 patients were withdrawn either during the short-term or during the extension period, 11 due to a non-medical reason, 6 due to adverse event, 2 due to lack of efficacy and one due to protocol deviation.

Overall disposition of patients and Analysis Sets

STATUS	**All (N = 64)**	**Subgroup A (N = 8)**	**Subgroup B (N = 51)**	**Subgroup C (N = 5)**
	n	**n**	**n**	**n**
Selected	**64**	**8**	**51**	**5**
Included	**62**	**6**	**51**	**5**
Withdrawn during the short-term period due to	**3**	**1**	**2**	**-**
adverse event	1	-	1	-
protocol deviation	1	1	-	-
lack of efficacy	1	-	1	-
Completed the short-term period	**59**	**5**	**49**	**5**
Inclusion in the extension period	**54**	**5**	**44**	**5**
Withdrawn during the extension period due to	**17**	**-**	**16**	**1**
adverse event	5	-	5	-
lack of efficacy	1	-	1	-
non-medical reason	11	-	10	1
Lost to follow-up	**1**	**-**	**1**	**-**
Completed the extension period	**36**	**5**	**27**	**4**
Included Set	**62**	**6**	**51**	**5**
Safety Set	**62**	**6**	**51**	**5**
Full Analysis Set (FAS)	**61**	**5**	**51**	**5**

The patients included ranged in age from 2 to 15 years, with a mean of 6.9 ± 3.8 years; 27 patients (43.5%) were from 2 to 6 years old, 27 (43.5%) from 6 to 12 years old and 8 (12.9%) were over 12. They were mainly male (62.9%) and Caucasian (90.3%). At selection, height ranged from 72 to 169 cm and weight from 8.2 to 83.2 kg.

Most of them had a treated and controlled hypertension (51 patients, subgroup B) while 6 had never been treated for hypertension (subgroup A) and 5 were treated but uncontrolled (subgroup C).

The mean overall duration of hypertension was 30.2 ± 30.1 months. The shortest duration was observed in Subgroup A corresponding to patients recently diagnosed as hypertensive (4.3 ± 3.7 months).

The SBP values ranged between 94 and 161 mmHg with a mean of 116.7 ± 13.5 mmHg. The DBP values ranged between 40 and 94 with a mean of 69.6 ± 11.7 mmHg. Consistently, the mean blood pressures tended to be higher in patients untreated (Subgroup A), or uncontrolled (Subgroup C) than in controlled patients (Subgroup B).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Main baseline characteristics are presented in the Table above:

Main baseline* characteristics in the Included Set

			ALL (N = 62)	Subgroup A (N = 6)	Subgroup B (N = 51)	Subgroup C (N = 5)
Age		Mean ± SD	6.9 ± 3.8	4.8 ± 1.6	6.8 ± 3.9	9.4 ± 3.8
		Min - Max	1** - 15	2 - 6	1* - 15	5 - 14
	< 6 years	n (%)	27 (43.5)	3 (50.0)	23 (45.1)	1 (20.0)
	[6 ; 12[years	n (%)	27 (43.5)	3 (50.0)	21 (41.2)	3 (60.0)
	[12 ; 16] years	n (%)	8 (12.9)	-	7 (13.7)	1 (20.0)
Sex	Male	n (%)	39 (62.9)	3 (50.0)	32 (62.7)	4 (80.0)
	Female	n (%)	23 (37.1)	3 (50.0)	19 (37.3)	1 (20.0)
Height (cm)		Mean ± SD	117.6 ± 22.7	108.3 ± 15.7	117.7 ± 23.7	128.6 ± 17.3
		Min - Max	72 - 169	82 - 124	72 - 169	105 - 146
Weight (kg)		Mean ± SD	25.50 ± 14.57	18.10 ± 5.25	25.35 ± 14.73	35.86 ± 16.45
		Min - Max	8.2 – 83.2	10.3 - 24.5	8.2 - 83.2	15.2 - 58.5
SBP (mmHg)		Mean ± SD	116.7 ± 13.5	123.5 ± 8.0	114.9 ± 13.6	126.8 ± 12.3
		Min - Max	94 - 161	113 - 136	94 - 161	114 - 141
DBP (mmHg)		Mean ± SD	69.6 ± 11.7	77.3 ± 8.4	68.0 ± 11.7	77.0 ± 8.8
		Min - Max	40 - 94	67 - 91	40 - 94	63 - 84
GFR		Mean ± SD	97.55 ± 39.13	82.25 ± 46.29	100.44 ± 39.94	86.52 ± 10.98
(mL/min/1.73m^2)		Min - Max	32.6 - 238.5	32.6 - 153.7	33.0 - 238.5	77.4 - 104.9
Duration of the disease		Mean ± SD	30.2 ± 30.1	4.3 ± 3.7	34.7 ± 31.0	14.8 ± 16.1
(months)		Min - Max	1 - 120	1 - 10	1 - 120	2 - 40
		Median	24.0	3.5	27.0	9.0

**Baseline: selection for age, height, weight and duration of the disease / inclusion for SBP, DBP and GFR*

***: Patient No. 001 250 0001 00008 was 2 years old 2 days after the inclusion date*

Most patients (93.5%) reported medical history related to hypertension, mainly Renal and urinary disorders (69.4% including 33.9% with chronic renal failure). More than one quarter of patients (27.4%) underwent renal transplant. A majority of patients (67.7%) reported medical history not related to hypertension, mainly Gastrointestinal disorders (17.7%) and Infections and infestations (16.1%).

ACE-inhibitors were the most frequent antihypertensive treatment received in the 3 months preceding selection (in 66.1% of the patients) and had been stopped at the time of inclusion. Consistently with the definition of the subgroup, no patient in Subgroup A was treated for hypertension at inclusion.

During the treatment period, the most frequently prescribed concomitant treatments were anilides (59.7% of the patients), glucocorticoids (43.5%), dihydropyridine derivatives (40.3%), vitamin D and analogues (38.7%) selective immunosuppressive agents (35.5%).

Overall, the mean total treatment duration was approximately 44 months. The compliance to the study treatment was satisfactory, with only a few patients suspected of poor compliance at each visit.

The acceptability of S 90052/S 90652, assessed by the withdrawal rate due to refusal of orodispersible tablets, was good as no patient withdrew from the study due to this reason.

During the dose-finding period (from inclusion to D30), the mean weight-adjusted dose increased from 0.0380 ± 0.0186 to 0.0552 ± 0.0296 mg/kg/day and tended to remain stable afterwards. The dose reported at the last visit was in average 0.0606 ± 0.0341 mg/kg/day.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Pharmacokinetic results:

Pharmacokinetics results are presented in a separate report (Internal report NP26859). Briefly, these results support similar plasma concentration-time profiles and PK/PD relationship of perindoprilat in paediatric patients and in adults. They are therefore expected to provide similar antihypertensive effects. The results also showed that the perindopril clearance and volume of distribution increase with body weight, supporting the dose in children on a mg/kg basis, and that the dose in children should be divided by half in case of moderate renal impairment.

EFFICACY RESULTS

The evolution over time of SBP and DBP in the FAS is summarised in the table below.

In patients from Subgroup A, *i.e.* not previously treated for arterial hypertension, the mean SBP and DBP decreased between baseline and D120, and then remained stable until last assessment (mean changes from baseline to last assessment = -7.8 ± 10.7 mmHg for SBP and -13.2 ± 12.1 mmHg for DBP).

In patients from Subgroup B, the mean SBP and DBP tended to remain stable or slightly decreased, consistently with the definition of the subgroup (hypertensive patients with BP controlled by their previous treatment), indicating that control of BP was maintained under perindopril treatment (mean changes from baseline to last assessment = 0.8 ± 16.4 mmHg for SBP and -1.0 ± 14.1 mmHg for DBP).

In patients from Subgroup C, *i.e.* with previously treated uncontrolled arterial hypertension, the mean SBP and DBP decreased between during the short-term period and then remained stable until last assessment (mean changes from baseline to last assessment = -9.6 ± 13.0 mmHg for SBP and -11.0 ± 4.8 mmHg for DBP).

The BP assessment adapted from Nancy abacus showed that most patients had SBP and DBP below the 97.5th percentile + 10 mmHg at their last assessment (96.7% of patients for SBP and 98.4% for DBP). It can be noted that 78.7% of patients for SBP and 85.2% for DBP had values below the 95th percentile at last assessment.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Changes over time in SBP and DBP (mmHg) - FAS

		All (N = 61)	**Subgroup A (N = 5)**	**Subgroup B (N = 51)**	**Subgroup C (N = 5)**
SBP					
INCLUSION		116.6 ± 13.6	124.0 ± 8.9	114.9 ± 13.6	126.8 ± 12.3
D120	n	59	5	49	5
	Mean ± SD	112.5 ± 14.7	115.2 ± 5.5	111.7 ± 14.9	118.2 ± 19.5
Change from inclusion	Mean ± SD	**-3.4 ± 14.5**	**-8.8 ± 8.8**	**-2.3 ± 14.8**	**-8.6 ± 15.8**
M12	n	52	5	42	5
	Mean ± SD	111.9 ± 12.1	109.4 ± 6.2	111.2 ± 10.7	119.8 ± 23.5
Change from inclusion	Mean ± SD	**-4.9 ± 13.8**	**-14.6 ± 11.8**	**-3.5 ± 13.3**	**-7.0 ± 18.2**
M24	n	48	5	38	5
	Mean ± SD	113.5 ± 12.3	116.8 ± 4.6	113.0 ± 12.4	113.8 ± 17.9
Change from inclusion	Mean ± SD	**-3.8 ± 14.3**	**-7.2 ± 11.8**	**-2.1 ± 14.5**	**-13.0 ± 13.4**
Last value	n	61	5	51	5
	Mean ± SD	115.9 ± 13.3	116.2 ± 5.4	115.7 ± 14.3	117.2 ± 8.2
Change from inclusion	Mean ± SD	**-0.8 ± 16.0**	**-7.8 ± 10.7**	**0.8 ± 16.4**	**-9.6 ± 13.0**
	E (SE)	-0.8 (2.05)	-7.8 (4.77)	0.8 (2.29)	-9.6 (5.84)
	95% CI	[-4.8 ; 3.3]	[-21.0 ; 5.4]	[-3.8 ; 5.4]	[-25.8 ; 6.6]
DBP					
INCLUSION		69.4 ± 11.7	76.6 ± 9.1	68.0 ± 11.7	77.0 ± 8.8
D120	n	59	5	49	5
	Mean ± SD	66.3 ± 11.4	63.0 ± 5.4	66.3 ± 11.4	69.0 ± 16.2
Change from inclusion	Mean ± SD	**-2.8 ± 14.3**	**-13.6 ± 13.4**	**-1.1 ± 14.3**	**-8.0 ± 10.5**
M12	n	52	5	42	5
	Mean ± SD	64.0 ± 9.8	65.4 ± 7.8	63.5 ± 10.1	67.4 ± 9.9
Change from inclusion	Mean ± SD	**-5.1 ± 12.6**	**-11.2 ± 12.4**	**-3.9 ± 13.0**	**-9.6 ± 7.3**
M24	n	48	5	38	5
	Mean ± SD	65.0 ± 8.2	63.2 ± 4.2	64.9 ± 8.5	67.6 ± 9.5
Change from inclusion	Mean ± SD	**-5.0 ± 11.5**	**-13.4 ± 10.4**	**-3.3 ± 11.5**	**-9.4 ± 8.8**
Last value	n	61	5	51	5
	Mean ± SD	66.6 ± 9.2	63.4 ± 5.0	66.9 ± 9.6	66.0 ± 8.3
Change from inclusion	Mean ± SD	**-2.8 ± 14.0**	**-13.2 ± 12.1**	**-1.0 ± 14.1**	**-11.0 ± 4.8**
	E (SE)	-2.8 (1.79)	-13.2 (5.41)	-1.0 (1.98)	-11.0 (2.17)
	95% CI	[-6.4 ; 0.7]	[-28.2 ; 1.8]	[-5.0 ; 3.0]	[-17.0 ; -5.0]

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SUMMARY – CONCLUSIONS (Cont'd)

ACCEPTABILITY AND SAFETY RESULTS (primary objectives of the study)

Acceptability

The acceptability criterion was assessed by taking into account the rate of treatment discontinuation due to the refusal of orodispersible tablets. No withdrawal due to refusal of orodispersible tablets was reported.

Adverse events

Analysis of adverse events is summarised below. In the Safety Set, 56 patients (90.3%) experienced 557 emergent adverse events, the mean total treatment duration being approximately 44 months.

Overall summary of safety results

		All (N = 62)
Patients having reported		
at least one emergent adverse event	n (%)	56 (90.3)
at least one treatment-related emergent adverse event	n (%)	6 (9.7)
Patients having experienced		
at least one serious adverse event	n (%)	37 (59.7)
at least one treatment-related serious adverse event	n (%)	1* (1.6)
Patients withdrawn		
due to an adverse event	n (%)	6 (9.7)
due to a serious adverse event	n (%)	4 (6.5)
due to a treatment-related adverse event	n (%)	1 (1.6)

** 4 SAEs in one patient were considered as not treatment-related by the investigator and related by the PV department*

The most frequently affected system organ classes were:

- Infections and infestations (38 patients; 61.3%), which consisted mainly of urinary tract infections (11 patients; 17.7%), acute bronchitis (10 patients; 16.1%), and respiratory tract infection (9 patients ; 14.5%).
- Respiratory, thoracic and mediastinal disorders (32 patients; 51.6%) mainly nasopharyngitis (15 patients; 24.2%), pharyngitis (12 patients; 19.4%) and rhinitis (10 patients; 16.1%).
- Gastrointestinal disorders (31 patients; 50.0%) mainly gastroenteritis (18 patients; 29.0%) and diarrhoea (9 patients; 14.5 %).
- Renal and urinary disorders (21 patients; 33.9%) mainly nephropathy (4 patients; 6.5%).

The adverse events observed in the study were consistent with the known safety profile of perindopril, with the age of the patients and their medical history, and with the duration of the study.

Emergent adverse events were mostly graded as mild (344/557) or moderate (186/557). Twenty-six severe emergent adverse events were reported. Of them, 3 were related to Vascular disorders (hypertensive crisis, hypertension aggravated and hypertension) and 3 were related to Renal and urinary disorders (nephrotic syndrome, neurogenic bladder, proteinuria aggravated). None was considered related to the study drug by the investigator.

During the study, moderate orthostatic hypotension was reported in two patients. These events, considered by the investigator unrelated to the study treatment, resolved.

Eight emergent adverse events in 6 patients (9.7%) were considered related to the study drug by the investigator. These events included 3 events related to Renal and urinary disorders (aggravated renal failure, aggravated chronic renal failure, renal failure), 2 events related to Investigations (increased blood potassium, immunosuppressant drug level decreased), one case of mild cough, one case of syncope and one case of hypotension. None of these events was severe and all were resolved.

Six emergent adverse events led to premature treatment discontinuation: glomerulonephritis/proteinuria aggravated, acute renal failure, aggravated renal failure, renal impairment, multiple epipyseal dysplasia and recidival of pneumococcal peritonitis. All events but 2 (aggravated renal failure and renal impairment) were serious. The outcome was favourable for all these events except for glomerulonephritis/proteinuria aggravated and renal impairment which were unchanged.

No patient died during the study.

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SUMMARY – CONCLUSIONS (Cont'd)

ACCEPTABILITY AND SAFETY RESULTS (primary objectives of the study) (Cont'd)

Adverse events (Cont'd)

Overall, 37 patients (59.7%) experienced 105 serious adverse events. The most commonly affected SOCs were Infections and infestations (24.2% of the patients), Investigations (19.4%), Gastrointestinal disorders (17.7%) and Renal and urinary disorders (12.9%). None of the serious adverse events was considered as related to the study drug by the investigator (nevertheless, the Sponsor's Pharmacovigilance Department considered gastroenteritis and acute renal failure [2 episodes each, *i.e.* 4 SAEs] in one patient as related to the study drug, while the investigator considered them as not related to the treatment).

Laboratory examination

Mean changes in biochemical and haematological parameters between baseline and the last value were small and without clinical relevance, except for an increase in creatininemia due to high values in a few patients.

Emergent potentially clinically significant abnormal (PCSA) biochemistry values were observed in 4 patients for potassium (3 patients with a high value and one patient with a low value), in 6 patients for creatinine (high values), in 5 patients for alkaline phosphatase (high values) and 1 patient for urea (high value). Emergent PCSA abnormal biochemistry values were considered by the investigator as clinically significant in 2 patients: one alkaline phosphatase increase and one potassium increase. In both cases, the value returned within the reference range at the last assessment.

Regarding haematological parameters, emergent PCSA were observed in 9 patients, including mainly 6 patients with low PCSA values for haemoglobin and/or haematocrit. Emergent PCSA abnormal haematology values were considered clinically significant by the investigator in 3 patients.

Vital signs

As expected in a paediatric population and considering the study duration, mean height and weight increased during the study.

At the time of PK assessment, the mean SBP decreased by -6.7 ± 11.1 mmHg from baseline to 3.5 hours after the study treatment intake (expected time of the perindoprilat maximum concentration).

The mean changes in heart rate during the study were small and devoid of clinical relevance.

ECG

Emergent ECG abnormalities were observed in 5 patients and were considered by the investigator as non significant. The mean QTc (Bazett's correction) interval duration slightly decreased between baseline and the last value.

Echocardiography

Echocardiographic results were obtained in 23 patients at baseline and during the follow-up. In these patients, no deleterious effect could be detected on left ventricular systolic function or mass.

CONCLUSION

In conclusion, the orodispersible formulation of perindopril led to a high acceptability in children suffering from hypertension (no withdrawal due to refusal of tablets). The safety was satisfactory and consistent with the known safety profile of perindopril, the duration of the study, and a paediatric population. In average, SBP and DBP remained stable from inclusion to the last assessment in patients controlled with their previous treatment and decreased by –7.8 / -13.2 mmHg, respectively, in children not previously treated for hypertension. More than 95% of children had SBP and DBP below the 97.5th percentile + 10 mmHg (Nancy abacus) at their last assessment. These results were obtained using mean weight-adjusted doses of perindopril within the recommended range of 0.025 to 0.135 mg/kg/day.

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