CLINICAL REVIEW

Application Type	NDA
Submission Number	20757
Submission Code	(b) (4)
Letter Date	July 30, 2004
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Reviewer Name: Abraham M. Karkowsky, M.D., Ph.D.

Review Completion Date	October 26, 2004
Established Name	Irbesartan
(Proposed) Trade Name	Avapro
Therapeutic Class	Angiotensin II blocker
Applicant	Sanofi-Synthelabo
Priority Designation	Pediatric
Formulation	Tablets
Dosing Regimen	18.75 to 300 mg daily
Indication	Pediatric hypertension
Intended Population	Pediatrics

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1 Executive Summary

1.1 Recommendation on Regulatory Action.

(b) (4)

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings.

1.3.1 Brief Overview of Clinical Program

The submission consists of a single dose-response study followed by a placebo-controlled 2-week withdrawal period. For safety, there was a 6 month open-label extension of those enrolled into this study. Also submitted was an analysis of adverse events in two "use" databases.

1.3.2 Efficacy.

The sponsor performed and submitted a single dose-ranging study with a subsequent placebo-controlled withdrawal period. (b) (4)

1.3.3 Safety.

Data in support of the safety profile for the use of Irbesartan in the pediatric population consists of the dose-ranging with withdrawal study as well as a 6 month open-label extension phase. The sponsor also submits information from two "use" databases. The sponsor submitted, in response to this reviewer's concern, an amendment on 18 November 2004 that addressed the

laboratory abnormalities in the pediatric patients from the single clinical trial. In particular, this amendment addressed cutoffs for defining abnormalities different from those cutoffs which were submitted in the original report as well as follow-up on laboratory abnormalities.

1.3.4 Dosing Regimen and Administration

The studied dosing regimen ranged from 0.5 to 4.5 mg/kg/day, with a maximum dose of 300 mg daily.

1.3.5 Drug-Drug Interactions.

No new information was submitted.

1.3.6 Special Populations

The study was limited to pediatrics.

2 Introduction and Background.

Currently, Irbesartan, an angiotensin II receptor blocker, is approved for the treatment of hypertension in adults as a once-daily dose. (b) (4) Irbesartan is also approved for the treatment of nephropathy associated with Type-2 adult diabetic patients.

2.1 Product Information.

2.2 Currently Available Treatment for Indications:

I do not know of any angiotensin receptor blockers approved for pediatric hypertension.

2.3 Availability of Proposed Active Ingredient in the United States.

Irbesartan is currently approved as Avapro® and marketed by Bristol-Myers Squibb.

2.4 Important Issues With Pharmacologically Related Products.

The major pertinent issue to the pediatric population is the concern related to the use of Angiotensin II blockers during the third trimester of pregnancy and the resultant consequence for the fetus of death and fetal deformation/malformations. A black-box warning is currently included on all Angiotensin II blocker labeling on the use of angiotensin receptor blockers during the third trimester of pregnancy.

2.5 Presubmission Regulatory Activity.

2.6 Other Relevant Background Information

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable).

The chemist did not note any deficiencies to be transmitted to the sponsor in the 74-day letter. No completed review is yet available. An additional dose strength (18.75 mg) was planned. The usefulness of this dose strength in the absence of a pediatric indication is unclear.

3.2 Animal Pharmacology/Toxicology

The pharmacologist noted no deficiencies in the 74-day review letter.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The sources for review included the electronic submission dated July 30, 2004 and an amendment dated 18 November 2004. The contents of these submissions contained the results of the single clinical study entitled "Study of Blood Pressure Reduction with Irbesartan in Children and Adolescents". The study as well as the submitted line listings and case report forms were reviewed.

A safety study entitled "Experience with Irbesartan Use in Children 16 years of age and Younger: A Descriptive Study in Two Medical Claims database" was also reviewed but its results add little to the overall safety conclusions.

4.2 Tables of Clinical Studies

Only a single study was supplied.

4.3 Review Strategy

The conclusion derived by this reviewer was largely based on the sponsor's analysis. This reviewer confirmed that the analyses, as performed by the sponsor, were pre-specified in the original protocol (dated 11 June 2002 and submitted to IND (b) (4)) and the subsequent amendments. The case report forms for those that discontinued or had serious adverse events were reviewed. The tabular listing for adverse events and laboratory values of concern were reviewed.

4.4 Data Quality and Integrity.

A DSI audit has been requested for the two sites in Smolensk, Russian federation. This inspection has not yet been performed.

The sponsor submitted in their amendment of 18 November 2004, additional laboratory data and follow-up laboratory data.

4.5 Compliance with Good Clinical Practices

From the information available, the study was carried out under Good Clinical Practice. The review assumes that no systemic deficiencies in those sites will turn up.

4.6 Financial Disclosures

The sponsor submits form 3454 asserting that the sponsor entered into no financial arrangement with investigators.

5 Clinical Pharmacology

5.1 Pharmacokinetics

The only pharmacokinetic study which was submitted enrolled a single patient before the study was discontinued. No specific information pharmacokinetic for this population was submitted with the current application. (b) (4)

An additional dose strength 18.75 mg, appropriate for pediatric use was included in this submission. The sponsor performed a study establishing the bioequivalence of this dose strength, which was used in the clinical study (b) (4)

5.2 Pharmacodynamics

The only pharmacodynamic information is the blood pressure effect during the pivotal clinical study.

5.3 Exposure-Response Relationships

Not applicable.

6 Integrated Review of Efficacy

6.1 Indication

(b) (4)

6.1.1 Methods

The single study planned to demonstrate efficacy by demonstrating a positive effect on the relationship between dose and blood pressure. Since there was no placebo group a non-significant slope could reflect one of two possibilities. The first possibility is that the drug is inactive in this population. The second possibility is that the dose selection only captured the flattened portion of the dose-response curve. To differentiate between the two possibilities, the protocol allowed for a placebo-controlled withdrawal period. The anticipation is that if the dose range was poorly chosen, the difference between those randomized to ongoing therapy compared to those who were withdrawn to placebo would be statistically different. A caveat, however, is that this reviewer would have expected the magnitude of difference between the placebo-withdrawn and maintained on-therapy to be quite large.

6.1.2 General Discussion of Endpoints

The end point was a positive slope of the dose response in the dose range of 0.5 to 4.5 mg/kg/day for sitting trough systolic blood pressure. If the results were not significant, the result of the placebo-withdrawal period was to be used to demonstrate that removal of Irbesartan by withdrawing to placebo induces increases in blood pressure.

6.1.3 Study Design

The one clinical study was a three week dose-ranging study followed by a two-week randomized placebo-withdrawal phase. The study also contained a subsequent 6-month open-label extension study.

6.1.4 Efficacy Findings

There was a non-significant slope for trough sitting systolic blood pressure, the primary metric of the study. Although there was a significant difference comparing those remaining on treatment compared to those randomized to placebo, the effect size was small (-2.3 mm Hg). Since this withdrawal portion of the study was to differentiate the situation where the doses chosen reflect the flat portion of the dose response curve, the small effect appears unlikely to be a true drug effect.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

There is insufficient information to conclude that Irbesartan at a dose of 0.5 to 4.5 mg/kg/day (maximum dose 300 mg), as a once daily regimen, is effective in pediatric patients who are hypertensive or who are borderline hypertensive with other confounding factors (such as diabetes).

7 Integrated Review of Safety

7.1 Methods and Findings

Safety for Irbesartan in a pediatric population was derived mostly from the pivotal clinical study and its long-term extension. Safety as derived from the two "use" databases did not substantially to the safety conclusions.

7.1.1 Deaths

There were no deaths.

7.1.2 Other Serious Adverse Events

There were 8 adverse events leading to discontinuation during periods B and C of this study. Most of these events likely reflect a blood-pressure of Irbesartan and include hypotension, syncope, headache and dizziness. There was one case of E. multiforme potentially could be related to the use of Irbesartan. A second adverse event of diabetic ketoacidosis occurred in a patient with Type-2 diabetes.

7.1.3 Dropouts and Other Significant Adverse Events

There were 8 dropouts for adverse events during period B and C of the study. One dropout was for increased for increased bilirubin. The other dropouts were related to hypotension, or headache.

7.1.3.1 Overall profile of dropouts

See above.

7.1.3.2 Adverse events associated with dropouts

See above.

7.1.3.3 Other significant adverse events

See above.

7.1.4 Other Search Strategies

A Pubmed search of Irbesartan AND safety (limited to age 0-18) did not reveal any unusual adverse events.

7.1.5 Common Adverse Events.

The most common adverse events are events frequent in a pediatric population including infections and infestations. Headaches were also frequently documented.

7.1.5.1 Eliciting adverse events data in the development program.

Adverse events were either spontaneously expressed by the subject or in response to the investigator's questioning.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Not applicable.

7.1.5.3 Incidence of common adverse events

See above.

7.1.5.4 Common adverse event tables.

The most common adverse events were infections and infestations and headache.

7.1.5.5 Identifying common and drug-related adverse events

The most common adverse event leading to discontinuation was hypotension.

7.1.5.6 Additional analyses and explorations

I've asked the sponsor for a complete line listing of laboratory data, or at least a listing of patients with missing values and those who had an abnormal value (to be defined by the index laboratory normals). These data were submitted in an amendment of 18 November 2004 and are included within this review.

7.1.6 Less Common Adverse Events

7.1.7 Laboratory Findings

See above.

7.1.7.1 Overview of laboratory testing in the development program.

The laboratory testing was apparently performed by a central facility. The resultant values were transmitted to the investigators. There were no laboratory values appended to the CRFs.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

Group means for laboratory values were only slightly changed. The dose-response effect in alkaline phosphatase indicates a drop in the value but inversely related to dose. Creatinine kinase was increased in all three dose groups but did not appear to decrease with re-randomization to placebo. The majority of the laboratory abnormalities of clinical significance which were documented during the double-blind, placebo-withdrawal or open label period either were subsequently shown to normalize, or per sponsor did not appear to be associated with adverse events.

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations.

This reviewer asked the sponsor for follow-up data on those patients who had abnormalities at the end of the study. This data was received on 18 November 2004 and the information was included in this review.

7.1.7.5 Special assessments

7.1.8 Vital Signs

Vital signs were collected as the primary metric of the study.

7.1.8.1 Overview of vital signs testing in the development program

This is the primary endpoint of the study.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons.

Only a single study for efficacy was submitted.

7.1.8.3 Standard analyses and explorations of vital signs data.

Not applicable.

7.1.8.3.1 Analyses focused on measures of central tendencies

Not applicable.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Not applicable.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities.

Several of the dropouts were for hypotension or other manifestations possibly related to vasodilatation.

7.1.8.4 Additional analyses and explorations.

None.

7.1.9 Electrocardiograms (ECGs)

None performed.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results.

The drug is currently approved for adults. No cautions related to ECGs are in the current labeling.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons.

Not applicable.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable.

7.1.9.4 Additional analyses and explorations.

None.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity.

No new data submitted.

7.1.12 Special Safety Studies

None requested.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

None known.

7.1.14 Human Reproduction and Pregnancy Data

Currently the package insert contains a black-box warning on the use during the third trimester of pregnancy.

7.1.15 Assessment of Effect on Growth

Not assessed.

7.1.16 Overdose Experience

None noted in current label.

7.1.17 Postmarketing Experience

One congenital abnormality was noted on the most recent safety update. Current labeling contains a block-box warning on the use of Irbesartan during the third trimester of pregnancy.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety.

The primary safety data was derived from the pivotal clinical study as well as a 6-month open-label extension. The mean duration of exposure was 190 days for any dose of Irbesartan.

7.2.1.1 Study type and design/patient enumeration

Not applicable.

7.2.1.2 Demographics:

The demographics of those enrolled in the single dose-ranging study are shown below. Those enrolled were between the ages of 6-16 years with approximately 50% < Tanner 3 stage. Approximately 10% of those enrolled were black.

Table 1 Demographic characteristics among those in study CV131-1154

	Period B: Irbesartan dose			Period C: Randomized withdrawal	
	0.5/0.5 mg/kg (N=108)	0.5/1.5 mg/kg (N= 107)	1.5/4.5 mg/kg (N= 103)	All Irbesartan (N= 150)	All Placebo (N= 148)
Age (years) mean ± SD	12.3 ± 2.8	12.5 ± 2.9	12.6 ± 2.8	12.5 ± 3	12.4 ± 3
6-12 years (N=; %)	52 (48%)	48 (45%)	46 (45%)	68 (46%)	69 (47%)
13-16 years (N=; %)	56 (52%)	59 (55%)	57 (55%)	82 (55%)	79 (53%)
Tanner scale					
6 years to < Tanner 3	61 (57%)	54 (51%)	44 (43%)	74 (49%)	73 (51%)
> Tanner 3 to < 17 years	47 (44%)	53 (50%)	59 (57%)	76 (51%)	73 (49%)
Gender male (N= ; %)	74 (69%)	71 (66%)	69 (67%)	104 (69%)	96 (65%)
Race: white/black/ other (% black)	94/9/5 (8%)	92/11/4 (10%)	89/12/2 (12%)	133/14/3 (9%)	125/17/6 (11%)
Weight (Kg) mean ± SD	61 ± 24	66 ± 25	67 ± 28	65.3 ± 26	65.5 ± 26
HBP/high normal/ normal	82 (76%)/22 (20%)/4(4%)	84(79%)/19 (18%)/4 (4%)	88(85 %) /14(14%)/1(1%)	118 (79%)/27 (18%)/5 (3%)	124 (84%)/ 23 (16%)/1 (1%)
Region					
North America	27(25%)	29(27%)	27 (26%)	37 (25%)	42 (28%)
Europe (includes Eastern Europe)	81 (75%)	78 (73%)	76 (74%)	113 (75%)	106 (72%)
Vital signs (mean ± SD)					
SiSBP (mm Hg)	133.9 ± 10	134.1 ± 10	135.0 ±11	135 ± 10	135 ± 11
SiDBP (mm Hg)	71.9 ± 9	70.7 ± 9	71.4 ± 8	70.6 ± 9	71.6 ± 9
Se HR (BPM)	89.2 ± 14	88.9 ± 14	89.2 ± 13	88.7 ± 14	89.6 ± 13
Previous hypertensive therapy	24.1%	25.2 %	24.3%		
Baseline genitourinary disease	22%	17%	13%		

7.2.1.3 Extent of exposure (dose/duration).

The mean dose of 331 mg of Irbesartan; the mean duration was 190 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.2.1 Other studies.

The "use" study was an uncontrolled database consisting of information on 21 patients. This database adds little to the controlled trial experience.

7.2.2.2 Postmarketing experience

There is no information, not included in the current labeling that is derived from the new database.

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

There is adequate safety experience in children > 6 years.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

7.2.5 Adequacy of Routine Clinical Testing

Not applicable.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new information was submitted.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study.

Given the exposure in adults, the safety exposure, with the exception on information on growth and development is acceptable.

7.2.8 Assessment of Quality and Completeness of Data

In general, the data is complete. Laboratory values were assessed by a central lab. The tabulated values were limited to those with "values of clinical significance". A full listing of the laboratory values, particularly with evidence that abnormal values have normalized was submitted in the amendment dated 18 November 2004.

7.2.9 Additional Submissions, Including Safety Update

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.4.1.1 Pooled data vs. individual study data

Not applicable.

7.4.1.2 Combining data

None.

7.4.2 Explorations for Predictive Factors

Not done.

7.4.2.1 Explorations for dose dependency for adverse findings.

Not done.

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable.

7.4.2.3 Explorations for drug-demographic interactions

Not applicable

7.4.2.4 Explorations for drug-disease interactions

Not applicable.

7.4.2.5 Explorations for drug-drug interactions

Not applicable.

7.4.3 Causality Determination

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

(b) (4)

8.2 Drug-Drug Interactions

8.3 Special Populations

8.4 Pediatrics

This submission was limited to pediatric patients aged 6-16 years.

8.5 Advisory Committee Meeting

None

8.6 Literature Review

See above

8.7 Postmarketing Risk Management Plan

None needed

8.8 Other Relevant Materials

Not applicable

9 Overall Assessment

9.1 Conclusions:

(b) (4).

9.2 Recommendation on Regulatory Action

The sponsor was granted pediatric exclusivity for this study. Pending DSI review of the clinical study and review of the laboratory data, that exclusivity appears warranted. (b) (4)

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

None

9.4 (b) (4)

(b) (4)

9.5 Comments to Applicant

None.

10 Appendices

10.1 Review of Individual Study Reports

Study # CV131-154

Title of Study: Study of Blood Pressure Reduction with Irbesartan in Children and Adolescents

Dates:

Original protocol: 11 June 2002
Amendment # 1: 24 March 2003

This amendment increased the size of the study by 81 subjects in order to rebalance the number of pre-adolescent and adolescent patients as indicated in the Written Request. There were corresponding changes in the statistical aspects of the study.

Amendment # 2: 30 May 2003

This review attempts to clarify the fraction of African-American to be enrolled.

First Patients Enrolled June, 2002
Last patient enrolled double-blind phase: October, 2003:

Protocol

Inclusion criteria:

Males or females with hypertension (Sitting DBP or SBP $\geq 95^{th}$ percentile adjusted for age, gender and height) should be between 6-16 years old (inclusive). Patients whose blood pressure is $> 90^{th}$ percentile are eligible if they have diabetes, have a strong positive family history of hypertension or who the investigator believes treatment is in the best interest of the patient. Approximately 50% of the population is to be > 6-12 years; and 50% between 12-16 years. Females, who have experienced menarche and are potentially fertile, need a negative pregnancy test for enrollment. Appropriate consent and assent forms are to be signed.

Exclusion criteria:

Patients are excluded for the following reasons:

- Hypersensitivity.
- Malignant hypertension.
- Previous inadequate response to AII blockers.
- Other metabolic (aside fro diabetes), cardiac, hepatic, neurologic or pulmonary disorder (excluding bronchospastic disease treated with bronchodilator).
- History of angioedema, collagen vascular disease or multiple drug allergies.
- Gilbert's disease.
- Inability to tolerate oral medication or a history of malabsorption.
- Obesity confounding accurate BP measurements.
- Need for prohibited medications.
- Bilateral renal artery stenosis, or single kidney.
- Coarctation of the aorta.
- Laboratory abnormalities.

Primary hypothesis and pivotal measurements:

- The primary end point is the slope of the sitting systolic blood pressure versus dose at the end of the 3-week double-blind period.

Secondary objectives:

- The main secondary objective, should the dose response slope not be different from zero, is sitting systolic BP at withdrawal comparing Irbesartan to placebo.
- Sitting DBP at the end of period B.
- Change in sitting DBP during the randomized withdrawal period (compare period B to period C).
- Categorical analysis of subjects whose seated DBP and SBP is < 90 percentile.
- Safety and tolerability.

Dosing:

During the double-blind portion of the study (period B), subjects are assigned to low, medium or high dose Irbesartan. The initial dose for those on the low or mid dose is approximately (based on the available dose strengths) 0.5 mg/kg; for those in the high dose the initial dose is to be approximately 1.5 mg/kg. At the end of week 1, the dose will be up-titrated to 1.5 mg/kg in the mid dose and 4.5 mg/kg in the high dose. The doses below reflect the doses after week 1 and correspond to approximately 0.5, 1.5 and 4.5 mg/kg.

Table 2: Dosing for study CV131-154

Body weight	Low	Medium	High
≥ 20 kg to < 30 kg	18.75	37.5	112.5
≥ 30 kg to < 40 kg	18.75	56.25	150
≥ 40 kg to < 50 kg	18.75	75	150
≥ 50 kg to < 60 kg	37.5	75	225
≥ 60 kg	37.5	112.5	300 (maximum dose)

For period C, patients are either randomized to the Irbesartan dose of period B or placebo.

For period D, all subjects will be started at 0.5 mg/kg dose and uptitrated to 1.5 mg/kg and 4.5 mg/kg. The timing of any dose increase is after 24 hours (± 3 hours).

Procedures:

The Study consists of 4 periods:

- Period A: Washout period from previous medication.
- Period B: Double-blind dose ranging study.
- Period C: Placebo controlled 2-week withdrawal study.
- Period D: Long Term safety.

The specific procedures scheduled during each period of the study are shown below. The first period, a washout period from previous medications is also the period when the subjects' eligibility is assessed. The duration of this period is for up to 2 weeks. The second period (Period B) is a dose ranging study. Subjects are randomized to low, medium or high dose. The first week is a titration step for those allocated to the mid or high dose of Irbesartan.

Blood pressure at trough (sitting systolic blood pressure) is the primary measurement of the study. After the dose-ranging study, patients enter the double-blinded, placebo-controlled withdrawal study (period C) and either continued treatment at the same dose or corresponding placebo. During period D subjects are re-titrated on Irbesartan and treated for up to an additional 26 weeks. The dose was increased in order to decrease BP measurements to < 90 percentile for both SiSBP and SiDBP. The specific procedures during each period of the study are shown below. Blood pressures were measured by DINAMAP.

Procedures for Periods A (washout) and period B (double-bind dose ranging):

Table 3: Specific procedures for study CV131-154 for periods A-D

	Lead-in (Period A)		Double-blind (Period B- numbers refer to weeks			
		EOW 1		EOW 1	EOW 2	EOW 3
Visit → Procedure↓	Screen/Enroll	AR	B1	B8	B15	B22
Consent/Assent, med hx; PE, tanner stage	X					
Vital signs	X	X	X	X	X	X
Adverse events		X	X	X	X	X
Concomitant meds	X	X	X	X	X	X
Labs	X				X	X
Enrollment	X					
Randomize		X	X			
Titration				X		
In clinic BP/HF monitor			X	X		
Medication dispensing		X	X	X		
				X	X	X

Period C-Randomized withdrawal period – procedures:

	DB Withdrawal (Period C- numbers refers to day)		
Visit→ Procedure↓	C1	C8	C15
Full physical exam	X		
BP/HR; adverse events; concomitant meds	X	X	X
Standard safety laboratory tests	X		X
Pregnancy test	X		X
Re randomize	X		
Medication dispensing	X		
Medication count		X	X

Period D: (open-label extension)-procedures:

		Open-Label Extension (Period D-number refers to week #)								
Visit → Procedure↓	Enroll	D1	D2	D3	D4	D10	D14	D18	D22	D26
Consent/assent, enrollment	X									
BP/HR	X	X	X	X	X	X	X	X	X	X
Labs	X		X							
Pregnancy test	X					X				X
Concomitant meds, adverse events	X	X	X	X	X	X	X	X	X	X
Medication dispensing		X	X	X	X	X	X	X	X	X
Medication count	X	X	X	X	X	X	X	X	X	

Footnotes

- Visits for Period A ,B and C are ± 3 days;
- The following medications are allowed, if doses were stable for >1 month: oral contraceptives, methylphenidate, and bronchodilator therapy.
- Oral, i.v or subcutaneous bronchodilators should not be used for 24 hours prior to measurements; Nebulizers, metered dose bronchodilator or nasal bronchodilator within 6 hours.
- For period A- patients without previous medications can be advanced to period B
- Enrollment into period B should be the same day as the last visit as the end of period A but may occur within 3 days. Visit C1 similarly should occur on the same day as the last visit in period B but may occur within 3 days. Period D1ahould occur on the same day as visit C15, but within 7 days of that visit is acceptable.
- Those not tolerating up-titration are discontinued and may be eligible to enroll in period D
- The results of the pregnancy test must be known prior to enrollment.
- If patients are on maximal doses visits D3 and D4 are not necessary.

Prohibited medications:

The following are prohibited medications or classes of medications: Indomethacin, cytotoxic drugs, chronic oral steroids, anabolic steroids, bile-acid binding resins, antipsychotic drugs, antidepressive drugs, MAO inhibitors, antihypertensives or other drugs known to have vascular effects, digitalis, decongestants and sympathomimetic drugs (within 24 hours).

Blinding- Randomization:

Assignment of an identification number occurs at the lead –in period. Once eligible, the subject is to receive via a central telephone randomization number, the subject's code and treatment. When entering period C, the investigator is to call the central phone number for subsequent placebo or continue therapy randomization.

Statistical Analysis:

The primary efficacy outcome for this study is trough SiSBP at the end of week 3 of period B. The first major secondary outcome is the change from the end of period B to the end of period C comparing placebo to ongoing treatment patients for SiSBP. The primary analysis is based on all randomized patients. Patients who discontinue early will be censored. Should there be > 10% of the subjects who discontinue in any group, an LOCF analysis will be used. The proposed analysis is the change in baseline by ANCOVA. The linear trend test is to have integer coefficients 0f -5, -2 and + 7 for the three dose levels. The covariate model will contain terms for baseline and treatment.

If the results of the dose ranging did not demonstrate a linear trend, then the next analysis is to examine the effect of drug comparing the effect during the withdrawal period of all Irbesartan to all placebo patients. The sponsor plans to take no penalty for the need for this secondary analysis.

To determine the sample size, the sponsor assumed a difference of 6.0 mm Hg with a SD of 12 mm Hg. These assumptions would allow with a power of 80% with a two-sided alpha of 0.05 if 63 subjects per dose group (n=189) were studied. The addition of an additional 81 patients should have increased the power of this study to determine a dose-effect on SiSBP.

Secondary efficacy outcomes include:

- Change from baseline in SiDBP during the dose-ranging portion of the study (Phase B).
- Change in pooled Irbesartan versus placebo for SiDBP from the end of Phase B to Phase C.
- The % of subjects achieving a SBP and DBP < 90^{th} percentile.

Results

Investigators and sites:

Table 4: List of investigators, sites and number enrolled.

Site #↓	Investigator and Site	# enrolled
001	Hazan, Lydie, MD; Sante LA; Los Angeles, CA	16
002	Batisky, Donald, MD; Pediatric Clinical Trials International; Colombus, OH	4
003	Cottrill, Carol, MD; Pediatric Cardiology, PSC; Lexington, KY	8
004	Cunningham, Robert, MD; Cleveland Clinic Foundation; Cleveland, OH	No data
005	Dresner, Ian, MD; Children's Hospital Medical Center of Akron; Akron, OH	No data
006	Gaona Sr., Raul, MD; Pro-research Group LLC; San Antonio, TX	5
007	Duffy Douglas, MD; Marshfield Clinic; Marshfield, WI	2
008	Havenold , Carol, MD; Medical College of Georgia; Augusta, GA	3
009	Harrison, Boyde J; MD; Winston Physician Services, LLC; Haleyville, AL	No data
011	Jenkins, Randall, MD; Northwest Pediatric Kidney Specialists, LLC; Portland, OR	13
013	Boyle, Gerard, MD; Children's Hospital of Pittsburgh; Pittsburgh, PA	1
015	Miller, Kenneth, MD; Nephrology & Hypertension; Park Ridge, IL	4
016	Musgrave, James, MD Kapiolani Medical Center for Women and Children; Honolulu, HI	1
017	Neufeld, Naomi, MD; Neufield Medical Group, Inc.; Los Angeles, CA	7
019	Paredes, Ana, MD; Miami Children's Hospital Pediatric Nephrology; Miami, Fl	4
020	Parikh, Sanjay, MD; Children's Heart Center At St. Vincent; Indianapolis, IN	No data
021	Portman, Ronald, MD; University of Texas Health Science Center; Houston, TX	No data
022	Ramirez, Jorge, MD; Nemours Children's Clinic Orlando; Orlando, FL	3
024	Singer, Melville, MD; Children's Hospital of Orange County; Orange, CA	No data
026	Sher, Lawrence D, MD; Peninsula Research Assoc; Rolling Hills Estates, CA	No data
028	Fallon, Judith, MD; Neurosciences Inc; Bethesda, MD	3
029	Blumer, Jeffrey, MD, Ph.D; University Hospitals of Cleveland; Cleveland, OH	No data
031	Mubarak, Phillip, MD; Neem Research Group, Inc. Colombus, SC	No data
032	Schwartz, George, MD; Golosano's Children's Hospital at Strong Petdiatric Nephrology; Rochester; NY	3
033	Feldenberg, L. Richard, MD; Children's Hosp Central California; Madera, CA	1
034	Cohen, A Jay, MD, The Endocrine Clinic, P.C.; Memphis, TN	No data
038	Kornyei, Vilmos, Drkaposi Mor County Hospital; Kaposvar, Hungary	1
039	Szamosi, Tamas Dr., Semmelweis University Department of Pediatrics; Budapest, Hungary	10
040	Canessa Leonardo, MD; Children's Medical Center; Dayton, OH	No data
041	Shkolnikova, Maria A.; MD, Ph.D,; Moscow Institute of Pediatry & Children's Surgery; Moscow, Russian Federation	18
042	Makarov, Leonid, MD, Ph.D; Moscow Institute of Pediatry & Children's Surgery; Moscow, Russian Federation	12
044	Samsygina, Galina, A, MD, Ph.D; Russian State Medical University; Moscow, Russian Federation	No data
045	Kislyak, Oksana, Prof. Russian State Medical University; Moscow, Russian Federation	11
046	Shlyakhto, Evegny, M.D., Ph.D; St Petersburg Cardiology Research Institute, St. Petersburg, Russian Federation	11
047	Titkov, Yuri, Dr. Central Medico-Sanitary Departments; St. Petersburg, Russian Federation	12
048	Zotov, Dmitry, MD; Central Medico-Sanitary Departments, St. Petersburg, Russian Federation	19
049	Kozlova, Ludmilla, MD; Smolensk State Medical Academy; Smolensk Medical Academy; Russian Federation	26
050	Jarkova, Ludmilla, MD; Smolensk State Medical Academy; Smolensk Medical Academy; Russian Federation	42
051	Dukalska, Masria, MD, Ph.D; Publiczny Szpital Kliniczny, Nr6; Katowice, Poland	1
052	Stanczyk, Jerzy, Prof.; Instytut Pediatrii Akedemii Medycznej; Lodz, Poland	No data
053	Rimarchuk, Galina V, MD, Ph.D; Moscow Regional Clinical research Institute; Moscow, Russian Federation	3
054	Wroblewska-Kaluzewska, Maria; Klinika Kardiologii Wieku Dzieciecego; Warszawa, Poland	3

055	Sancewicz-Pach Krystyna, Prof.; Uniwersytecki Szpital Dzieciecy; Krakow, Poland	3
056	Bertrand, Helen, MD; Neem Research Group of Charleston, LLC; Charleston, SC	4
057	Cofie, Abelard Kpakpo, MD ; Neem Research Group of Charleston, LLC; Charleston, SC	No data
058	Dovgalevsky, Pavel, Prof;. Saratovsky Scientific Research Institute; Saratov, Russian Federation	14
059	Bogoslovskaya, Svetlana I, Dr. Saratov Association Korpu; Saratov, Russian Federation	20
060	Reshetko, Olga, Dr.; Saratovsky Scientific Research institute, Saratov, Russian Federation	17
061	Gibson, Gwendolyn, MD; The University of Oklahoma College of Medicine; Tulsa, OK	1
062	Zukrowska, Aleksandra, Dr.; Samodzielny Oubliczny Szpital; Gdansk, Poland	7
064	Melamud, Issac, MD; 1st Allergy and Clinical Research Center, Centennial, CO	5?
067	Finch, Ana, MD; Ponce School of Medicine Urb; Ponce, Puerto Rico	No data

The two largest sites were in the Russian Federation #049 and #050. These two sites accounted for approximately 17% of the total enrolled (58 patients.

Formulations and Lots:

The following formulations and corresponding Lots were used during this study

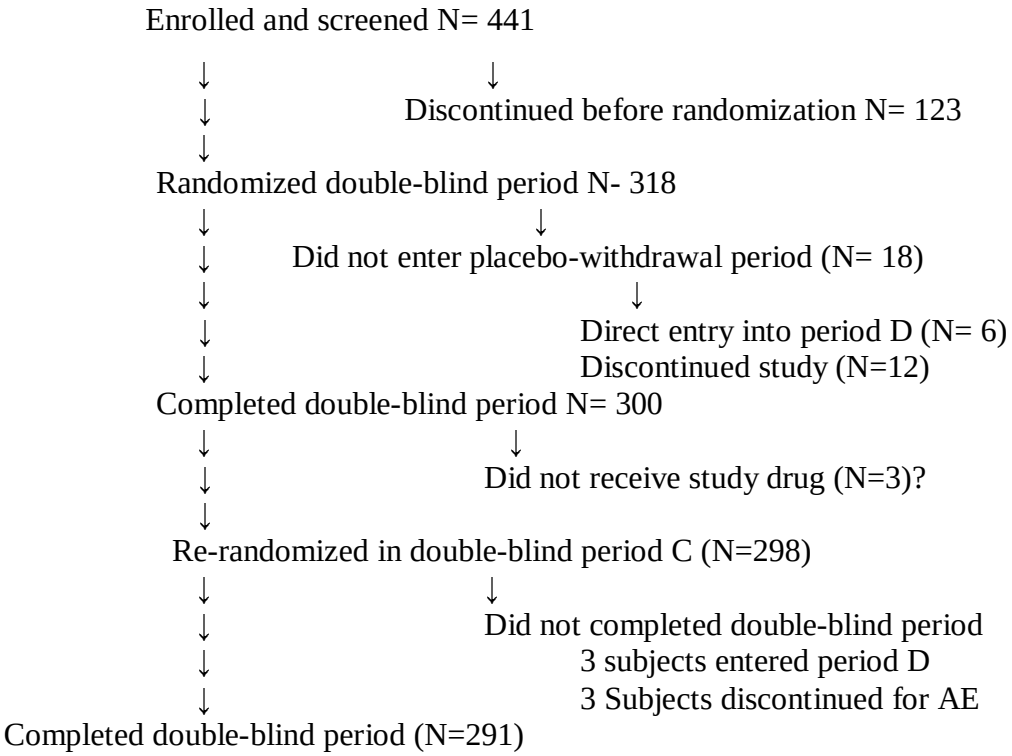
Table 5: Formulations and lot numbers.

Dose	10.8 x 5.8 mm; Product Code (Lot #)	13.6 mm x 7.3 mm; Product Code (Lot #)
18.75 mg	186295-A18X169; (2B59342)	
37.5 mg	186295-A37X170; (2B59596)	18629-A37X-168; (2D64021)
75 mg	186295-A075-104; (B5306/8MDM206)	18629-A075-164; (2C56882)
150 mg		18629-A150-105; (8MAE421 3A67597)
PBO	186295-A000X136; (B5304/8MDM200-75)	18629-A000-137; (8MAE420)

Patients Disposition:

The disposition of patients from screening and enrollment through the completion of the open-label portion of the study is shown below.

Figure 1: Patient flow through Study CV131-154



Protocol Violations:

The sponsor lists 24 protocol violations scattered among the clinical sites. No site had greater than 3 protocol violations. The majority of the violations were in the low dose group (0.5/0.5, n=14); the mid-dose group (0.5/1.5 and the high (1.5/4.5) dose group each had 5 subjects with protocol violations.

The nature of the violations is shown in the table below (derived from Appendix 7.38).

Table 6; List of protocol violations

Specific Violation	Low (0.5/0.5)	Mid (0.5/1.5)	High (1.5/4.5)
Time of measurement outside pre-specified times	4	2	2
Chemistry value outside range	4	0	2
Hematology value outside range	2	0	0
Qualifying measurement not within pre-specified values.	3	3	1
Hypersensitivity to ACE-I	1	0	0

Demographics:

The demographic characteristics of those enrolled into this study are shown in the following table. The groups generally appear to be evenly balanced both during Period B and

period C. There were, however, more "younger" patients in the low dose group than the mid and high dose group. Approximately ¾ of the patients were randomized from non-US sites

Table 7: Demographics (adapted from Sponsor's Table 8.3 A, 8.3C and 8.3 D) period B and Period C by dose.

Parameter	(Period B) Irbesartan Dose (initial/final)			Period C: Placebo Withdrawal	
	0.5/0.5 mg/kg (N=108)	0.5/1.5 mg/kg (N= 107)	1.5/4.5 mg/kg (N= 103)	All Irbesartan (N= 150)	All Placebo (N= 148)
Age (years) mean ± SD	12.3 ± 2.8	12.5 ± 2.9	12.6 ± 2.8	12.5 ± 3	12.4 ± 3
6-12 years (N=; %)	52 (48%)	48 (45%)	46 (45%)	68 (46%)	69 (47%)
13-16 years (N=; %)	56 (52%)	59 (55%)	57 (55%)	82 (55%)	79 (53%)
Tanner scale					
6 years to < Tanner 3	61 (57%)	54 (51%)	44 (43%)	74 (49%)	73 (51%)
> Tanner 3 to < 17 years	47 (44%)	53 (50%)	59 (57%)	76 (51%)	73 (49%)
Gender male (N= ; %)	74 (69%)	71 (66%)	69 (67%)	104 (69%)	96 (65%)
Race: white/ black/ other (% black)	94/9/5 (8%)	92/11/4 (10%)	89/12/2 (12%)	133/14/3 (9%)	125/17/6 (11%)
Weight (Kg) mean ± SD	61 ± 24	66 ± 25	67 ± 28	65.3 ± 26	65.5 ± 26
HBP/ high normal/ normal	82 (76%)/22 (20%)/4(4%)	84(79%)/19 (18%)/4 (4%)	88(85%) /14(14%)/1(1%)	118 (79%)/27 (18%)/5 (3%)	124 (84%)/ 23 (16%)/1 (1%)
Region					
North. America	27(25%)	29(27%)	27 (26%)	37 (25%)	42 (28%)
Europe (includes Eastern Europe)	81 (75%)	78 (73%)	76 (74%)	113 (75%)	106 (72%)
Vital signs (Mean ± SD)					
SiSBP (mm Hg)	133.9 ± 10	134.1 ± 10	135.0 ±11	135 ± 10	135 = 11
SiDBP (mm Hg)	71.9 ± 9	70.7 ± 9	71.4 ± 8	70.6 ± 9	71.6 ± 9
SiHR (BPM)	89.2 ± 14	88.9 ± 14	89.2 ± 13	88.7 ± 14	89.6 ± 13
Previous hypertensive therapy	24.1%	25.2 %	24.3%		
Baseline genitourinary disease	22%	17%	13%		

Blood pressure and heart rate period B (Dose –ranging)

The baseline blood pressure and heart rate as well as the change from blood pressure during the dose ranging portion of the study is shown in the table below. There was a large decrease from baseline in systolic blood pressure but no dose response relationship was present. There was a small decrease in diastolic blood pressure but the nominal p-value though significant nominally is uninterpretable.

Table 8: The effect on BP at the end of period B (adapted from sponsor's Table 10.1.1 and 10.1.3)

Parameter	Irbesartan Dose (initial/final) in mg/Day		
	0.5/0.5 (N=101)	05/1.5 (N=107)	1.5/4.5 (N=100).
Sitting systolic blood pressure			
Baseline mean ± SD	134.3 ± 10	134.5 ± 9.9	135.1± 11.2
On-therapy mean ± SD	122.8 ± 12	125.3 ± 11.7	121.8 ± 13
Adjusted mean mean ± SD	-11.7 ± 1.1	-9.3 ± 1.1	-13.2 ± 11.0
p-value= 0.118			
Sitting Diastolic Blood Pressure			
Baseline mean ± SD	71.4 ± 9	70.9 ± 9	71.1± 8.4
On-therapy mean ± SD	67.4 ± 8	67.8 ± 8	65.5 ± 8
Adjusted mean ± SD	-3.8 ± 1	-3.2 ± 1	-5.6 ± 1
P=0.024			
Responder rate end of period B	56/101 (0.55)	41/101 (0.41)	51/100 (0.51)
Sitting heart rate			
Baseline mean ± SD	88.9 ± 14	89.2 ± 14	89.3± 13
On-therapy mean ± SD	85.3 ± 14	87.6 ± 13	87.8 ± 14
Adjusted mean ± SD	-3.6 ± 12	-1.6 ± 12.8	-1.5 ± 13

The primary end-point that is, the slope of sitting systolic blood pressure, as the dependent variable with dose as the independent variable is non-significant. Of note is the large decrease in on-therapy blood pressures among each of the three doses compared to baseline. Assuming the low dose group can be treated as a pseudo-placebo, the magnitude of the drug effect at high dose compared to low dose is approximately 1.5 mm Hg. With respect to seated diastolic blood pressure, the p-value is nominally significant. Since, however, the primary endpoint is not significant, the interpretation of the diastolic effect is unclear. Of note, assuming the low dose is considered a "pseudo-placebo" the magnitude of effect is approximately 1.8 mm Hg for change in seated DBP. An additional secondary end-point, i.e., responder rate, did not indicate benefit base on dose (defined as both a seated systolic and diastolic blood pressure of < 90^{th} percentile)(see above).

Blood pressure and heart rate Part C (Randomized placebo-withdrawal):

During this portion of the study, subjects were, in a blinded manner, either maintained on their original dose or randomized to placebo. Pooled placebo versus on-therapy measurements after the 2-week withdrawal period for seated systolic blood pressure was the primary metric of interest. The results are tabulated below.

Table 9: Vital signs during the placebo-withdrawal phase: period C

	Any Placebo	Any Irbesartan	
SiSBP			
N=	141	145	
End of period B mean ± SD	122.7 ± 12	124.0 ± 12.5	
Change mean ±SE	2.4 ± 0.9	0.1 ± 0.8	P= 0.05
SiDBP			
N=	141	145	
End of period B mean ± SD	67.3 ± 6.9	66.3 ± 8.2	
Change mean ±SE	2.0 ± 0.5	-0.3 ± 0.5	P=0.00143
Seated heart rate			
N=	141	145	
End of period B mean ± SD	88.2 ± 13.4	87.3 ± 13.0	
Change mean ±SD	-1.9 ± 12.2	-1.5 ± 12.2	

There did not appear to be a time course to the washout when comparing the week 1 to week 2 data SiSBP during the randomized withdrawal phase (data not included in this review).

Period D (Long term data)

Of those enrolled into the study 294 subjects entered the open-label uncontrolled long term portion of the study. The patient disposition of the patients is shown below;

Table 10: Patient outcome period D

Number of subjects enrolled	294
Number who discontinue and reason:	11
Adverse event	1
Lost to follow-up	2
Non-compliance	4
Withdrew consent	4

Dose during period D.

During this period of the study patients were started at the low dose 0.5 mg/kg and increased as needed to attain a coal blood pressure of SiSBP and SiDBP < 90th percentile. The mean exposure during this period of the study was 177.6 days. The mean maximum dose was 307 mg (range 8.5 to 887 mg).

Pharmacokinetics:

No pharmacokinetics analyses were collected.

Safety:

Deaths, Dropouts and Discontinuations:

There were no deaths in the study.

Discontinuations from the various periods of the study (B and C) are shown below.

Table 11: Discontinuation from period B and C study CV131-154

Pt ID	Demographics	Dose	Adverse event
CV131154 1-10	7 y/o F/ other	1.5	E. Multiforme
CV131154 41-6	15 y/o /M/W	0.5	Dizziness
CV131154 41-11	15 y/o W/M	4.5	Hypotension
CV131154 41-16	14 y/o W/F	0.5	Hypotension
CV131154 42-4	15 y/o W/F	1.5	Hypotension
CV131154 48-9	16 y/o W/M	1.5	Dizziness
CV131154 50-21	15 y/o W/M	1.5	Increased bilirubin
CV131154 62-5	8 y/o W/M	0.5	Headache

During period B there were eight discontinuations for adverse events, three in the low dose regimen, four in the mid-dose regimen and one in the high dose regimen.

Overall Adverse Events

Overall adverse events by organ class for period B is shown below.

Table 12: Adverse events period B (dose response study)

System	Irbesartan regimen		
	0.5/0.5	0.5/1.5	1.5/4.5
Total subjects with adverse events	34 (32%)	39 (36%)	36 (35%)
Cardiac disorders	0	2(2%)	0
Ear and Labyrinth disorders	1 (1%)	0	0
Eye disorders	3 (3%)	3 (3%)	2 (2 %)
Gastrointestinal disorders	3 (3%)	3 (3%)	2 (2%)
General Disorders and Administration site conditions	3 (3%)	2 (2%)	0
Infections and infestations	12 (11%)	14 (13%)	7 (7%)
Injury, poisoning and procedural complications	0	1 (1%)	2 (2%)
Investigations	1 (1%)	0	1(1%)
Musculoskeletal and connective tissue disorders	1 (1%)	0	2 (2%)
Nervous system disorders	18 (17%)	16 (15%)	17 (16%)
Respiratory, thoracic and mediastinal disorders	6 (6%)	5 (5%)	8 (8%)
Skin and subcutaneous tissue disorders	0	2 (2%)	1 (1%)
Vascular disorders	2 (2%)	3 (3%)	2 (2%)

Table 13: Adverse events during period C (randomized withdrawal 2 weeks):

System	Any Placebo (n=146)	Any Irbesartan (N=149)
Total subjects with adverse events	48 (33%)	40 (27%)
Blood and lymphatic system disorders	2 (1%)	2 (1%)
Cardiac disorders	1 (1%)	0
Ear and labyrinth disorders	0	0
Eye disorders	1 (1%)	0
Gastrointestinal disorders	1 (1%)	3 (2%)
General disorders and administration site conditions	1 (1%)	0
Infections and infestations	11 (8%)	13 (9%)
Injury, poisoning and procedural complications	1 (1%)	0
Investigations	6 (4%)	5 (3%)
Metabolism and nutrition disorders	0	2 (1%)
Musculoskeletal and connective tissue disorders	2 (1%)	1 (1%)
Nervous system disorders	18 (12%)	18 (12%)
Renal and urinary disorders	0	1 (1%)
Respiratory, thoracic and mediastinal disorders	12 (8%)	5 (3%)
Skin and subcutaneous tissue disorders	3 (2%)	1 (1%)
Vascular disorders	0	1 (1%)

During this period, the most common adverse events were Headache, cough, upper respiratory tract infection, and pharyngitis. There were 3 patients with hyperkalemia all in the Irbesartan patients.

Table 14: Adverse events during period D (Open-label portion 26 weeks):

System	N= 294
Total subjects with adverse events	183 (62%)
Blood and lymphatic system disorders	3 (1%)
Cardiac disorders	4 (1%)
Ear and labyrinth disorders	3 (1%)
Eye disorders	4 (1%)
Gastrointestinal disorders	11 (4%)
General disorders and administration site conditions	14 (5%)
Hepatobilliary disorders	2 (1%)
Infections and infestations	102 (35%)
Injury, poisoning and procedural complications	4 (1%)
Investigations	25 (9%)
Metabolism and nutrition disorders	2 (1%)
Musculoskeletal and connective tissue disorders	7 (2%)
Nervous system disorders	89 (30%)
Renal and urinary disorders	0
Psychiatric disorders	5 (2%)
Respiratory, thoracic and mediastinal disorders	45 (15%)
Skin and subcutaneous tissue disorders	9 (3%)
Vascular disorders	9 (3%)

During this period the most common adverse events were headache nasopharyngitis, upper respiratory tract infection, cough, rhinitis, dizziness, pharyngitis, epistaxis and viral infection. None of these events are unusual in this population.

Serious Adverse events:

Serious adverse events during each of the period are shown below.

Table 15: Serious adverse events periods B-D

Identification	Demographics	Dose	Specific
Period B (Dose Range)			
CV 131154-1-10	7 y/o F	Mid	Erythema multiforme
Period C (placebo withdrawal)			
CV131154-1-19	16 y/o M	High	Diabetic ketoacidosis
CV131154-63-7	10 y/o F	High	Syncope
Period D (Open label phase)			
CV131154-19-2	8 y/o M	0.5	Stomatitis
			Recurrent stomatitis
CV131154-39-8	6 y/o F	1.5	Bronchitis
CV131154-62-6	7 y/o F	0.5	Gastritis

With the exception of the patient with E. Multiforme, none of the other adverse events suggest a drug-related effect.

Events listed as “severe” or “very severe” in intensity are shown below.

Table 16: Adverse events with intensity listed as "severe" or "very severe", periods B-D

Identification	Demographics	Dose at event	Day	Specifics
Period B				
CV1311154-3-5	8 y/o M/W	0.5	20	Sinusitis
CV113154-11-18	15 y/o M/B	1.5	19	Headache
CV113154-41-11	15 y/o M/W	4.5	16	Hypotension
CV113154-41-16	14 y/o F/W	0.5	21	Hypotension
CV113154-42-4	15 y/o F/W	1.5	8	Hypotension
Period C				
CV113154-3-9	13 y/o /M/B	PBO	24	Nasopharyngitis
CV113154-47-11	13 y/o M/W	1.5	22	Headache
CV113154-47-16	11 y/o F/ W	1.5	28	Dizziness, giddiness
Period D				
CV131154-3-3	11 y/o M/W	4.5	156	Headache
CV1311154-3-5	8 y/o M/W	0.5	103	Sinusitis
CV113154-3-7	14 y/o M/W	1.5	77	Fracture
CV113154-11-6	7 y/o M/W	4.5	73	Strep throat

			145	Pharyngitis
CV113154-15-3	14 y/o M/B	1.5	69	Dizziness
CV113154-42-11	14 y/o M/W	1.5	106	Ventricular extrasystoles
CV113154-47-3	14 y/o M/W	4.5	113	Acute respiratory disease
CV113154-47-4	15 y/o M/W	4.5	53	Headache
CV113154-47-9	15 y/0 M/W	1.5	49	Acute rhinopharyngitis
CV113154-47-16	11 y/o F/ W	1.5	200	Headache
CV113154-62-4	8 y/o M/ W	0.5	41	Viral infection
CV113154-62-6	7 y/o F/ W	0.5	170	Gastroenterocolitis and diarrhea

Labs:

During the dose-ranging (Period B) and placebo-withdrawal (period C) laboratory values were drawn at baseline and day 22 of period B and upon entry into period C and day 15 of that period (equivalent to day 37). The submitted data was limited to those values that the sponsor considered significant. Complete listings of laboratory values were not submitted. In reviewing the available case report forms, there did not appear to be any tabulation of laboratory values. For some abnormal measurements, normalized values at some more distant time were not available.

Group means changes suggest small increase in BUN with dose, and a small decrease in serum sodium with dose. The randomized withdrawal period does not, however, suggest any reversal upon placebo withdrawal.

Table 17 : Group Averages Labs period B and C-Change from baseline (mean ± SD)

	Irbesartan dose			All Irbesartan (N=123)	All Placebo (N=122)
	0.5 mg/kg/day (N=107)	1.5 mg/kg/day (N=107)	4.5 mg/kg/day (N=102)		
Albumin (g/dL)	-0.1 ± 0.3	-0.1 ± 0.3	-0.1 ± 0.3	-0.1 ± 0.3	-0.1 ± 0.3
Alkaline phosphatase (U/L)	-13 ± 63	-8 ± 38	-5 ± 44	-2 ± 47	-18 ± 59
Alanine aminotransferase (U/L)	0 ± 8	0.6 ± 11	0.5 ± 9	-2 ± 8	1 ± 12
Aspartate aminotransferase (U/L)	-0.3 ± 6	0.6 ± 10	-0.2± 6	-1 ± 6	-1 ± 5
Blood urea nitrogen (mg/dL)	-1 ± 3	1 ± 4	1 ± 3	0 ± 4	0 ± 3
Total cholesterol (mg/dL)	-7 ± 23	-8 ± 22	-4 ± 30	-3 ± 23	-6 ± 28
Creatinine kinase (U/L)	9 ± 121	12 ± 361	0 ± 110	30 ± 312	-10 ± 155
Creatinine (mg/dL)	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1
Serum glucose (mg/dL)	-1.8 ± 13	-1.4 ± 13	0.5 ± 17	-0.8 ± 15	-0.2 ± 29
Lactate dehydrogenase (U/L)	-3 ± 45	1 ± 44	-7 ± 45	-3 ± 40	-6 ± 33
Uric acid (mg/dL)	-0.2 ± 0.7	-0.2 ± 0.9	-0.2 ± 1.1	0 ± 0.9	0.1 ± 3
Sodium (mEq/L)	0 ± 2.5	-0.5 ± 2.4	-1.2 ± 3.6	-0.2 ± 2.1	0.1 ± 2.5
Potassium (mEq/L)	0 ± 0.4	0 ± 0.3	0 ± 0.4	0 ± 0.4	0 ± 0.4
Chloride (mEq/L)	0.4 ± 3.7	-0.6 ± 4	-0.5 ± 3	0 ± 3	-0.1 ± 2
Calcium (mg/dL)	-0.1 ± 0.7	-0.1 ± 0.6	-0.1 ± 0.6	-0.1 ± 0.6	-0.3 ± 0.5
Magnesium (mEq/L)	0 ± 0.2	0 ± 0.1	0 ± 0.1	0 ± 0.1	0 ± 0.1
Phosphorous (mEq/L)	0 ± 0.6	0.1 ± 0.8	0.1 ± 0.7	0.1 ± 0.7	0 ± 0.7
Hemoglobin (g/dL)	-0.3 ± 0.8	-0.2 ± 0.8	-0.4 ± 0.8	-0.3 ± 0.7	-0.6 ± 1.1
Hematocrit (%)	-1.0 ± 2.7	-0.7 ± 2.6	-1.2 ± 2.8	-0.9 ± 2.7	-1.6 ± 3.5
Platelet count 10^9 /L	-9.1 ± 41	3 ± 43	4 ± 50	-8 ± 45	0.7 + 49

Marked abnormalities -hematology Period B and C.

The values in bold below were values of concern to this reviewer. The original submission did not have the latest follow-up on these patients. The sponsor subsequently submitted additional data. The sponsor's response is capture in the right-most column.

Table 18: Hematology abnormalities Period B and C

Parameter	ID	Dose	Demography	Baseline	Day 22	Day 37	Other?	BMS comment
Hemoglobin g/dL (Range 11.6-4.8)	CV 131154-45-5	1.5	16 y/o M	16.6	15.6	**12.8**		Day 96-121= 14.0 Day 219 = 15.3
	CV 131154-48-18	0.5	12 y/o M	13.2	13.0	**9.6**		Day 96-121= 9.6 Day 219 = 13.7
	CV 131154-48-20	4.5	12 y/o M	17.3	**13.2**	17.7		**Day 96-121= 9.3** **Day 219= 13.5**
	CV 131154-48-22	0.5	11 y/o M	15.8		**8.8**		Day 96-121= 12.6 Day 219 = 16.2
	CV 131154-49-34	4.5	11 y/o F	16.2		**12.2**		Day 96-121= 12.6 Day 219 = 13.0
	CV 131154-58-12	4.5	15 y/o M	15.8	13.0	**12.7**		**Day 96-121= 12.7** Day 219 = 14.8
	CV 131154-60-12	0.5/pbo	14 y/o M	15.7	15.4	**12.1**		Day 96-121= 15.8 Day 219 = 15.5
Neutrophils x 10^3 c/uL Range not stated)	CV 131154-48-2	1.5/pbo	15 y/o M	3.4	**0.8**	4.5		Day 96-121= 2.7 Day 219 = 2.1
	CV 131154-49-19	0.5	15 y/o M	1.32	1.4	**0.97**		Day 96-121= 1.4 Day 219 = 2.1
	CV 131154-49-23	4.5	9 y/o M	4.2	**0.8**	1.7		Day 96-121= 2.7 Day 219 = 3.1

Hematology Period D:

Table 19: Hematology abnormality Period D

Parameter	ID	Dose	Demographics	Baseline	Day ~100	Day ~225	Other	BMS comment
Hemoglobin g/dL (> 3 g/dL decrease from baseline)	CV 131154-45-1	0.5	13 y/o M	16.6		**12.5**		**F/U 13.9**
	CV 131154-48-1	0.5	16 y/o M	16.0	14.6	**8.7**		No F/U
	CV 131154-48-17	0.5	14 y/o F	14.0		12.3	9.8 (day 36)	
	CV 131154-48-18	0.5	12 y/o M	13.2	**9.6**	13.7		
	CV 131154-48-20	0.5	12 y/o M	17.3	**9.3**	**13.5**		NCS per investigator
	CV 131154-48-21	0.5	11 y/o F	12.5	**9.0**	13.2	13.2 (day 36)	
	CV 131154-49-23	0.5	11y/o M	15.8	**12.6**	16.2		
	CV 131154-49-4	1.5	16 y/o M	16.7	**12.5**	15.2		
	CV 131154-49-9	4.5	16 y/o M	15.9		**12.0**		No AEs reported post-study
	CV 131154-49-34	1.5	11 y/o F	16.2	**12.6**	**13.0**		No AEs reported post-study

	CV 131154-58-12	1.5	15 y/o M	15.8	12.7	14.8		
	CV 131154-58-15	4.5	16 y/o M	15.4	**8.5**		14.4 (day 120)	
	CV 131154-60-4	4.5	16 y/o M	16.5		**12.0**		NCS per investigator
	CV 131154-60-7	4.5	16 y/o M	16.6	**11.7**	16.3		
Neutrophils X 10 ^3 c/uL	CV 131154-13-1	0.5	6 y/o M	4.0	5.6	4.1	1.0 (day 38) 2.1 (day 45) 2.8 (day 52)	2.0

Table 20: Chemistry Period B and C

Parameter	ID	Dose	Demography	Baseline	Day 22	~Day 37	Other?	BMS comments
AST U/L range 0-40	CV 131154-46-3	pbo	16 y/o M	21	**130**	24		
ALT U/L range 0-40	CV 131154-60-3	1.5	16 y/o M	12	**91**	**126**		
Creatinine mg/dl (Range 0.3-.0.7)	CV 131154-15-2	1.5/pbo	8 y/o M	0.3	0.5	0.5		
	CV 131154-19-3	1.5	9 y/o M	0.5	0.9	1.0		
	CV 131154-33-4	0.5	8 y/o M	0.4	0.7			
	CV 131154-56-2	pbo	6 y/o F	0.5	0.8	0.5		
Creatinine mg/dl (Range 0.5-.1.5)	CV 131154-46-7	1.5	9 y/o M	0.4	0.7	0.8		
	CV 131154-46-8	4.5	12 y/o F	0.5	0.9	0.9		
	CV 131154-49-26	0.5	11 y/o M	0.5	0.9			
Sodium meq/L Range (135-152)	CV 131154-50-37	4.5	10 y/o F	139	**112**	136		
Glucose mg/dL Range < 60 to > 300?)	CV 131154-1-7	1.5	8 y/o F	105	55			
	CV 131154-1-13*	4.5	10 y/o M	97	**35**		93/35 (day 41/42)	
	CV 131154-1-19	4.5	16 y/o M	163			452 (day 40)	
	CV 131154-17-3	4.5/pbo	11 y/o F	**49**	**44**	109		
	CV 131154-17-7	1.5	15 y/o F	72	57	**36**		36 NCS per investigator No post-study follow-up obtained
Albumin g/dL (range 3.5 to 5.5)	CV 131154-17-7	0.5/pbo	7 y/o F	5.4	4.5	3.7		
	CV 131154-50-37	4.5	10 y/o F	4.7	3.4	4.4		
Cholesterol mg/dL Range 100 -169)	CV 131154-45-5	1.5	16 y/o M	152	174	**333**		Day 108=238; Day 218= 312
Creatinine Kinase U/L (range 34-221)	CV 131154-11-13	4.5/pbo	15y/o M	115	**808**	**465**		Day 106= 120 Day 220 =102
	CV 131154-11-17	0.5/pbo	15 y/o M	130	**748**	75		
	CV 131154-41-19	4.5	12y/o M	70	74	38		
Creatinine Kinase U/L (range 24-221)	CV 131154-46-3	pbo	16 y/o M	138	**4597**	142		
	CV 131154-46-5	1.5	13 y/o F	76	**2842**	66		
	CV 131154-47-10	0.5	15 y/o M	156	**667**			Day 107= 148 Day 135= 264 Day 225=175
	CV 131154-49-4	1.5/pbo	16 y/o M	103	138	**3346**		Day 108= 113 Day 220 =260
	CV 131154-50-65	0.5	13 y/o F	58	**235**			

	CV 131154-59-18	1.5/pbo	13 y/o F	45	**233**	46		
Uric acid mg/dL (Range 2.4-8.2)	CV 131154-45-11	1.5	14 y/o M	3.3	7.8			
	CV 131154-41-19	1.5	11 y/o F	3.6	3.4	33.3		

*early discontinuation for lost to follow-up.

Table 21: Chemistry Period D

Parameter	ID	Dose	Demographics	Baseline	Day ~100	Day ~225	Other	BMS response
AST U/L (< 40)	CV 131154-45-5	0.5	16 y/o M	14	13	**225**		NCS per inv 1 mo post-study AST=21
ALT U/L (< 40)	CV 131154-45-5	0.5	16 y/o M	12	10	**318**		NCS per investigator 1 mo post ALT = 33
Creatinine (mg/dl) > 1.5 pre-dose	CV 131154-15-2	1.5/4.5	8 y/o M	0.3	0.4	0.6		
	CV 131154-19-3	0.5/1.5	9 y/o M	0.5	0.8	0.6		
	CV 131154-45-8	0.5	15 y/o M	0.7	**1.6**	0.7		
	CV 131154-45-11	0.5	14 y/o M	0.7	0.6	**1.3**		NCS per inv
	CV 131154-45-12	1.5	13 y/o M	0.7	0.9	**3.0**		NCS per inv 1 wk post study =0.7
	CV 131154-46-7	0.5	9 y/o M	0.4	0.9	0.6		
	CV 131154-47-21	0.5	10 y/o F	0.5	0.9	0.5		
	CV 131154-47-22	0.5	8 y/o M	0.5	0.9	0.5		
	CV 131154-48-10	0.5	14 y/o F	0.5	0.6	0.8		
	CV 131154-48-11	0.5	13 y/o M	0.6	0.8	**1.2**		NCS per investigator No AEs post study
	CV 131154-48-21	0.5	11 y/o F	0.5	0.9	0.8	0.7 (day 36)	
	CV 131154-49-11	1.5	9 y/o M	0.4	0.7	0.5		
	CV 131154-50-7	0.5	11 y/o M	0.4	0.8	0.4		
	CV 131154-50-10	0.5	13 y/o F	0.6	1.0	0.7		
	CV 131154-50-15	4.5	15 y/o M	0.7	**1.1**	0.8		
	CV 131154-50-60	0.5	9 y/o M	0.4	0.8	0.5		
	CV 131154-58-16	4.5	12 y/o F	0.5	0.8	0.5		
	CV 131154-59-19	1.5	11 y/o F	0.5	0.9			
Serum glucose < 60 or> 300	CV 131154-8-2	0.5/1.5	14 y/o M	57	82	76	58 (day 50)	
	CV 131154-17-2	0.5/1.0	13 y/o M	83	66	104	42 (day 36)	
	CV 131154-17-7	1.0	15 y/o F	72	70	**38**		NCS per investigator, No F/U obtained
	CV 131154-59-15	1.5	16 y/o F	100	**20**	98		
Serum K+ mEq/L <3.0 or > 6.0	CV 131154-17-2	0.5/1.0	13 y/o M	4.3	**8.4**	3.9	4.8 (day 36)	
	CV 131154-45-12	1.5	13 y/o M	4.1	4.4	**6.1**		NCS per investigator 1 week post-study K+=4.6
	CV 131154-48-5	0.5	14 y/o M	4.1	**6.3**	5.2		
Albumin g/dL <0.75 pre value	CV 131154-15-1	0.5/1.5 /4.5	15 y/o F	4.1	3.1	3.2	3.2 (day 42) 2.9 (day 64) 3.1 (day 187)	
Creatinine	CV 131154-41-11	0.5	15 y/o M	86	249	**667**		NCS per

Kinase U/L > 4x pre value								investigator 2 wk post study CK=58
	CV 131154-45-1	0.5	13 y/o M	105		**430**		2 wk post-study CK=68
	CV 131154-45-12	1.5	13 y/o M	54	65	**401**		NCS per investigator 1 wk post0stdy CK=60
	CV 131154-49-1	4.5	15 y/o M	142	152	**874**		NCS per investigator 2 wk post-study CK=104
	CV 131154-58-9	4.5	15 y/o M	124	94	**629**		NCS per investigator No AEs by telephone contact
	CV 131154-60-3	4.5	16 y/o M	92		**478**		NCS per investigator No AEs by telephone contact
Uric Acid mg/dL > 2x baseline	CV 131154-45-11	0.5	14 y/o M	3.3	4.7	**9.3**		NCS per investigator No AEs noted on phone F/U
	CV 131154-47-22	0.5	8 y/o M	2.4	7.7	3.8		

The values in bold are values that would concern this reviewer.

The majority of the meaningful abnormalities normalized upon subsequent testing and when not assessed, the sponsor noted no adverse events on contact.

ECGs:

No ECGs were available.

Vital signs:

Vital signs were part of the primary end point.

Conclusions:

(b) (4)

The study consisted of four periods. The first is an eligibility and enrollment period. The second period is the 3-week dose-ranging with patients randomized to doses of 0.5, 1.5 or 4.5 mg/kg. For the two higher doses, there was an intermediate titration step. The third period was a two-week randomized withdrawal period. Patients were either maintained on the randomized dose or withdrawn to placebo. The intent of this portion of the study was to determine if the reason for the lack of a significant slope was the dose level was too great and the effect reflected the flattened portion of the dose-response curve.

A withdrawal study therefore would define the maximum magnitude of the blood pressure effect. The last proportion of the study was an open-label 6 month safety study.

The primary metric of the study was the establishment of a dose response for slope. The doses chosen were approximately 0.5, 1.5 and 4.5 mg/kg/min. To place these pediatric doses in perspective to adult doses, if one assumes that the average weight of a subject enrolled in the adult blood pressure studies of Irbesartan was approximately 80 kg, the corresponding dose range as used in this study would equal 40, 120 and 350 mg daily for adults. The effect of these doses on blood pressure for adults is in the Figures below. Based on these data, the estimated effect would be approximately 9 mm Hg in the 350 mg dose and 2.5 mm Hg in the 40 mg dose, a net of approximately 6.5 mm Hg in comparing the low dose to high dose regimen for sitting systolic blood pressure. For diastolic blood pressure the effect would be approximately 4.5 mm Hg. Since blood pressure baseline measurements in children are somewhat less than those in adults, the effect of irbesartan on blood pressure would be anticipated to be slightly less in the children. The systolic effect was sized to approximately 6 mm Hg with a SD of 12 mm Hg in performing the power calculations. The study size was furthermore increased by 81 children. Consequently, the study should have been able to detect a difference between the high and low dose groups of 6 mm Hg.

Figure 2; Dose-response of Irbesartan in adults with hypertension

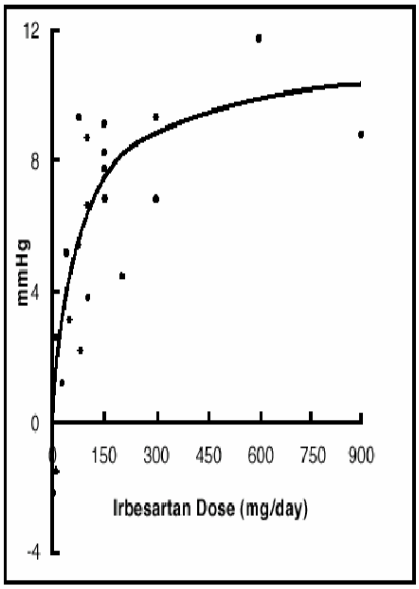


Figure 1. Placebo-subtracted reduction in trough SeSBP; integrated analysis

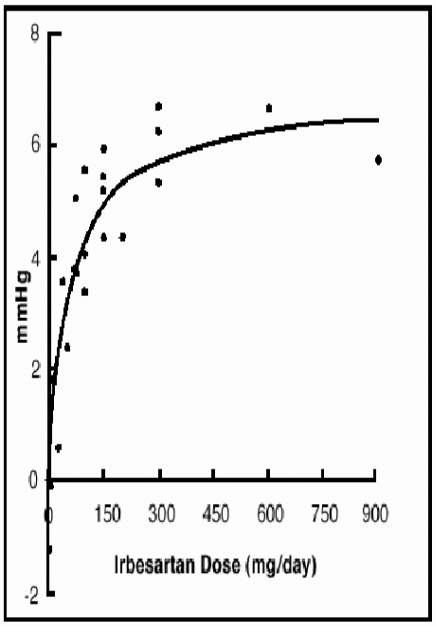


Figure 2. Placebo-subtracted reduction in trough SeDBP; integrated analysis

With respect to the slope of the dose response curve, although there was a significant blood pressure decrease from baseline, there was no significant dose-related slope for seated

systolic blood pressure versus dose at the inter-dosing interval. For diastolic blood pressure, not the primary endpoint, the nominal p-value of the trend by the sponsor's analysis was 0.05.

During the randomized placebo-withdrawal period, there was a statistically significant effect of remaining on drug, but the effect was extremely small (placebo-subtracted effect was 2.3 mm Hg). Since the purpose of the randomized withdrawal study is to confirm that the choice of the dose range corresponded to the upper, flat portion of the dose-response curve. The placebo-withdrawal effect should correspond to the maximum blood pressure effect of Irbesartan.

A more likely interpretation is that the study allowed two potential ways for the demonstration of an effect of Irbesartan. The first is the demonstration of a positive dose-response slope. The second is the demonstration of a placebo-controlled withdrawal effect. The outcome of a positive placebo-withdrawal effect that is nominally statistically significant, but appears to be inconsistent with a maximum drug effect on blood pressure, argues against accepting this result as demonstrating efficacy and suggests that the effect may more reflect the play of chance.

Title of Study: Experience with Irbesartan Use in Children 16 years of age and Younger: A Descriptive Study in Two Medical Claims database.

This report consists of an analysis of two databases for pediatric use of Irbesartan. The databases were screened by National Drug Codes specific for Irbesartan or Irbesartan/ hydrochlorothiazide. After obtaining a waiver from the Privacy Board of the New England Institutional Review Board, the sponsor attempted to review the appropriate medical records.

The two databases that were screened for pediatric subjects (< 16 years old) were the Ingenix Research Database (RDB) and the Premier Healthcare Informtics (Premier). The RDB population included pediatric subjects (N= (b) (4)) enrolled from January, 1997 through June, 2003. The population reflects patients who received prescriptions as outpatients. The Premier population (n= (b) (4)) received Irbesartan from a hospital pharmacy from January 2001 through Dec 2003.

Once patients were identified from the database, charts were abstracted for information when available, in particular the chart review in part determined whether the patient was exposed to Irbesartan. The specifics of the database are abstracted from Table 1 of the sponsor's report.

Table 22: Description of "use" data

Source	# pts identified from claims	# excluded*	# pts from chart abstraction	Records obtained	Info obtained verbally from provider	No additional data available	Confirmed user	Confirmed non-user	Unknown
RDB	(b) (4)								
Premier									
Total									

(b) (4)

(b) (4)

Conclusion:

This was a small, uncontrolled and largely uninterpretable database. There is little reassurance or discomfort that is raised by the analyses of these patients.

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References

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