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ABREVIATIONS

SSBP: Seated systolic blood pressure
SDBP: Seated diastolic blood pressure

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EXECUTIVE SUMMARY

Conclusion/Summary

Based on the results of the us01 pivotal study, benazepril is effective in lowering both systolic and diastolic blood pressure in the study population. (b) (4) At dose ranges of 5 to 20 mg and 10 to 40 mg in children 7 to 16 years old who weigh 20 to 50 kg and more than 50 kg respectively benazepril lowered blood pressure but was associated with symptoms of angioedema and liver function abnormalities (see Appendix1: Safety details).

(b) (4)

(b) (4)

Summary of Clinical Findings

There were two studies in which benazepril was given at steady state levels and patients were followed up in an experimental design. The pivotal us01 was a multicenter, three-phase, six-month long study that was conducted to evaluate the safety and efficacy of benazepril in 107 hypertensive subjects 7 to 16 years of age. The us03 study was a multicenter, 5 to 14 days long, steady state study to evaluate the pharmacokinetics of benazepril in 57 children ranging in age from one month to 16 years.

One hundred and seven were enrolled in the pivotal study. Eighty eight completed the dose-escalation phase in which subjects were exposed to low (5 or 10 mg), medium (10 or 20 mg) or high (20 or 40 mg) depending on their weight. Eighty five subjects entered the randomized withdrawal phase and seventy two completed it. Subjects received low, medium or high doses irrespective of their weight in this phase. Seventy six subjects volunteered to continue in the open-label phase and were given the maximum dose they can tolerate. Sixty four completed six months of follow-up.

Doses evaluated in this study included 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg and 0.6 mg/kg. The sponsor used tablet formulations of 5, 10 and 20 mg strengths. Doses were selected based on the maximum recommended dose for a 70 kg adult person.

(b) (4)

Safety

Overall safety

With respect to safety the database includes:
--a pivotal safety and efficacy study with a four-week dose escalation phase, a two-week randomized, withdrawal, double blind placebo-controlled phase and an optional open-label extended, six-month phase.
--two pharmacokinetic studies, with benazepril evaluated at steady state in one and as a single dose in the other.
--a summary of spontaneous reports compiled from the Novartis global drug safety database of all adverse events reported in children up to 16 years of age [CS&E Report].

Integrated Summary of Safety

Nine subject discontinued benazepril as a result of adverse events (see Details of adverse events that led to discontinuation of the study), nine developed serious adverse events (see Details of cases with serious adverse events), and seven developed clinically significant laboratory abnormalities. The clinically significant laboratory abnormalities included three liver function abnormalities, two hyperkalemia, one proteinuria and increased BUN and one neutropenia.

Benazepril use in this pediatric program was associated with the following:

- Symptoms of angioedema in three patients in the pivotal study (see Details of cases that developed symptoms of angioedema).
- Liver function abnormalities (see Details of cases with clinically significant laboratory changes). There were a total of six liver function abnormalities between the two studies.
  --Three of these were clinically significant including one significant ALT and AST elevation that led to drug discontinuation but the levels remained elevated at a lab test that was performed six days after discontinuation. The second one was hyperbilirubinemia, and the third one has resolved toward the end of the study.
  --The other three include one mild increase of AST and ALT, one worsening of liver function abnormalities which resolved by the end of the study and the third was an increased AST on a background of hyperbilirubinemia the outcome of which is not known.
- Other adverse events which were most commonly experienced include headache, dizziness, GI disorders, cough and infections and infestations (see Table 8 Number (%) of subjects with most frequent adverse events (≥ 3%) seen in the dose escalation phase, Table 9 Adverse events observed in the randomized withdrawal phase, Table 10 Number (%) of subjects with most frequently occurring adverse events (~ 5%) seen in the open-label phase

Summary safety in the us01 study

The us01 is a dose ranging study of benazepril in 107 pediatric patients aged 6-16 years. The results demonstrated a number of safety concerns including angioedema and liver function changes. There were a total of 9 (8.4%) that discontinued as a result of adverse events with five in the dose-escalation phase, 1 in the randomized withdrawal phase and three in the open-label phase (see Details of adverse events that led to discontinuation of the study). These AEs include one angioedema, one liver function abnormality, one

blood creatinine abnormality, two kidney transplant rejections, one aggravated cough, one rash, one hypertensive crisis and one hyperactivity and insomnia.

Nine subjects (8.4%) developed serious adverse events (see Details of cases with serious adverse events). Five of these were related to the urinary apparatus including two acute renal failure and rejection of kidney transplants, one increased creatinine in patient with history of kidney transplant and two multiple hospitalizations for urinary tract infections. The remaining four serious adverse events include a hypertensive crisis that resolved after discontinuation of benazepril, one bowel obstruction, one severe sleep apnea and one severe depression.

Seven subjects (6.5%) developed clinically significant laboratory abnormalities while they were in the study. Three of these were liver function abnormalities. From screening to Visit 5, the laboratory tests for which the percentage of subjects with a laboratory test that worsened exceeded the percentage of subjects whose values improved by at least 5% were AST (16.7% worsened; 7.6% improved), BUN (7.6% worsened; 1.5% improved), hematocrit (10.6% worsened; 1.5% improved), hemoglobin (10.6% worsened; 4.5% improved), and RBC count (12.1% worsened; 4.5% improved).

Other adverse events include the ones commonly seen in association with the use of ACE inhibitors such as cough (9% in the dose escalation phase) and rash (6.5%) including two cases with urticaria. Others include headache, dizziness and GI disorders.

Some adverse events were found to be significantly different between groups including ear and labyrinth disorders (9% in females vs. 0 in males); GI disorders (0 in blacks and Orientals vs. 21% and 14% in whites and the "other" race category respectively); infections and infestations (32% in the 6-11 years old vs. 12% in the older kids); and reproductive system and breast disorders (9% in females vs. 0 in males, and 21% in the "other" race category vs. 0 in Orientals and Blacks and 2% in Caucasians).

Summary safety in the us03 study

A multicenter open-label, steady state study to evaluate the pharmacokinetics of benazepril in pediatric subjects

Fifty seven subjects ranging between one month and 16 years of age were enrolled. Doses ranged between 0.2 and 0.5 mg/kg in subjects six years of age or younger and between 0.1 and 0.5 mg/kg in older subjects.

Subjects received benazepril for at least five days with the goal of reaching a steady state distribution. No subjects were discontinued from this study as a result of adverse events. 14 (24.6%) developed at least one adverse event. Among the ones reported, there were two edema cases (one associated with nephrotic syndrome and the other one not known), one severe increased creatine phosphokinase, and one increased liver enzymes (increased AST level on a background of hyperbilirubinemia (at baseline)).

Summary of safety in the us03A1 study

A single center, single dose, open-label study to evaluate the pharmacokinetics of benazepril in pediatric subjects

This study enrolled 30 children between the ages of one month to 16 years of age. Doses ranged between 0.2 and 0.5 mg/kg in children younger than 6 years and between 0.1 and 0.5 mg/kg in older children. The children were evaluated up to 24 hours post dosage. Nine subject developed adverse events. The adverse events that were observed in two or more subject were diarrhea and somnolence.

Efficacy

Eighty five out of 88 patients who responded to therapy in the dose-escalation phase (per BP measurement on day 29) entered the randomized withdrawal phase of the study. Twenty four patients were randomized to low dose, 23 were randomized to medium dose, 19 were randomized to high dose and 19 were randomized to placebo. Unlike what the protocol predicted not all study groups had similar mean SSBP at the beginning of the randomized phase. Only the group assigned to high dose had a mean SSBP similar to that of placebo, 121 mm Hg. The low and medium dose groups had mean SSBP levels 3 mm Hg bellow and above that of placebo respectively.

After two weeks on the randomized regimen, the mean SSBP in all dose categories and in placebo increased. The mean SSBP of the group randomized to placebo changed the most, it increased by 7.5 mm Hg. The mean change in SSBP was not proportional to the dose. The group randomized to medium dose changed the least, it increased by 0.9 mm Hg, the mean SSBP of the group randomized to high dose changed by 2.2 mm Hg, and the mean SSBP of the group randomized to the lowest dose changed by 4 mm Hg.

The difference in change in the mean SSBP between placebo and the groups randomized to benazepril was statistically significant for the group randomized to medium dose, it approached statistical significance for the group randomized to high dose but not significant for the group randomized to low dose. The difference in change in the mean SDBP was similar to that seen in the mean SSBP but here the difference from placebo was statistically significant for both medium and high dose groups

Subjects on the low and high dose despite the increase in their mean SSBP at the end of two weeks in the randomized withdrawal phase, their BP was still bellow the 95th percentile for their gender, height and age, a cutoff that qualified them into the study.

Before the end of the randomized withdrawal phase, about one third of all subjects taking placebo (6 out of 19) discontinued the study as a result of unsatisfactory therapeutic effect. Only two in the low dose group (2/24), two in the medium dose group (2/23) and 1 in the high dose group (1/19) discontinued for unsatisfactory therapeutic effect.

Recommendations

CLINICAL REVIEW METHOD

This reviewer utilized the data submitted electronically on April 25, 2003. The main review of efficacy was done on the report of the us01 clinical pivotal study (Study No: CIB824E US01) submitted as a pdf file. The review of safety was completed using the latter report and the us03 pharmacokinetic study (Study No: CIB824E US03) submitted as a pdf file as well. More analyses and detailed information regarding safety not submitted with the main report were requested by the reviewer and used in drawing conclusions.

CLINICAL REVIEW

Overall Pediatric Clinical Program

Table 1 Summary of pediatric clinical program

Study	Design and Type	No. of subject	Dose/duration	Objective
Us01	Multicenter, three-phase study -Dose escalation phase	107 pediatric subjects	Low, medium or high (5, 10, 20 mg) or (10, 20, 40 mg) depending on weight for 29 days	Assess safety and efficacy
	-Randomized withdrawal, placebo controlled phase	85	Low, medium or high irrespective of weight for two weeks	
	-Open-label phase	76	Maximum tolerated dose for up to six months	
Us03	Open-label, multicenter, steady state study	57 pediatric subjects	0.1 to 0.5 mg/kg depending on age for at least 5 days	Pharmacokinetic study
Us03A1	Single center, open-label single dose	30 pediatric subject	0.1 to 0.5 mg/kg depending on age, one time dose only	Pharmacokinetic study
Us02	Randomized, open-label, two-way crossover study	30 healthy adult subjects	10 mg per period	Biopharmaceutical study

Pivotal Study: Us01

Title "A multicenter study to evaluate the pharmacokinetics, dose-response, efficacy, and safety of benazepril in pediatric subjects"

The us01 study is multicenter study that consisted of a screening phase, a dose-escalation, a double-blind randomized withdrawal, and an optional open-label treatment phase. It was designed to evaluate the pharmacokinetics, efficacy and safety of benazepril in hypertensive pediatric subjects ranging between 6 and 16-years of age. The substudy that was designed to evaluate the pharmacokinetics was discontinued because of low enrollment.

One hundred and seven subjects whose seated diastolic or systolic BP was greater than the 95th percentile for age, sex and height, who met other inclusion criteria and who could be managed with a single anti-hypertensive medication were enrolled in twenty seven centers in the US. Patients were divided into two weight categories, fifty kilos or less and greater than 50kg. The range of doses for light-weight patients was 5, 10 and 20 mg and that for the heavier kids was 10, 20 and 40 mg.

Study Dates and amendments

There were five protocol amendments. Included here are the ones that are relevant to the clinical review of this program.

Amendment 1 (14 December 1999) incorporated the following:

• Changed the logistics of home blood pressure monitoring.
• Changed the duration of treatment with low- dose benazepril during the dose- escalation phase from 7 to 8 days.

Amendment 2 (14 February 2000) prohibited the use of nifedipine as " rescue" medication in the study because of cautions issued by the Institutes for Safe Medication Practices against the use of sublingual nifedipine in adults.

Amendment 3 (23 February 2000) added, at the recommendation of the FDA, a microscopic examination for urinary casts and crystals to the urinalysis at the screening visit and Visit 7.

Amendment 4 (16 August 2000) revised the study exclusion criteria so that renal transplant subjects on multiple immunosuppressive medications could be enrolled in the study.

Amendment 5 (27 February 2001) incorporated the following:
• Revised the definition of hypertension. Hypertension redefined as either a SSBP or SDBP $\geq$ 95th percentile for age, sex, and height.

• Changed the primary efficacy variable to SSBP at Visit 5 and changed SDBP at Visit 5 to a secondary efficacy variable.

• Changed the criteria used for the computation of the study sample size, which reduced the number of subjects to be enrolled from 120 to 116.

Study design

The study was designed to respond to the division's Pediatric Written Request (FDA Request Letter for NDA (b) (4)) dated November 2, 1999.

This was a dose ranging trial investigating the effect of three dose levels (low, medium and high) in the treatment of hypertension in pediatric patients. The trial had four phases: A screening phase followed by a dose escalation phase, a randomized withdrawal and an open-Label phase.

In the screening phase patients were withdrawn from anti-hypertensive medication if they were taking any, were to have their BP monitored daily at home by monitors provided by the study sites. Patients whose home BP is $\geq 95^{th}$ percentile for age, sex and height were to return to the study site to confirm their eligibility. Hypertension is confirmed by two sets of seated BP measurements at least one hour apart and each set of measurements comprised three readings at least five minutes apart that were averaged. Hypertension was confirmed when the average of both measurements sets for either SSBP or SDBP were $\geq 95^{th}$ percentile for age, sex, race and height.

In the dose escalation phase patients were initiated on low and then up titrated to medium and high doses before they entered the randomized withdrawal phase.

Patients who completed the dose escalation phase and whose mean SSBP and SDBP were $< 95^{th}$ percentile for age, sex and height entered the double-blind randomized withdrawal phase. In this phase patients were randomly assigned to placebo, or to a low, medium or high dose in a ratio of 1:1:1:1 and remained on the randomized regimen for two weeks. Patients whose SSBP or SDBP was $\geq 95^{th}$ percentile were not enrolled in this phase of the study. They were either withdrawn from the study or optionally enrolled in the Open-Label phase using benazepril as a combination therapy with a second antihypertensive medication selected by the investigator. If at the one-week clinic-visit that follows randomization hypertension was confirmed, subjects were to be discontinued.

After the completion of the randomized withdrawal phase patients were optionally enrolled in the open-label phase where they were given the maximum tolerated dose.

Study Population

One hundred and sixteen patients were calculated as a sample size to meet the study's primary endpoint, but only a total of 107 were enrolled and received treatment between 02 February 2000 and 14 October 2002. Twenty seven centers enrolled between one and 14 subjects each.

Inclusion criteria

Six to 16 year old male and female subjects who weigh at least 20 kg and are able to swallow tablets were targeted for enrollment. They were eligible for inclusion if their mean SSBP or mean SDBP was equal to or greater than the 95^{th} percentile for age, sex, and height while off antihypertensive medication during the screening period.

Exclusion criteria

Patients with the following are not to be enrolled in the study.

- GFR < 30 mL/min/1.73 m^2
- Severe hypertension requiring emergent treatment as evidenced by a SSBP or SDBP greater than 3 standard deviations from the mean for age, sex, and height, or by organ involvement.
- End organ involvement including CHF or hypertensive encephalopathy
- Coarctation of the aorta or renal artery stenosis
- Solid organ transplant
- Renal transplant if less than one year prior to enrollment if not clinically and therapeutically stable
- Hypertension requiring more multiple antihypertensive medications
- Taking hypertension medication and hypertension confirmed within 24 hours of last dose
- Nephrotic syndrome and not on stable maintenance therapy
- Laboratory abnormalities indicative of clinically significant neurologic, respiratory, GI, hepatobiliary or hematologic disease
- Significant structural heart disease, cardiomyopathy, or atrio-ventricular conduction disturbance
- Pregnancy
- Sensitivity to ACEI or a history of angioneurotic edema
- Intake of methylphenidate (Ritalin) or similar agents, MAOIs, lithium, potassium supplements, diuretics, major tranquilizers or catecholamine analogues.

Formulation and Dosing

All doses were provided in the form of tablets. Dosing for the study was based on the maximum recommended adult dose of 40mg per day for a 70kg man which is the equivalent of ~0.6mg/kg/day. Dosage was determined by patients weight and study phase. In the dose escalation phase, two weight categories were defined and assigned to two escalating regimens of three dose categories each: low, medium and high. Subjects weighing 20 to 50 kg were assigned to a low dose regimen and those weighing greater than 50 kg were assigned to higher dose regimen. Subjects were started on low [5mg (~0.1mg/kg/day) OR 10mg (~0.2mg/kg/day)] and then up titrated to medium [10mg (~0.2mg/kg/day) OR 20mg (~0.3mg/kg/day)] and high [20mg (~0.3mg/kg/day) OR 40mg (~0.6mg/kg/day)] doses. In the withdrawal phase subjects were randomized to low, medium or high dose or to a matching placebo regardless of their weight. In the open-label phase, patients were given the maximum tolerated dose.

Study Procedures

Patients were washed out from previous antihypertensive medication on day –21. Blood pressure was to be monitored at home three times daily with three readings each time and the parent guardian was to call the investigator if one the readings met the criteria for study entry or for an urgent clinic visit for safety purposes.

When subjects were found to be hypertensive (either SSBP or SDBP $\geq 95^{th}$ percentile for age, sex and height) at the confirmation visit, they were enrolled and started on the lowest dose of the dose-escalation regimen.

Table 2 Visits and assessments

	Screening	Dose-escalation			Randomized Withdrawal			Open-label	
Visit Number	1	2	3	4	5	6	7	8	9
Visit day	-21 to -1	0	7	15	28	35	42	+ 3 mo	+ 6 mo
Dose started		Low	Med.	High	Double-Blind			Open-Label	
Demographics	x								
PE	x						x	x	x
Vital signs	x	x	x	x	x	x	x	x	x
ECG	x				x		x	x	x
Lab: blood chemistry, hematology	x				x		x	x	x
Lab: urinalysis	x						x		
Home-based BP monitoring	x	x	x	x	x	x	x		
Adverse event assessment	x----------as needed----------x								
Blood collection for PK		x							

Study treatment discontinuation and Protocol Violation

Subjects who interrupt their study medication were considered protocol violators and were considered for exclusion from the study.

Investigators were allowed to withdraw subjects from the study for adverse events, abnormal laboratory values, abnormal test procedure results, unsatisfactory therapeutic effect, condition no longer requiring study treatment, protocol violation, loss to follow-up, administrative problems or death.

Subjects withdrawn from the study must have all tests required at the final follow-up visit performed.

Concomitant antihypertensive therapy

During the screening period patients were to discontinue anti-hypertensive therapy if taking any before they were evaluated for eligibility. Subjects were instructed not to take concomitant antihypertensive medication except in the open-label phase.

Study Objectives

The primary objective of the study (not stated in the protocol) was to obtain Pediatric Exclusivity which was granted on July 02, 2003.

The stated study primary objective was to evaluate the efficacy of benazepril in pediatric hypertension, the dose response relationship, and to determine the PK profile of benazepril in the studied population.

The secondary objective was to determine the three and six-month safety and tolerability of benazepril in 6 to 16-year old hypertensive children.

Study Endpoints

Primary Efficacy Endpoints

- Change in SSBP from baseline to Visit 5 (end of dose escalation phase)

Secondary Efficacy Endpoints

- Change in SSBP from Visit 5 (end of dose escalation phase and beginning of randomized withdrawal phase) to Visit 7 (end of randomized phase)
- Change in SDBP from baseline to Visit 5
- Change in SDBP from Visit 5 to Visit 7
- Proportion of subjects who achieved blood pressure control (SSBP and SDBP < 95^{Th} percentile) during the dose-escalation phase

Statistical Methods and Analyses

Sample Size calculations

Sample size calculations were based on the following assumptions:

- A difference of 11 mm Hg was considered clinically relevant to detect.
- SD of 12 mm Hg is applicable to this population
- 20% will not achieve BP control by the end of the escalation dose phase and will not enter the randomized withdrawal phase.
- An additional 10% of subjects would drop out for other reasons including non-compliance and AEs in both the dose-escalation and randomized phases.

In order to detect a difference between any of the three dose groups and placebo with 80% power and a Type 1 error of 0.05, a total of 116 subjects were to be enrolled so that 84 subjects would complete the study with 21 evaluable subjects per treatment group.

With a sample size of 84, it was estimated that a safety event, occurring at a rate of 1.9%, would be observed with a probability of 80%.

Efficacy Analyses

Primary Efficacy Analysis

Change in SSBP from baseline to day 28 was to be calculated for all subjects in the ITT1 population and a paired t-test to be performed at the 0.05 level. The last observed values (LOCF) were to be used for subjects who drop out of the study.

Secondary Effic*a*cy Analyses

Change in systolic and diastolic blood pressure during the withdrawal phase was to be calculated. An ANOVA approach was to be used to compare this change between groups.

- It was expected that sitting BP would be comparable in all groups at the end of the escalation phase and the analysis would not have to correct for the difference in this variable.

Populations intended for statistical analyses

Four populations were defined, ITT1 and ITT2 (Intent To Treat 1 and 2); and PP1 and PP2 (Per Protocol 1 and 2). ITT1 included all subjects enrolled in the study and who received at least one dose of benazepril and had at least one post-dose BP measurement. The PP1 included all subjects who entered and completed the dose-escalation phase and were compliant with the protocol.

The ITT2 included all subjects who entered the randomized withdrawal phase (achieved BP control in the dose-escalation phase), received at least one dose of the study medication and had at least one BP measurement. The PP2 are subjects who entered and completed the randomized withdrawal phase and were compliant with the protocol.

Safety analyses included all subjects who received at least one dose of benazepril.

Results

Patient Disposition

Thirty seven subjects (34%) discontinued from the study. There was total of 44 discontinuations with nineteen during the dose escalation phase, thirteen during the randomized withdrawal phase, and 12 during the open-label phase.

Number of discontinuations is greater than the number of patients that discontinued because some subjects that were discontinued in the doe-escalation and randomized withdrawal phases were enrolled in the open label phase, and were discontinued again.

Eighty eight patients completed the dose-escalation phase but three of these were not randomized in the second phase of the study.

- Subject 15-1003: Investigator decided it was necessary for patient to remain on high benazepril dose for one more week.
- Subjects 31-1002 and 31-2005: Patients entered the randomized withdrawal phase but did not have any recorded vital signs at any visit after randomization and were excluded from the ITT2 population.

Patients disposition in the randomized withdrawal phase

Table 4 Disposition of randomized patients

	Low Dose	Medium Dose	High Dose	Placebo	Total
Entered	24	23	19	19	85
Completed	22(91.7)	21(91.3)	18(94.7)	11(57.9)	72(85)
Discontinued	2	2	1	8(42.1)	13(15.3)
Clinical adverse events				1	1
Laboratory adverse events					
Lost to follow-up					
Protocol deviation				1	1
Consent withdrawal					
Lack of efficacy	2	2	1	6	11

Randomized withdrawal phase dropouts

Thirteen patients were discontinued in the randomized withdrawal phase. Eight of these were taking placebo and the other five (2 + 2 +1) were taking low, medium and high doses respectively. All five, and six out of the 8 placebo discontinuations were due to unsatisfactory therapeutic response.

Table 5 Dropouts and discontinuation in the other study phases

	Dose escalation phase	Open-Label phase
	Total n(%)	Total n(%)
Entered	107(100)	76(71.0)
Completed	88(82.2)	64(60)
Discontinued	19(17.8)	12
Adverse events	5(4.7)	3
Lost to follow-up		1
Protocol deviation	2(1.9)	3
Consent withdrawal	1(0.9)	3
Lack of efficacy	11(10.3)	1
Administrative reasons		2

Protocol violations

There were six protocol violations overall that resulted in the discontinuation of treatment

Dose- escalation phase

Subject 13- 2001: had a SDBP that was greater than the 95th percentile for age, sex, and height

Subject 35- 1003: did not have his benazepril dose escalated to a higher level because the Investigator was concerned that the subject's blood pressure would go too low

Randomized withdrawal phase

Subject 20- 1004: lost medication bottle after taking medication for 1 week

Open- label phase

Subject 25- 2002: non- compliance

Subject 28- 2001: cut study medication tablets in half to achieve prescribed dose

Subject 45- 2002: became sexually active and was not using birth control

Other protocol deviations

These were made of intake of prohibited medications such as paracetamol, ibuprofen and prednisone in all study phases. These deviations did not result in study termination or exclusion from the efficacy analyses.

In the randomized withdrawal phase twice as many subjects (17) on active study drug vs. placebo (8) were taking paracetamol and 8 vs. 5 were taking ibuprofen.

Demographics

Overall subjects were 6 to 16 years of age. Forty five percents of study patients were ≤12 years or Tanner stage < 3, 43% were 12 years of age or younger and 28% were Tanner stage < 3.

Table 6 Demographics of the population that was enrolled in the trial

		Weight Categories			
		20-50 kg N=26	> 50 kg N=81	Overall N=107	p-value
Age (years)	Mean	10.7	13.5	12.9	0.0001
	SD	2.5	2.1	2.5	
	Range	7-15	7-16	7-16	
Sex –n(%)	Male	14(53.8)	49(60.5)	63(58.9)	0.65
	Female	12(46.2)	32(39.5)	44(41.1)	
Race –n(%)	Caucasian	19(73.1)	44(54.3)	63(58.9)	0.20
	Black	4(15.4)	20(24.7)	24(22.4)	
	Oriental	2(7.7)	4(4.9)	6(5.6)	
	Other	1(3.8)	13(16.0)	14(13.1)	
Weight (Kg)	Mean	40.1	81.1	71.1	0.0001
	SD	7.1	21.2	25.8	
	Range	25-49	51-147	25-147	
Height (cm)	Mean	141.7	163.9	158.5	0.0001
	SD	12.8	10.6	14.7	
	Range	121-164	135-192	121-192	

Source: Table 7-6 from sponsor's report

Table 7 Demographic and background characteristics by treatment group, intent-to-treat for randomized withdrawal phase

	Low Dose N = 24	**Medium Dose N = 23**	**High Dose N = 19**	**Placebo N = 19**	**Overall N = 85**	**P-value**
Age (years)						
Mean	11.8	13.3	13.4	13.5	12.9	0.0501
S.D.	2.9	1.6	2.6	2.1	2.5	
Range	7 - 16	10 - 16	7 - 16	8 - 16	7 - 16	
Sex (N, %)						
Male	10 (41.7)	16 (69.6)	15 (78.9)	10 (52.6)	51 (60.0)	0.0610
Female	14 (58.3)	7 (30.4)	4 (21.1)	9 (47.4)	34 (40.0)	
Race (N, %)						
Caucasian	14 (58.3)	15 (65.2)	9 (47.4)	10 (52.6)	48 (56.5)	0.7650
Black	3 (12.5)	5 (21.7)	6 (31.6)	5 (26.3)	19 (22.4)	
Oriental	1 (4.2)	1 (4.3)	2 (10.5)	1 (5.3)	5 (5.9)	
Other	6 (25.0)	2 (8.7)	2 (10.5)	3 (15.8)	13 (15.3)	
Weight (kg)						
Mean	61.5	76.7	80.2	75.3	72.9	0.0935
S.D.	22.2	27.7	30.5	25.1	26.9	
Range	28 - 128	30 - 132	36 - 147	25 - 124	25 - 147	
Height (cm)						
Mean	151.9	163.4	163.1	160.0	159.3	0.0252
S.D.	14.0	12.1	15.7	15.6	14.9	

Range	126 - 173	139 - 187	121 - 181	122 - 192	121 - 192	

Source: Post-text Table 2.2 of the Sponsor's final report

Safety Results

Pediatric program safety results

Adverse events by study phase

Dose escalation phase

Table 8 Number (%) of subjects with most frequent adverse events (≥ 3%) seen in the dose escalation phase

Total number of subjects Total number with AEs	107 66 (61.7)
Discontinuation due to AEs	5 (4.7)
Serious AEs	4(3.7)
Body system affected/ Adverse event Ear and labyrinth disorders	 4(3.7)
Eye disorders	5(4.7)
Gastrointestinal disorders Nausea Vomiting	15 (14.0) 5(4.7) 6(5.6)
General disorders and administration site conditions Fatigue Pyrexia	9 (8.4) 5(4.7) 4(3.7)
Infections and infestations Nasopharyngitis	18(16.8) 5(4.7)
Injury, poisoning and procedural complications	4 (3.7)
Investigations	4(3.7)
Musculoskeletal and connective tissue disorders	5 (4.7)
Nervous system disorders Dizziness Headache	33 (30.8) 11(10.3) 25 (23.4)
Reproductive system and breast disorders Dysmenorrhea	 4 (3.7)
Respiratory, thoracic, and mediastinal disorders Cough Pharyngolaryngeal pain	16 (15.0) 10 (9.3) 6(5.6)

Skin and subcutaneous tissue disorders	7(6.5)
Vascular disorders	4(3.7)

Source: Table 10-1 (Sponsor's report) modified by medical reviewer

Randomized withdrawal phase

Table 9 Adverse events observed in the randomized withdrawal phase

Total number of subjects	Low dose 24	Med. dose 23	High dose 19	All doses 66	Placebo 19
Total number of subjects with AEs	10 (41)	11(47.8)	5 (26.3)	26 (39)	6 (31.6)
Discontinuation due to AEs				1	
Serious AEs				1	
Body system affected/Adverse event					
Eye disorders	2 (8.3)	0(0.0)	0(0.0)	2 (3.0)	0(0.0)
Nervous system disorders	4(16.7)	3(15.8)	1(5.3)	8(12.1)	3(15.8)
Headache	3(12.5)	2(8.7)	1(5.3)	6(9.1)	2(10.5)
Respiratory, thoracic, and mediastinal disorders	5(20.8)	6(26.1)	3(15.8)	14(21.2)	0(0.0)
Cough	3(12.5)	6(26.1)	1(5.3)	10(15.2)	0(0.0)
Pharyngolaryngeal pain	1(4.2)	0(0.0)	2(10.5)	3(4.5)	0(0.0)
Sneezing	0(0.0)	2(8.7)	0(0.0)	2(3.0)	0(0.0)
Skin and subcutaneous disorders	2(8.3)	0(0.0)	0(0.0)	2(3.0	0(0.0)
Laboratory abnormalities	0(0.0)	1(4.3)	1(5.3)	2(3.0)	1(5.3)*

Source: Post-text Table 15.2.1 of the Sponsor's final report modified by statistician reviewer
* The lab results in this patient were assessed the day he/she was withdrawn from 40 mg of benazepril to placebo

Open-label phase

Table 10 Number (%) of subjects with most frequently occurring adverse events (~ 5%) seen in the open-label phase

Total number of subjects Total number with AEs	76 48 (63.2)
Discontinuation due to AEs	3 (3.9)
Serious AEs	4 (5.3)
Body system affected/ Adverse event	
Gastrointestinal disorders Vomiting	9(11.8) 6(7.9)
General disorders and administration site	4 (5.3)
Infections and infestations Nasopharyngitis Upper respiratory tract infection Urinary tract infection	23 (30.3) 6(7.9) 4(5.3) 4(5.3)
Investigations	5(6.6)
Metabolism and nutrition disorders Musculoskeletal and connective tissue disorders	5 (6.6) 4 (5.3)
Nervous system disorders Headache	16(21.1) 12(15.8)
Respiratory, thoracic, and mediastinal disorders Cough	12 (15.8) 4(5.3)
Skin and subcutaneous tissue disorders	8 (10.5)

Source Table 10-4 of (Sponsor's Report) modified by medical reviewer

Postmarketing and other data relevant to safety

There is no postmarketing experience with the pediatric formulation of benazepril. However, a search with data lock point 05- Feb- 2003 was performed in the Novartis global drug safety database for all adverse events reported in children up to 16 years of age [CS& E Report]. The search for cases from spontaneous reporting revealed seven adverse experiences involving a total of four children since registration:

PHEH2002US08783: A poorly documented case of anxiety in a male child of 5 months of age. No medical history provided.

PHNU1996DE00505: An intentional overdose in a 15 year old female patient, resulting in nausea, paresthesia, and vertigo. No medical history provided.

PHRM1993FR01314: Coughing in a 13 year old male patient with a medical history of congestive heart failure and Friedreich's ataxia. Similar symptoms had previously been experienced with captopril.

PHRM1996FR00851: Fetal distress in a newborn female patient, whose mother had been treated with Cibacene during the first trimester of pregnancy.

10.3 Worldwide literature search

Not informative.

Efficacy Results

As can be seen in the efficacy summary tables below, the change in SSBP and SDBP after randomized withdrawal from high dose was greatest in the placebo group, followed by the low dose group, the high dose group and lastly the medium dose group. The difference in change between placebo and medium dose was statistically significant for both SSBP and SDBP. The difference in change between placebo and high dose approached statistical significance for SSBP and was statistically significant for SDBP.

Dose response analysis did not confirm a dose effect on blood pressure. The slope is positive for both SSBP and SDBP but not statistically different from 0.

Table 11 Change in SSBP (mm Hg) from Visit 5 to Visit 7, randomized withdrawal phase, ITT population

	Low Dose N = 24	Medium Dose N = 23	High Dose N = 19	Placebo N = 19
Visit 5				
Mean	117.9	124.0	121.2	121.0
Standard Deviation	11.5	11.9	10.2	13.4
Visit 7				
Mean	121.8	124.9	123.4	128.5
Standard Deviation	11.1	10.9	10.6	9.2
Change: Visit 5 to Visit 7				
Mean	+3.9	+1.0	+2.2	+7.5
Standard Deviation	8.8	8.7	6.8	9.5
P-value	0.171	0.015*	0.058	
Difference in Change (vs. Placebo)				
Mean	3.6	6.6	5.3	
Confidence Interval	(-2.6 – 9.8)	(0.3 – 12.9)**	(-1.3 – 11.9)	

Source: Post-text Table 8.1 of the Sponsor's final report and reviewer's analysis

*Significantly different from placebo, after adjusting for multiplicity using the conservative Bonferroni method

** Significantly different from placebo using Dunnett's 2-sided t-test

Table 12 Change in SDBP (mm Hg) from Visit 5 to Visit 7, randomized withdrawal phase, ITT population

	Low Dose N = 24	Medium Dose N = 23	High Dose N = 19	Placebo N = 19
Visit 5				
Mean	69.1	71.0	67.6	69.7
Standard Deviation	8.0	8.1	11.6	9.2
Visit 7				
Mean	73.0	73.0	69.8	77.6
Standard Deviation	8.7	9.9	9.9	12.4
Change: Visit 5 to Visit 7				
Mean	+3.9	+1.9	+2.3	+7.9
Standard Deviation	6.4	7.9	7.4	8.7
P-value	0.089	0.013*	0.025	
Difference in Change (vs. Placebo)				
Mean	4.0	6.0	5.6	
Confidence Interval	(-1.6 – 9.6)	(0.4 – 11.6)**	(-0.3 – 11.5)	

Source: Post-text Table 10.1 of the Sponsor's final report and reviewer's analysis
*Significantly different from placebo, after adjusting for multiplicity using the conservative Bonferroni method
** Significantly different from placebo using Dunnett's 2-sided t-test

Table 13 Dose-response analyses of changes in SSBP and SDBP from Visit 5 to Visit 7, randomized withdrawal phase, ITT population

Parameter	Estimator	S.E. of Estimator	T-value	P-value
SSBP				
Intercept	-5.61	1.40	-3.99	0.0001
Slope	0.13	0.07	1.96	0.053
SDBP				
Intercept	-5.62	1.26	-4.45	< 0.0001
Slope	0.11	0.06	1.83	0.071

Source: Le, Charles' analysis. The dependent variable is the change from Visit 5 to Visit 7 in SSBP or SDBP, the independent variable is dosage

Table 14 Changes from Visit 5 to Visit 7 in SSBP and SDBP (mm Hg) by subgroup, randomized withdrawal phase, ITT population

		Low Dose	Medium Dose	High Dose	Placebo
SSBP	Gender				
	Male (N)	10	16	15	10
	Mean (S.D.)	+1.0 (10.1)	+0.5 (9.8)	+3.7 (5.6)	+7.1 (7.8)
	P-value	0.112	0.058	0.333	
	Female (N)	14	7	4	9
	Mean (S.D.)	+6.0 (7.5)	+2.0 (5.7)	-3.5 (8.6)	+8.0 (11.5)
	P-value	0.589	0.175	0.033	
	Race				
	Caucasian (N)	14	15	9	10
	Mean (S.D.)	+2.9 (8.8)	+0.87 (8.9)	+1.9 (8.1)	-10.5 (11.3)
	P-value	0.053	0.015	0.050	
	Non-Caucasian (N)	10	8	10	9
	Mean (S.D.)	+5.4 (9.0)	+1.1 (8.8)	+2.5 (5.7)	+4.2 (5.9)
	P-value	0.734	0.400	0.620	
	Weight				
	20-50 kg (N)	9	3	4	4
	Mean (S.D.)	+1.2 (7.2)	+6.7 (6.7)	+3.5 (6.4)	-10.5 (11.2)
	P-value	0.069	0.535	0.229	
	> 50 kg (N)	15	20	15	15
	Mean (S.D.)	+5.5 (9.5)	+0.1 (8.7)	+1.9 (7.0)	-6.7 (9.2)
	P-value	0.706	0.029	0.130	
	Age				
	7 – 11 Years Old (N)	10	2	3	3
	Mean (S.D.)	+5.0 (6.5)	-16.5 (4.9)	+4.0 (5.6)	-1.0 (3.5)
	P-value	0.321	0.006	0.544	
	12 – 16 Years Old (N)	14	21	16	16
	Mean (S.D.)	+3.1 (10.3)	+2.6 (6.9)	+1.9 (7.1)	-8.8 (9.8)
	P-value	0.076	0.033	0.025	

SDBP					
	Gender				
	Male (N)	10	16	15	10
	Mean (S.D.)	+1.9 (4.2)	+2.2 (7.8)	+3.4 (6.2)	-6.9 (9.0)
	P-value	0.120	0.105	0.231	
	Female (N)	14	7	4	9
	Mean (S.D.)	+5.3 (7.4)	+1.3 (8.7)	-2.0 (11.0)	-9.0 (8.8)
	P-value	0.312	0.080	0.039	
	Race				
	Caucasian (N)	14	15	9	10
	Mean (S.D.)	-2.9 (5.9)	-3.0 (7.3)	-1.3 (9.2)	-9.5 (10.3)
	P-value	0.051	0.053	0.032	
	Non-Caucasian (N)	10	8	10	9
	Mean (S.D.)	+5.3 (7.1)	+0.1 (9.1)	+3.1 (5.7)	+6.1 (6.7)
	P-value	0.807	0.083	0.368	
	Weight				
	20-50 kg (N)	9	3	4	4
	Mean (S.D.)	-1.9 (3.6)	+5.0 (12.3)	+2 (10.1)	+5.3 (9.9)
	P-value	0.152	0.968	0.569	
	> 50 kg (N)	15	20	15	15
	Mean (S.D.)	+7.3 (5.1)	+1.5 (7.4)	+2.3 (7.0)	+8.6 (8.6)
	P-value	0.630	0.005	0.020	
	Age				
	7 – 11 Years Old (N)	10	2	3	3
	Mean (S.D.)	+2.0 (6.7)	-6.0 (15.5)	+6.7 (4.6)	+8.0 (7.8)
	P-value	0.251	0.064	0.833	
	12 – 16 Years Old (N)	14	21	16	16
	Mean (S.D.)	+5.2 (6.1)	+2.7 (7.0)	+1.4 (7.7)	+7.9 (9.1)
	P-value	0.340	0.042	0.019	

Source: Le, Charles analysis (Statistician). P-values were from ANOVA. The dependent variable is the change from Visit 5 to Visit 7 in SSBP or SDBP, the independent variable is treatment group.

APPENDICES

Appendix1: Safety details

Details of adverse events that led to discontinuation of the study

Subject 01-2002: Discontinued from the study because of insomnia and hyperactivity after being in the study for eight days and after starting his/her medium dose (20 mg).

Subject 15-2002: Discontinued for acute renal failure and kidney transplant rejection 16 days after enrollment while on high dose (40 mg).

Subject 15-2007: Discontinued for tongue edema six days after enrollment while taking low dose (10 mg). Patient also developed rash and pruritus.

Subject 35-1002: Discontinued for increased blood creatinine 12 days after enrollment and while taking medium dose (10 mg).

Subject 36-2001: Discontinued for hypertensive crisis five days after enrollment in the study while on low dose (10 mg).

Subject 44-1003: Discontinued because of kidney transplant rejection based on her end of dose-escalation phase lab evaluation. Patient was taking high dose (20 mg) up to the day prior to diagnosis.

Subject 44-2004: Discontinued because of a second episode of non-specified rash in the open label phase while he/she was taking 40 mg.

Subject 46-2001: Discontinued because of increased ALT in the open-label dose phase while he/she was taking 60 mg.

Subject 46-2003: Discontinued because of aggravated cough 36 days since the beginning of the open-label dose phase and while taking 40 mg.

Details of cases that developed symptoms of angioedema

Subject 15-2007: Patient was on low dose (10 mg) in the dose-escalation phase. Two days after being on study drug he/she developed edema of the tongue, two days later he/she developed a macular rash and another two days later he/she had pruritus. Patient was not discontinued until six days after beginning of treatment. Race is caucasian.

Subject 21-2002: Developed edema of the face five days after being on low dose (10 mg) in the dose-escalation phase. Patient was not discontinued from study and nothing is known about the date of resolution. Race is black.

Subject 28-1001: Developed eyelid edema two days after being started on low dose (5mg) in the open-label phase. He was not discontinued from study and duration of AE is reported to be one day and no treatment was given. Race is caucasian.

Details of cases with serious adverse events

Dose Escalation Phase

Subject 15- 2002: hospitalized for acute renal failure and kidney transplant rejection 15 days after the start of treatment with 40 mg benazepril. Patient is a 16 year- old, black female who had a history of end stage renal disease. She was treated with intravenous prednisone and recovered.

Subject 35- 1002: routine post renal transplant labs revealed an increased creatinine (1.6 mg/ dL) 11 days after beginning of treatment with 5 mg benazepril. The subject discontinued further use of benazepril because of her elevated creatinine. An ultrasound performed two days later showed hydronephrosis/ obstruction of the kidney. The subject was hospitalized for a urology work-up and possible stent surgery. She is an 11 year- old, Caucasian female with a history of renal transplant, grade 2- 3 vesico-ureteral reflux, and post infectious glomerular nephritis.

Subject 36- 2001: hospitalized for hypertensive crisis 4 days after the start of benazepril treatment. Patient is a 16 year- old, Oriental male and his hypertension resolved two days after discontinuation of benazepril.

Subject 44- 2002: Seventeen days after enrollment patient was hospitalized for treatment of a urinary tract infection while taking 10 mg benazepril. During the open- label phase, the subject again was hospitalized for an urinary tract infection and was discontinued from the study because of administrative problems. Patient was a 14 year- old, black female with a history of urinary tract infection.

Randomized Withdrawal Phase

Subject 44- 1003: The end of dose-escalation phase laboratory work revealed an increased creatinine level in this patient while she was taking 20mg of the study drug. The subject was hospitalized for kidney transplant rejection that was confirmed by a kidney biopsy. Patient is a 12 year- old, black female with a history that included renal failure, kidney transplant, and acute renal rejection. Patient was discontinued from study.

Open- Label Phase

Subject 01- 2008: severe sleep apnea during the open- label. The subject had a tonsillectomy and adenoidectomy for his sleep apnea and was hospitalized overnight for observation. Patient is an 11 year- old, black male.

Subject 06- 1002: two hospitalizations during the open-label phase for pyelonephritis, and for urinary tract infection and increased blood creatine. Patient is a 10 year- old, Caucasian female with a history of recurrent urinary tract and cytomegalovirus infections. The subject completed the dose escalation phase but because of an unsatisfactory therapeutic response did not enter the randomized withdrawal phase. The subject was entered directly into the open- label phase on a 20 mg dose of benazepril.

Subject 25- 1002: hospitalization for bowel obstruction during the open-label phase while patient was taking 10 mg. Patient is a 12 year- old, Caucasian male, with a history that

included congenital tracheo- esophageal fistula, gastro- esophageal reflux disease, renal failure, and various surgical procedures including multiple bladder surgeries, colostomy, duodenal operation, and urethral repair.

Subject 36- 2012: hospitalization for expressing suicidal thoughts at a group therapy meeting during the open-label phase. Patient is a 15 year- old, Caucasian male, had a medical history that included depression.

Details of cases with clinically significant laboratory changes

Subject 36-2012: Patient had an AST level of 22 at screening which increased to 28 U/L at the end of the dose escalation phase, reached a level of 42 U/L by the end of the randomized phase during which the patient was taking 20 mg of benazepril. This change in liver function was reported to be clinically significant. At visits 8 and 9 this level has come down to 22 and 24 U/L respectively.

Subject 36-2009 developed hyperbilirubinemia by the end of the open-label phase, month six of the study. Bilirubin level went from 0.87 prior to the open-label phase to 2.5 mg/dL at the end of this phase.

Subject 46-2001 was discontinued from the study because of increased AST and ALT levels at the three-month follow-up of the open-label phase while he was taking 60 mg of benazepril. Over the course of the study The AST and ALT levels went from 23 U/L and 21 U/L at visit 1 to 34 U/L and 52 U/L at visit 8. Repeated measurements one month later showed a sustained increase which led to discontinuation from the study. Six days after drug discontinuation AST and ALT levels were still high and even went higher to 46 and 72 U/L. No CRF was provided and no information on patient's medical history except that he is a 14-year old Caucasian male who weighs 93 kg and who has no remarkable medical history.

Subject 06-1001: Patient entered the study with a high proteinuria (≥ 2000 mg/dL) but this was not assessed at other visits. He developed hyperkalemia (5.8mEq/L) at the end of the randomized withdrawal phase during which he received placebo. He remained hyperkalemic throughout the open-label phase and his potassium level at the end of this phase was 6.3 mEq/L.

Subject 20-1004: Patient entered the study with a moderately high creatinine level (1.6 mg/dL) that was maintained at the same level between 1.4 and 1.6 mg/dL at further study visits. Patient also developed proteinuria that went from 30 at screening to 300 mg/dL at the end of the randomized phase and his/her BUN level increased from 18 prior to the open-label phase to 27 mg/dL at the end of the open-label phase.

Subject 20-2003: Patient developed hyperkalemia. His/her potassium level increase from 4.6 assessed at the end of the dose escalation phase to 5.6 mEq/L at the end of the randomized withdrawal phase during which patient was taking 40 mg of benazepril.

Subject 46-2003 developed neutropenia at the end of the randomized withdrawal phase during which he/she was taking 20 mg of benazepril. His/her WBC count went from 5.4 at screening to 2.6 $10^3/mm^3$ at visit 7.

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