I. SCIENTIFIC DISCUSSION

1.1 Introduction

Following a request from the EMEA regarding the obligation to submit all paediatric data, the MAH submitted the results two Phase I studies, including pharmacokinetic data, and one clinical dose-ranging study of ibersartan in paediatric patients with hypertension. Further to the assessment of these data, the CHMP requested an update of sections 4.2, 4.4, 4.8, and 5.1 of the SPC.

The MAH has applied to update the SPC in line with the conclusions adopted by the CHMP on 14 December 2005, with the exception of the wording for section 4.8. In addition, the MAH has proposed a minor change to the wording of a sentence in section 2 of the PL for clarity. Also, to be in alignment with the QRD templates, the MAH would like to make a correction in the section 9 of the SmPC of the film-coated tablets.

1.2 Clinical aspects

The MAH has submitted 2 pharmacokinetic studies in hypertensive children and adolescents and 1 study assessing the dose-response relationship in hypertensive patients aged 6 - 16 years - see table below.

Study ID Status Type of report	Main Objetive	Design	Number of treated subjects	Duration of treatment
CV131076 Completed Full	Evaluate PK and antihypertensive response in hypertensive children and adolescents.	Open-label, randomised, two period group with PBO lead-in	23 children enrolled and 22 completed	Period A: 7 - 14 day withdrawal period Period B: 2 - 4 weeks
CV131141 Prematurely stopped Abbreviated	single dose PK in children 1 month to 6 yrs of age with a secondary goal of assessing the safety of irbesartan in children 1 month to 6 yrs	Open-label, Multi-site, single dose study	2 subjects enrolled 1 dosed	Single Dose
CV131154 Completed Full	Evaluate the dose-response relationship in change from baseline in trough SeSBP with high, medium, and low doses of irbesartan in children and adolescents aged 6 - 16 years with baseline SeSBP $\geq 90^{th}$ percentile for age/gender/height.	Dose-ranging study with placebo controlled withdrawal period, followed by open-label, long-term extension period	441 subjects enrolled	Period B, 3 weeks Period C, max treatment 2 weeks Period D, 26 weeks:

Study CV131076

Study CV131076 was an open-label, multicentre study to evaluate the pharmacokinetics of irbesartan capsules (12.5, 25, 37.5, 50, 75 and 100 mg) in hypertensive children and adolescents. The secondary objective was to evaluate the change from baseline in seated systolic (SeSBP) and diastolic blood pressure (SeDBP) on days 1 and 29 of the second study period. The study had 2 treatment periods. In period A subjects were withdrawn from antihypertensive medication for 7 days (or 14 days if a longer washout period was needed). A stable dose of nifedipine and/or hidrochlorotiazide was allowed if

necessary. In period B, subjects received approx 2 mg/kg irbesartan qd for 4 weeks (or 2 wks if subject participation for 4 weeks was not possible) up to a maximum dose of 150 mg qd. For each individual patient the dose was kept constant throughout the study. PK sampling was performed on the first day of period B and on day 15 (or on any day between days 15 and 29). The dissolution profile of the irbesartan capsule formulation was equivalent to that of irbesartan capsule granulation mixed with apple sauce. Subjects whose BP could not be adequately controlled were discontinued.

Subjects included were hypertensive male or non-pregnant female children/adolescents, 1 to 16 years of age with a SeSBP and/or SeDBP ≥ 95th percentile for the child's sex/age/height.

The primary *efficacy endpoints* were; AUC_{∞} on day B1, AUCτ on day B15 (trapezoidal area under the concentration-time curve in one dosing interval), C_{max} adjusted to that of a 70kg adult, Clt $t_{1/2}$ and accumulation index (AUCτ on day B15/AUCτ on day B1). Regarding *safety*, a complete physical examination and a 12-lead ECG were performed at screening and prior to study discharge. Additionally safety assessment was based on adverse events (AE) reports and clinical laboratory tests.

The *sample size* was calculated based on the 37.9% reported coefficient of variation CV(%) for AUC after 29 days of treatment from a previous study where 100 mg qd of irbesartan was administered to male and female adult subjects with mild to moderate hypertension. According to the MAH the proposed sample size of 24 subjects allowed approximately 95% confidence that the estimated AUC mean would differ from the true population mean by at most 16%.

Results

Of the 23 subjects enrolled and randomised, 22 completed the study. Of those 12 were adolescents >12 years, 9 were children between 6-12 years and 2 were children < 6 years. The majority of them were black and all 3 age groups were balanced regarding gender.

Pharmacokinetic results
Plasma samples were collected immediately prior to dosing, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dosing on Days 1 and 15 (or later). The samples were assayed for irbesartan by a validated HPLC/fluorescence method with a lower limit of quantitation of 1.0 ng/ml.

Irbesartan pk parameters and the dose-normalised AUC and C_{max} were tabulated and 95% confidence intervals (CI) were constructed around the dose-adjusted mean parameter. Pk parameters were pooled by age groups as the MAH states that no specific trend for gender-related difference in the pk of irbesartan was evident. An accurate estimation of the terminal elimination half-life could not be obtained after the first dose because the plasma samples were collected only up to 24 hours post-dose (less than three half-lives) in most of the subjects.

The results for the 2 children < 6 years included in this study have been omited. A summary of the pharmacokinetic parameters (single dose and steady state) in the 6-12 years age group and in the 13-16 years age group are shown in the tables below.

Summary of Pharmacokinetic Parameters of Irbesartan in the 6-12 Year Age Group Following a Single and Repeated Daily 2 mg/kg Oral Doses of Irbesartan in Study CV131-076

Parameter		Pharmacokinetic Sampling Interval	
		Single Dose (N=9)	Steady State (N=9)[2]
CMAX (ng/mL)	Geo. Mean (CV %)	1625 (35.0)	1969 (54.1)
TAUC[1] (ng•h/mL)	Geo. Mean (CV %)	8512 (35.6)	8957 (58.6)
TMAX (h)	Median (Min-Max)	2.0 (1.0, 4.0)	2.0 (0.5, 4.0)
CLT/F (L/min)	Mean (SD)	0.20 (0.06)	0.21 (0.12)
AI	Geo. Mean (CV %)	—	1.09 (35.0)
Dose Normalized CMAX[3] [(ng/mL)/(mg)]	Geo. Mean (95% C.I.[4])	17.0 (12.7, 22.8)	20.6 (13.8, 30.8)
Dose Normalized TAUC[1,3] [(ng•h/mL)/(mg)]	Geo. Mean (95% C.I.[4])	85.3 (68.9, 105.5)	93.7 (61.1, 143.7)

CV131-076
1 TAUC is TAUC(0-T) for single dose and TAUC(0-24h) for steady state.
2 N=8 for AI
3 The parameters CMAX and AUC were dose normalized based on the actual dose given to the subjects.
4 C.I.: Confidence Interval.

Summary of Pharmacokinetic Parameters of Irbesartan in the 13-16 Year Age Group Following a Single and Repeated Daily 2 mg/kg Oral Doses of Irbesartan in Study CV131-076

Parameter		Pharmacokinetic Sampling Interval	
		Single Dose (N=12)	Steady State (N=12)
CMAX (ng/mL)	Geo. Mean (CV %)	1925 (45.1)	1812 (47.7)
TAUC[1] (ng·h/mL)	Geo. Mean (CV %)	9973 (42.0)	10340 (40.2)
TMAX (h)	Median (Min-Max)	2.0 (1.5, 4.0)	1.5 (0.5, 4.0)
CLT/F (L/min)	Mean (SD)	0.24 (0.12)	0.23 (0.11)
AI	Geo. Mean (CV %)	—	1.18 (27.6)
Dose Normalized CMAX[2] [(ng/mL)/(mg)]	Geo. Mean (95% C.I.[3])	14.8 (10.7, 20.4)	13.9 (9.7, 19.9)
Dose Normalized TAUC[1,2] [(ng•h/mL)/(mg)]	Geo. Mean (95% C.I.[3])	76.5 (56.3, 104.0)	79.3 (58.3, 108.0)

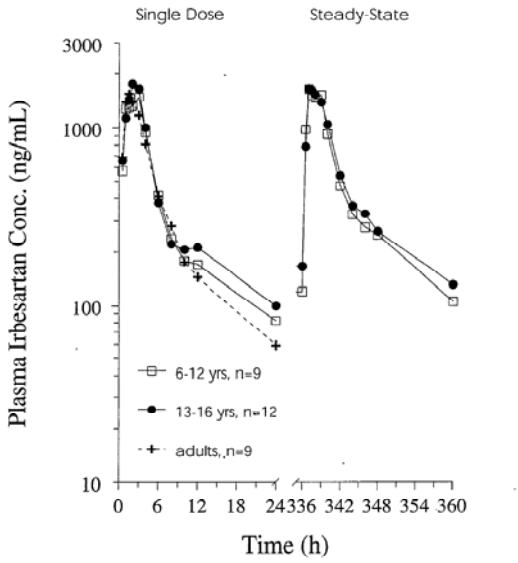
CV131-076
1 TAUC is TAUC(0-T) for single dose and TAUC(0-24h) for steady state.
2 The parameters CMAX and AUC were dose normalized based on the actual dose given to the subjects.
3 C.I.: Confidence Interval.

According to the MAH, pk parameters were comparable between the 6-12 year and the 13-16 age groups. The absorption of irbesartan was rapid, with peak plasma concentrations attained 1.5-2 hours after dosing. Limited accumulation of irbesartan (18%) was observed in plasma upon repeated once daily dosing in these subjects.

These plasma concentrations were, in general, associated with decreases in SeDBP and SeSBP, irrespective if the subject was receiving other concomitant antihypertensive medications (see pharmacodynamic results).

According to the MAH, in the light of the results provided a 2 mg/kg dose in paediatric patients resulted in an exposure comparable to that of adults receiving the 150 mg dose. For reference, the mean C_{max} and AUC values of irbesartan following a single 150 mg oral in young adults (18-40 years) were 1854 ng/ml and 9715 ng/ml respectively.

Mean plasma concentration-time profiles of irbesartan in children and adolescents following single and repeated daily 2mg/kg oral doses in study CV131-076, and in adults following a single 150 mg dose in Study CV131-045



Pharmacodynamic results

Individual and Mean Change from Baseline in SeSBP/SeDBP on Days B1 and B29.

Subject No.		SeSBP/SeSDP (mmHg)			Δ SeSBP/Δ SeSDP (mmHg)	
		Baseline[a]	B15	B29	B15-Baseline	B29-Baseline
Subjects not receiving concomitant antihypertensive medications						
001	001	138 / 98	136 / 94	126 / 78	-2 /-4	-12 /-20
001	002	138 / 72	124 / 80	108 / 84	-14 /8	-30 /12
001	003	132 / 78	108 / 78	110 / 80	-24 /0	-22 /2
001	004	122 / 84	122 / 80	107 / 64	0 /-4	-15 /-20
001	005	110 / 82	110 / 71	104 / 74	0 /-11	-6 /-8
001	006	132 / 98	124 / 88	122 / 76	-8 /-10	-10 /-22
003	001	149 / 74	149 / 72	-- -- --	0 /-2	-- -- --
003	002	134 / 73	139 / 66	-- -- --	5 /-7	-- -- --

In both treatment groups (patients receiving and not receiving concomitant antihypertensive medication), the administration of 2 mg/kg irbesartan was associated with decreases in SeSBP and SeDBP, except for 2 subjects; one on day B15 (004/014) and one on day B29 (004/003). Subject 004/003 showed an increase in SeSBD/SeDBP of +35/+22 mmHg at B29 that was attributed to medication non-compliance.

Mean decreases in SeSBD/SeDBP for the 12 subjects that did not receive concomitant antihypertensive therapy were -8/-7 and -16/-10 mmHg after 14 and 28 days of dosing with ibersartan, respectively, while the 11 subjects who continued to receive concomitant antihypertensive therapy had additional mean decreases in SeSBD/SeDBP of -5/-8 and -5/-4 mmHg after 14 and 28 days of dosing with ibersartan, respectively.

Safety
There were 14 AEs reported by 9 subjects. The most frequently reported were headache and pahryngitis; 2 headaches (1 reported as severe) were judged as possibly related to the study drug. Urinary red blood cells was the most frequently reported laboratory abnormality in 3 out of 14 notified marked abnormalities. There were no deaths and no subjects discontinued from the study because of vital sign, ECG or laboratory abnormalities.

Study CV131154

This was a multicentre, randomised, double-blind, dose-ranging study to evaluate the safety and effectiveness of 3 irbesartan oral tablet dose regimens in the treatment of children (6 years - Tanner stage < 3) and adolescents (Tanner stage ≥ 3 - < 17 years) with hypertension or high-normal BP. After a lead-in period lasting a maximum of 14 days (Period A), patients were randomised to one of three doses of irbesartan (0.5, 1.5 or 4.5 mg/kg) that they received for 3 weeks (Period B). Then patients were re-assigned at random to either placebo or irbesartan at the dose taken previously during a maximum period of 4 weeks (Period C). In adittion, for safety reasons, a 6 month open-label extension was also included (period D). The study 4 study periods are described below in more detail:

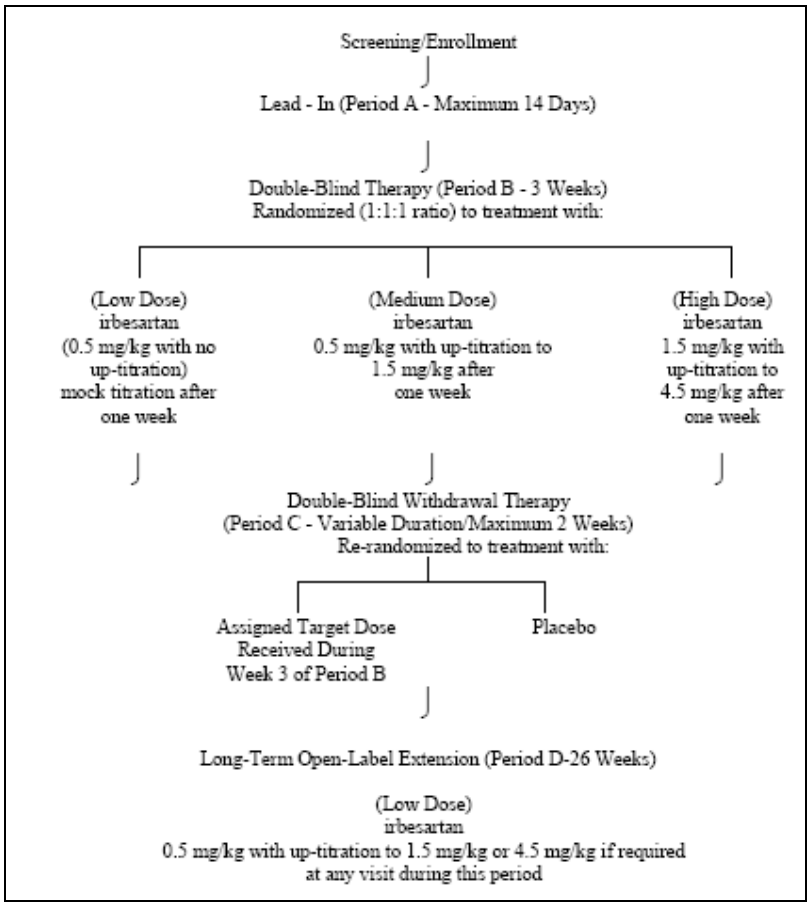
Period A: During this lead-in period, previous antihypertensive therapy and prohibited concomitant medications were withdrawn. At all visits during the study, BP measurements were obtained using the Device for Indirect Noninvasive Automatic Mean Arterial Pressure (DINAMAP).

Period B: Subjects were randomly assigned to double-blind treatment with one of 3 irbesartan regimens (see study scheme). Following the initial dose, subjects showing signs/symptoms associated with hypotension or decreases of ≥ 20 mmHg from baseline in SeSBP/SeDBP were to be discontinued from the study. Study medication was titrated up to the assigned target dose after the first week (Visit B8); this dose was continued for the remaining 2 weeks of Period B. Subjects who were unable to tolerate up-titration to the assigned target dose were eligible for open-label therapy (Period D).

Period C: Subjects were re-assigned to either placebo or irbesartan at the assigned target dose last taken during Period B. BP measurements were taken at the end of Week 1 and Week 2. Subjects who discontinued from Period C could be enrolled directly into Period D, if the investigator felt that continuing in Period C was no longer in the best interest of the subject, the subject experienced an increase in BP, or if the subject showed clinical signs or symptoms of uncontrolled hypertension.

Period D: Subjects who completed Period C and subjects who met the Period B or Period C discontinuation criteria for direct enrolment into Period D entered the open-label extension period of 26 weeks. Subjects were reintroduced to irbesartan at 0.5 mg/kg. After the initial dose of open-label treatment, irbesartan could be titrated from 0.5 mg/kg to 1.5 mg/kg to achieve BP control. The dose could be titrated again from 1.5 mg/kg to 4.5 mg/kg 24 ± 3 hours after the previous titration. Irbesartan doses were adjusted upward or downward as needed throughout Period D. The use of adjunctive antihypertensive agents was allowed only during Period D.

Study Scheme



The *primary objective* was to evaluate the dose-response relationship in change from baseline in trough SeSBP at the end of treatment Period B with low, medium, or high doses of irbesartan. Secondary objectives were; i) to evaluate the change in trough SeSBP for irbesartan (all 3 dose levels combined) versus placebo from the end of treatment Period B to the end of the Period C. ii) to evaluate the dose-response relationship in change from baseline in trough SeDBP at the end of Period B. iii) to evaluate the change in trough SeDBP for irbesartan (all three dose levels combined) versus placebo from the end of Period B to the end of Period C. iv) to evaluate the percentage of subjects who reach a target BP of < 90th percentile for both SeSBP and SeDBP at the end of the treatment Period B v) to assess the safety and tolerability of irbesartan in the paediatric population (Periods B and C and D).

The *target population* included children and adolescents (male and female, aged 6 - 16 years inclusive) with hypertension (SeSBP or SeDBP ≥ 95th percentile for age, gender, and height) or with high-normal BP (SeSBP or SeDBP ≥ 90 to < 95th percentile for age, gender, and height) and either diabetes mellitus, or family history of hypertension, or any other condition for which, in the opinion of the investigator, the reduction of BP would be in the best interest of the child or adolescent. Study participants entering the study based on hypertension criteria were to have 3 qualifying BP measurements ≥ 95^{th} percentile for gender, age, and height.

The *sample size* was based on the primary analysis, which tested linear trend across the low, medium, and high doses of irbesartan in adjusted mean change from baseline in through SeSBP after 3 weeks of double-blind treatment during period B. During the course of the study, the number of adolescents exceeded the planned number. To keep the intended children:adolescent balance as per the FDA request the planned number of 189 evaluable subjects was increased to 270 (90 per dose level). This number would provide a power of 80% to detect a significant trend across the 3 dose groups assuming the smaller difference of 5.0 mmHg between high and low groups. A standard deviation of change

from baseline in SeSBP of 12 mmHg was assumed. A 10% dropout rate between the original randomisation and the end of Period B was factored in.

Doses of irbesartan were selected based on the adult daily dose, the comparable pk profile between children and adults observed in the CV131076 study and the safety of irbesartan.

Table 5.5.1: Irbesartan Target Dose Assignments for Children and Adolescents

Body Weight	Low (0.5 mg/kg)	Medium (1.5 mg/kg)	High (4.5 mg/kg)
≥ 20 kg to < 30 kg	18.75	37.5	112.5
≥ 30 kg to < 40 kg	18.75	56.25	150.0
≥ 40 kg to < 50 kg	18.75	75.0	150.0
≥ 50 kg to < 60 kg	37.5	75.0	225.0
≥ 60 kg	37.5	112.5	300.0[a]

CV131154
Source: Appendix 5.1A
[a] Maximum allowable dose

The *primary efficacy outcome measure* was the change from baseline in trough SeSBP at Week 3 of Period B. The most important secondary efficacy outcome measure was the change in trough SeSBP from the end of Period B to the end (Week 2) of Period C. Other efficacy measurements were the changes from original baseline at each visit in trough SeSBP and SeDBP, and the number of subjects normalised at each visit during the study. Normalised (target) BP was when the trough SeSBP and SeDBP were each less than the respective 90th percentile for a subject's age, gender, and height.

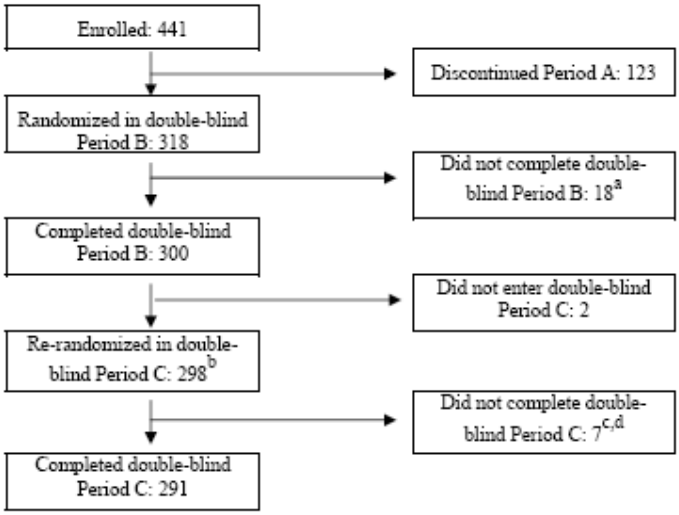
The *primary statistical analysis* was a test for linear trend across the 3 dose groups with respect to changes from baseline in trough SeSBP at Week 3 of Period B. The analysis was carried out using a linear contrast applied to the adjusted mean changes from an ANCOVA model having a term for group and baseline value as covariate. As this test was not significant, a comparison of the changes in trough SeSBP between the two groups, any placebo and any irbesartan, from the end of Period B to Week 2 of Period C was carried out to evaluate the effect of withdrawal from irbesartan over the 2-week period. This comparison was also carried out for changes in trough SeDBP using a similar ANCOVA model. Missing efficacy assessments were not imputed in any way except for the last-observation-carried-forward (LOCF) analyses. Thus, subjects were excluded from treatment comparisons of changes from baseline at any visit for which they had a missing baseline value and/or a missing assessment at that visit. Similarly, the proportion of therapeutic responders at each visit was based only on those subjects with available BP values at that visit. Since the number of subjects who discontinued from Period B in each of the treatment groups was less than 10% of the number randomised to the group, LOCF analyses were not performed.

Results

A total of 441 subjects were enrolled into the study. The figure below shows the disposition of all randomised patients.

Disposition of patients

Figure 8.1: Subject Disposition



CV131154

Source: Appendices 8.1.1, 8.1.2, 8.1.3

a In Period B, 6 subjects discontinued Period B and enrolled directly into Period D and 12 subjects discontinued the study.

b In Period C, 3 subjects (2 assigned to placebo and 1 assigned to irbesartan 1.5-mg/kg) did not receive study drug.

c Two subjects randomized to placebo and 1 subject randomized to irbesartan discontinued Period C and enrolled directly into Period D, and 2 subjects receiving placebo and 1 subject receiving irbesartan discontinued the study.

d Subject CV131154-62-7 was randomized but not treated and appears in this figure because no reason for discontinuation was entered in the CRF.

Baseline demographics

Baseline Demographic and Disease Characteristics

Demographic Characteristic	Irbesartan 0.5/0.5 mg/kg N = 108	Irbesartan 0.5/1.5 mg/kg N = 107	Irbesartan 1.5/4.5 mg/kg N = 103	Total Subjects N = 318
Age (years)				
n	108	107	103	318
Mean (SD)	12.3 (2.8)	12.5 (2.9)	12.6 (2.9)	12.5 (2.8)
Range	6 - 16	6 - 16	6 - 16	6 - 16
Age Group: n (%)				
6 - 12 years	52 (48.1)	48 (44.9)	46 (44.7)	146 (45.9)
13 - 16 years	56 (51.9)	59 (55.1)	57 (55.3)	172 (54.1)
Gender: n (%)				
Male	74 (68.5)	71 (66.4)	69 (67.0)	214 (67.3)
Female	34 (31.5)	36(33.6)	34 (33.0)	104 (32.7)
Race; n (%)				
White	94 (87.0)	92 (86.0)	89 (86.4)	275 (86.5)
Black	9 (8.3)	11 (10.3)	12 (11.7)	32 (10.1)
Other	5 (4.6)	4 (3.7)	2 (1.9)	11 (3.5)
Weight (kg)				
n	108	107	103	318
Mean (SD)	60.9 (24.0)	66.1 (24.8)	67.4 (28.3)	64.8 (25.8)
Range	19.7 - 136.0	21.0 - 172.1	20.6 - 165.6	19.7 – 172.1
Hypertensive Status: n (%)				
Hypertension	82 (75.9)	84 (78.5)	88 (85.4)	254 (79.9)
High-normal BP	22 (20.4)	19 (17.8)	14 (13.6)	55 (17.3)
Normal	4 (3.7)	4 (3.7)	1 (1.0)	9 (2.8)
Hypertension Duration (months)				
n	108	107	103	318
Mean (SD)	15.7 (21.3)	18.3 (24.4)	14.8 (20.0)	16.3 (22.0)
Range	0.0 - 102.4	0.1 - 135.8	0.0 – 101.3	0.0 – 135.8
Region: n (%)				
North America	27 (25.0)	29 (27.1)	27 (26.2)	83 (26.1)
Europe	81 (75.0)	78 (72.9)	76 (73.8)	235 (73.9)
Tanner Scale: n (%)				
6 years to < 3 Tanner stage	61 (56.5)	54 (50.5)	44 (42.7)	159 (50.0)
≥ 3 Tanner stage to < 17 years	47 (43.5)	53 (49.5)	59 (57.3)	159 (50.0)

CV131154

Efficacy results

Double-blind Treatment (Periods B and C):
Mean changes in trough SeSBP and SeDBP from baseline to the end of Week 3 in Period B and mean changes from the end of Period B to Week 2 of Period C in trough SeSBP and SeDBP are shown in the following tables.

Mean Changes from Baseline in Trough SeDBP and SeSBP at Week 3 of Period B: Randomized Subjects

	Irbesartan 0.5/0.5 mg/kg N = 108	Irbesartan 0.5/1.5 mg/kg N = 107	Irbesartan 1.5/4.5 mg/kg N = 103
Trough SeSBP (mmHg)			
n	101	101	100
Baseline Mean (SD)	134.3 (9.7)	134.5 (9.9)	135.1 (11.2)
Period B On-Therapy Mean (SD)	122.8 (12.1)	125.3 (11.7)	121.8 (12.9)
Adj. Mean Change from Baseline (SE)	-11.7 (1.1)	-9.3 (1.1)	-13.2 (1.1)
95% Confidence Interval	(-13.8, -9.6)	(-11.5, -7.2)	(-15.3, -11.0)
P-value for the overall trend test			0.118
Trough SeDBP (mmHg)			
n	101	101	100
Baseline Mean (SD)	71.4 (8.8)	70.9 (8.7)	71.1 (8.4)
Period B On-Therapy Mean (SD)	67.4 (7.9)	67.8 (7.8)	65.5 (7.7)
Adj. Mean Change from Baseline (SE)	-3.8 (0.7)	-3.2 (0.7)	-5.6 (0.7)
95% Confidence Interval	(-5.2, -2.4)	(-4.6, -1.8)	(-7.0, -4.3)
P-value for the overall trend test			0.024

CV131154
N = number of subjects randomized into Period B
n = number of subjects with available efficacy data at Week 3 (Period B)

All the treatment groups showed mean decreases in trough SeSBP and SeDBP at the end of Period B. The adjusted mean reduction from baseline in trough SeSBP was similar for subjects treated with low

(11.7 mmHg), medium (9.3 mmHg) and high (13.2 mmHg) dose irbesartan. There was no evidence of a significant dose-response relationship for changes in trough SeSBP ($p>0.05$). The adjusted mean changes for SeDBP revealed a statistically significant linear trend ($p<0.05$).

Mean Changes from End of Period B in Trough SeSBP and SeDBP to Week 2 of Period C: Randomized Subjects

	Any Placebo N = 148	Any Irbesartan N = 150
Trough SeSBP (mmHg)		
n	141	145
End of Period B Mean (SD)	122.7 (11.9)	124.0 (12.5)
Adj. Mean Change from End of Period B (SE)	2.4 (0.8)	0.1 (0.8)
Est. Difference between treatment and placebo		-2.3
95% CI for estimated difference		(-4.63, -0.01)
P-value for between group comparison		0.04997
Trough SeDBP (mmHg)		
n	141	145
End of Period B Mean (SD)	67.3 (6.9)	66.3 (8.2)
Adj. Mean Change from End of Period B (SE)	2.0 (0.5)	-0.3 (0.5)
Est. Difference between treatment and placebo		-2.3
95% CI for estimated difference		(-3.75, -0.92)
P-value for between group comparison		0.00143

CV131154
N = number of subjects randomized into Period C
n = number of subjects with available efficacy data at Week 2 (Period C)

From the end of Period B to Week 2 of Period C small mean changes in SeSBP and SeDBP were noted in the group remaining on irbesartan, whereas increases of 2.4 mmHg and 2.0 mmHg for SeSBP and SeDBP, respectively, were observed in the group withdrawn from irbesartan (Any Placebo).

The proportion of subjects reaching target BP at the end of Week 3 in Period B was 55% in the 0.5/0.5 mg/kg group, 41% in the 0.5/1.5 mg/kg group, and 51% in the 1.5/4.5 mg/kg group. By the end of Period C, only 35% of subjects randomised to placebo achieved target BP, whereas 46% of subjects remaining on irbesartan achieved target BP.

For Period D, when all irbesartan subjects were combined, starting on 0.5 mg/kg and titrating as required, the mean reductions from original baseline were between 12.3 and 16.4 mmHg for trough SeSBP and between 4.1 and 5.6 mmHg for SeDBP at the various timepoints over a 26-week period. Proportions of subjects reaching target BP ranged from 53%-66%. These proportions were sometimes comparable to and sometimes slightly higher than the proportions reaching target BP during Period B.

Safety results

Summaries of adverse events (AEs) during Period B and Period C are presented in the following table.

Summary of Adverse Events During Period B and Period C

Event	Number (%) of Subjects				
Period B; Treatment Groups (mg/kg)	**Placebo NA**	**Irb 0.5/0.5 N = 108**	**Irb 0.5/1.5 N = 107**	**Irb 1.5/4.5 N = 103**	**Any Irb N = 318**
Total AEs	NA	34 (31.5)	39 (36.4)	36 (35.0)	109 (34.3)
Related AE[a]	NA	10 (9.3)	19 (17.8)	15 (14.6)	44 (13.8)
SAE[a]	NA	0	1 (0.9)	0	1 (0.3)
Death	NA	0	0	0	0
D/Cs due to AEs[a]	NA	3 (2.8)	4 (3.7)	1 (1.0)	8 (2.5)
Period C; Treatment Groups (mg/kg)	**Placebo N = 146**	**Irb 0.5 N = 49**	**Irb 1.5 N = 49**	**Irb 4.5 N = 51**	**Any Irb N = 149**
Total AEs	48 (32.9)	9 (18.4)	12 (24.5)	19 (37.3)	40 (26.8)
Related AE[a]	17 (11.6)	5 (10.2)	8 (16.3)	4 (7.8)	17 (11.4)
SAE[a]	0	0	0	2 (3.9)	2 (1.3)
Death	0	0	0	0	0
D/Cs due to AEs[a]	0	0	0	0	0

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Abbreviations: AE=adverse event; SAE=serious adverse event; D/C=discontinuation; NA=not applicable
a Subsets of all AEs: Subjects may be represented in more than one AE category.

No deaths were reported during the study. One subject in Period B and two subjects in Period C experienced serious adverse events (SAEs) during double-blind therapy. One subject was discontinued from Period B because of an SAE (erythema multiforme) attributed to irbesartan. SAEs in two subjects (diabetic ketoacidosis and syncope) were categorised as unrelated and unlikely related to study drug.

AEs in Period B led to discontinuation of study drug in 8 subjects; 4 subjects were enrolled directly in Period D and 4 subjects discontinued the study. Hypotension led to discontinuation of study drug in 5 subjects and was reported as severe in 3 of them. Another subject was discontinued from Period B because of dizziness and enrolled in Period D.

Period B: Headache of mild to moderate intensity was the most frequently reported AE, occurring in 14.5% of subjects receiving any irbesartan treatment. Other AEs that occurred in ≥ 3% of subjects in any treatment group were upper respiratory infection (URI), nasopharyngitis (both considered unrelated) and cough. AEs in 44 (13.8%) subjects receiving any irbesartan treatment were attributed to the study drug. Headache (25 subjects; 7.9%) was most frequently reported AE categorised as related to irbesartan; other related AEs were hypotension (2.2%), dizziness (1.9%) and cough (0.9%).

Period C: The overall incidence of AEs was greater in the placebo group (32.9%) than in subjects treated with any irbesartan (26.8%). Among the irbesartan treatment groups, the incidence of AEs appeared to increase with each dose of irbesartan, a trend not observed for the related AEs. Headache was the most common AE reported during Period C. The incidence of study drug-related headache was similar in the placebo subjects (5.5%) and in the combined irbesartan-treated subjects (5.4%). Three subjects receiving irbesartan had mild elevations of blood potassium levels, which resolved spontaneously within 13 to 89 days post onset. Other AEs that occurred in ≥ 3 % of subjects in any treatment group were cough, nasopharyngitis, URI, and pharyngitis.

Period D: The following table presents a summary of AEs during Period D.

Summary of Adverse Events During Open-Label Period D

Events	Any Irbesartan (N = 294)
	Number (%) of Subjects
AE, total	183 (62.2)
Related AEs[a]	73 (24.8)
SAE[a]	3 (1.0)
Deaths	0
Discontinuations due to AE[a]	1 (0.3)

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Abbreviations: AE = adverse event; SAE = serious adverse event; D/C = discontinuation

[a] Subsets of all AEs: Subjects maybe represented in more than one AE category.

SAEs were generally of mild to moderate intensity and deemed by the investigator as unrelated or not likely related to irbesartan. One subject discontinued the study because of mild elevations of blood bilirubin categorised as possibly related to irbesartan. Consistent with the double-blind treatment phase, the most frequently reported AEs were headache (27.2%), and nasopharyngitis (10.5%). Generally, headache was of mild to moderate intensity, although in 3 subjects (1.0%), headache was categorised as severe. It was also the most frequently occurring AE that was categorised as related to study drug (39 subjects; 13.3%). Other AEs that occurred in ≥ 3 % of subjects were: URI, cough, rhinitis, dizziness, pharyngitis, epistaxis, and viral infection.

Laboratory Evaluations:

Period B: During Period B, laboratory marked abnormalities (MAs) were most commonly observed for serum creatinine (ie, >1.5 times pretreatment) and creatine kinase (CK, ie, > 4 times pretreatment). In 3 subjects, creatinine marked abnormalities (MA) continued into Period C. Creatinine returned to baseline levels at the end of Period C in 1 subject, and 2 subjects did not continue in the study beyond Period B. Six subjects had elevated CK levels that met the MA criteria. There were no reports of concurrent myalgia, muscle aches, or myositis in any of the subjects.

Period C: Four subjects, 3 assigned to placebo and 1 subject in the irbesartan high-dose group, had elevated CK levels that met the MA criteria. There were no reports of concurrent myalgia, muscle aches or myositis in any of the subjects. Four subjects (2 placebo group and 2 irbesartan 1.5 mg/kg group) had creatinine levels that met the MA criteria.

Period D: The most frequently observed MAs during Period D were elevated creatinine levels (19 subjects; 6.5%). Generally, creatinine MAs did not exceed the laboratory reference range. In 12 subjects, creatinine MAs were single occurrences that returned to baseline levels at the end of Period D. In one subject creatinine increased from baseline, 0.7 mg/dl, to 3.0 mg/dl at the end of open-label dosing. Fourteen subjects (4.8%) had low haemoglobin (Hb) levels that met the MA criteria (ie, > 3g/dl decrease from pretreatment). In 8 subjects, Hb MAs were single occurrences and returned to baseline levels at the end of open-label treatment. Five subjects also had low Hb MAs during Period B or Period C. Six subjects (2.0%) were found to have MAs of CK at the end of open-label treatment. There were no associated AEs of myalgia, muscle aches, or myositis.

Discussion

Efficacy
Limited pharmacokinetic data of irbesartan in children and adolescents were obtained from a small study of 23 hypertensive children and adolescents (CV131076) with an inadequate representation of children under 6 years of age. Although some PK parameters of interest, like C_{min} and $T_{1/2}$, were not evaluated, the results showed that C_{max}, AUC and clearance rates were comparable to those observed in adults receiving 150 mg irbesartan daily. A limited accumulation of irbesartan (18%) in plasma was observed upon repeated once daily dosing. A brief summary of these findings has been included in section 5.2 of the SPC.

Regarding pharmacodynamic effects in study CV131076, greater reductions in SBP and DBP were observed in patients taking concomitant antihypertensive medication. These drugs probably did not affect the pharmacokinetics of irbesartan but a possible effect of these antihypertensive on the reduction of BP observed in this trial cannot be ruled out. Thus, this study provides no conclusive information on the pharmacodynamics of irbesartan in children and adolescents.

Study CV131154 was a dose ranging clinical trial that evaluated the efficacy and safety of a range of doses of irbesartan in 318 children and adolescents with hypertension or borderline hypertension. The analysis of the main endpoint showed a positive effect of irbesartan on the reduction of SeSBP at the end of the double-blind period. This effect was not dose-dependent and a similar reduction of SeSBP was observed with the 3 doses administered (-11.7 mm Hg for the lowest dose, -9.3 with the medium dose and -13.2 with the highest dose). As this period did not include a placebo arm it is difficult to know whether this flat response to irbesartan was due to the fact that all doses selected were in the flat portion of the dose-response curve or to a relative lack of efficacy of irbesartan in this population.

When the effect of irbesartan both in SeSBP and SeDBP was analysed over the subsequent 2-week period where patients were re-randomised to either irbesartan or placebo, an increase in trough SeSBP and SeDBP towards baseline was observed. The placebo group showed a 2.3 mm Hg greater increase in the adjusted mean change for SeSBP and SeDBP versus irbesartan. Although the difference was statistically significant, the small magnitude of the effect casts doubt on the true effect of irbesartan on BP in hypertensive children, suggesting that irbesartan would not constitute a useful antihypertensive regimen for paediatric patients. These findings have been included in section 5.1 of the SPC.

Regarding the responder rate, 55%, 41% and 51% of patients in the low, middle and high dose groups, respectively, reached the target BP at the end of Week 3 in Period B reflecting the lack of dose-response relationship. At the end of Period C, 35% of subjects randomised to placebo and 46% of subjects remaining on irbesartan achieved target BP. These results are in line with the data on BP reduction.

To conclude, the efficacy results from this study are inconclusive and cannot determine the adequate therapeutic doses to be administered in hypertensive children. Moreover, these results do not establish the efficacy of irbesartan in hypertensive children and adolescents and are insufficient to support the use of irbesartan in children, as reflectected in sections 4.2 and 4.4 of the SPC.

Safety
Overall, the incidences of AEs and related AEs did not appear to be dose related. The following related AEs occurred in the 3-week double-blind phase: headache (7.9%), hypotension (2.2%), dizziness (1.9%), cough (0.9%). Mean changes from baseline in standard laboratory tests within treatment groups were generally small and clinically unremarkable; the most frequent laboratory abnormalities observed n the 26-week open-label period of this trial were creatinine increases (6.5%) and elevated CK values (2%). This information has been included in section 4.8 of the SPC.

Conclusions and benefit risk assessment

Only limited information on the pharmacokinetics and pharmacodynamics of irbesartan in children and adolescents has been provided. Results from the dose-ranging study showed a positive effect of irbesartan on the reduction of BP but this effect was not dose-dependent. When the effect on BP was analysed in the withdrawal period, an increase in BP towards baseline was observed. The placebo group showed a 2.3 mm Hg greater increase in the adjusted mean change for systolic and diastolic blood pressure versus irbesartan. This difference was statistically significant, but its magnitude was small, casting doubt on the true effect of irbesartan in hypertensive children. These results are insufficient both to demonstrate the efficacy of irbesartan on hypertensive children and adolescents and to determine the adequate therapeutic doses to be administered in this population.

The adverse events seem to be similar to those reported in adults receiving irbesartan but data on safety in children is still limited.

In summary, the data provided on the effect of irbesartan in children and adolescents are limited and insufficient to support the use of irbesartan in children. However, the CHMP considers that it would be useful for practising paediatricians to have a summary of the data from the studies included in the SPC (sections 5.1 5.2, 4.8 and 4.2), provided that a statement explaining that existing data are insufficient to recommend its use in children is included in sections 4.2. and 4.4. of the SPC. Therefore, the SmPC has been updated to reflect the data provided, in accordance with the currently approved Guideline on Summary of Product Characteristics (October 2005).