Medical Review

NDA No.: 19-915 (S-037)
Drug Name: Monopril® (fosinopril sodium)
Sponsor: Bristol-Myers Squibb
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EXECUTIVE SUMMARY

INTRODUCTION

Monopril® (fosinopril sodium, tablets of 10, 20 and 40 mg strength), NDA 19-915, is approved for the treatment of hypertension and the management of heart failure as adjunctive therapy when added to conventional therapy.

This medical review evaluates the results from two pediatric studies submitted by the sponsor, Bristol-Myers Squibb, in response to a written request for studies in pediatric hypertensive patients for fosinopril sodium. The sponsor provided full reports for the following studies: Protocol CV118-027 entitled "The Pharmacokinetics of Fosinopril in Children and Adolescents" a pharmacokinetics study of fosinoprilat, the active metabolite of fosinopril, and Protocol CV118-028 entitled "Study of Blood Pressure Reduction with Fosinopril in Children and Adolescents" a clinical study to assess the antihypertensive effect of fosinopril.

SUMMARY/CONCLUSIONS

The study Protocol CV118-028 had a randomized, double blind, placebo-controlled and dose-ranging design. Doses evaluated of fosinopril sodium, in the treatment of children and adolescents (age 6 to 16 years) with hypertension and high-normal blood pressure, included 0.1 mg/kg, 0.3 mg/kg and 0.6 mg/kg. In this study the sponsor used a tablet formulation of fosinopril with the following strengths: 1.25 mg, 2.5 mg, 5 mg, 10 mg, and 20 mg. Study medication was titrated up to the assigned target dose after the first week of study treatment. The fosinopril sodium doses that were used in this dose-ranging study were selected by determining the per kilogram dose of fosinopril for a 70 kg adult for both the lowest and highest doses approved for the treatment of hypertension. The sponsor selected trial design C, i.e., placebo withdrawal phase, to test the efficacy of fosinopril sodium as an antihypertensive drug in subjects within the pediatric age group. Thus, the study evaluated the effectiveness of a range of fosinopril doses in the treatment of male (65.6%) and female (34.4%) children [6 to 12 years of age, n=140 (55%)] and adolescents [13 to 16 years of age, n=113 (45%)] with hypertension or high-normal BP. The distribution (%) of races between placebo- and fosinopril-treated subjects in the double-blind placebo-controlled phase of study protocol CV118-028 was as follows: White 59.1% vs. 60.2%, Black 23.6% vs. 16.7%, Asian 2.4% vs. 1.9%, Hispanic 11.0% vs. 18.5%, Native American 0.8% vs. 0.0%, and Other 3.1% vs. 2.8%. Hypertension was defined as SeSBP or SeDBP $\geq$ 95th percentile for gender, age, and height, on at least 3 sequential occasions. High-normal BP was defined as SBP or DBP $\geq$ 90th percentile and $< 95^{th}$ percentile for gender, age, and height, on at least 3 sequential occasions and with any one of the following clinical conditions: diabetes mellitus (either Type I or Type II), or positive family history of hypertension, or any other condition for which, in the opinion of the investigator, the reduction of BP would be in the best interest of the child or adolescent. Based on the above definition the hypertensive status of the randomized population was as follows: Hypertension 85.8% and High Blood Pressure 14.2%. Two hundred and fifty three subjects were randomized to three doses of fosinopril sodium, 0.1 mg/kg (n=83), 0.3 mg/kg (n=87) and 0.6 mg/kg (n=83), and were treated in a double-blind manner for 4 weeks. Thereafter they were re-randomized in a blinded fashion either to their previous treatment or to be withdrawn to placebo for a total of two more weeks of treatment. Changes in trough SeSBP from baseline at the end of treatment, with an assessment for trend with dose (i.e., a non-zero slope with dose), was the primary response variable. The pre-specified analysis was an intent-to-treat. For SeSBP and SeDBP, the adjusted mean changes from baseline were -10.9, -11.3, and -11.9 mmHg, and -4.5, -4.2, and -5.1 mmHg, respectively. Thus after 4 weeks of treatment the three regimen groups showed adjusted mean decreases from baseline which were similar. The test for trend across these regimen groups revealed no evidence of a dose-response relationship (p=0.53 and p=0.52, respectively). Without evidence of a dose-response relationship, the withdrawal phase provided the opportunity to establish that there was a positive drug effect. In the placebo group, the adjusted mean change for SeSBP represented a statistically significant (p = 0.013) withdrawal effect, which was 3.7 mmHg greater than the mean change in the fosinopril group. The adjusted mean change for SeDBP was 1.6 mmHg higher for the placebo group than for the fosinopril group (p = 0.104). Of note, none of the individual dose groups was significantly different than placebo in the randomized withdrawal phase.

Study protocol CV118-027 assessed the PK of fosinoprilat in 43 hypertensive patients[1] from four pediatric age groups: infants and toddlers (1 month to 2 years, n=10), pre-schoolchildren (>2 years to 6 years, n=14), school-age (>6 years to 12 years, n=10) and adolescents (>12 years to 16 years, n=9). The study had a multicenter, open-label, and single-dose (0.3 mg/kg fosinopril) design. Fosinopril was administered as an oral solution of fosinopril sodium reconstituted with water and diluted with simple syrup. Cmax, and AUC increased with age. There was a marked correlation between both Cmax and AUC and age, body weight and body surface area. On average drug exposure for children up to 6 years of age were ~60% less than those seen in older children. It is not understood whether the noted difference is due to an increase in fosinoprilat clearance and/or a decrease in fosinopril absorption. Cmax and AUC values of fosinoprilat in pediatric patients from 6 to 16 years of age were comparable to those seen in adult patients receiving 20 mg of fosinopril solution. Tmax and T-Half were not significantly affected by age.

Safety outcomes in the sponsor's report included reported adverse events, changes in vital signs, physical examination findings and laboratory test abnormalities. The safety data provided in this submission have been derived from studies protocol CV118-027 and CV118-028. The safety data from the latter study, the major contributor to our understanding of the safety profile of fosinopril sodium in subjects within the pediatric age groups (age 6 to 16 years), come from the double-blind (4 weeks, n=253), double-blind placebo controlled (2 weeks, n=235), and long-term open-label extension (52 weeks) periods. In the double-blind phase of the study 105 and 127 subjects were exposed to fosinopril sodium and placebo, respectively. A total of 209 subjects were enrolled in the long-term open-label, and the mean duration of exposure to any fosinopril sodium dose was 166.9 days (ranging from 1 day to 365 days). No deaths were reported during the studies and there were no cases of angioedema. Overall, with the caveat of few patients evaluated and the short-term exposure, fosinopril appears safe and well tolerated in hypertensive patients within the pediatric age groups age 6 to 16 years, with an adverse event profile similar to that observed in adult patients with hypertension. However, whether the long-term administration of fosinopril to patients within the four pediatric age groups studied would affect their growth and development, including sexual maturation, cannot be determined from the available clinical data. In addition, the safety profile of fosinopril in hypertensive patients within the pediatric age groups 0 months to 16 years have not been studied by the sponsor.

In conclusion, albeit the clinical trial CV118-028 failed to demonstrate a dose-response relationship, the withdrawal phase provided the opportunity to establish that there was a positive drug effect in that a statistically significant difference in changes in SeSBP was demonstrated between the pooled results from the fosinopril groups and placebo group (p=0.0132). Thus, the therapeutic dose range of fosinopril remains indefinable. The long-term safety of fosinopril is not adequately characterized.

RECOMMENDATIONS
Because of the aforementioned deficiencies, including those identified in the Clinical Pharmacology and Biopharmaceutics review, this supplemental application is deemed approvable.

[1] Hypertensive children as determined by blood pressure consistently above the 95th percentile as defined by the 1996 update of the 1987 Task Force Report on Blood Pressure Control in Children criteria or children with blood pressure consistently above the 90th percentile with other risk factors, such as family history of hypertension, renal disease, target organ damage, diabetes mellitus Type I or bronchopulmonary dysplasia.

Protocol No.: CV118028
Phase: III
Title Of Study: Study of Blood Pressure Reduction with Fosinopril in Children and Adolescents
Study Initiation Date: 05-April-2001
Study Completion Date: Short-Term, Double-Blind Portion: 01-April-2002
Open-Label (Period D): Ongoing
Investigators: 78
Study Centers: 78 (62 in the U.S., 4 in Israel, and 12 in Russia)

INVESTIGATIONAL PLAN[2]
Objectives: The primary objective for this study was to evaluate the dose-response relationship in change from baseline in trough seated systolic blood pressure (SeSBP) after 4 weeks of double-blind treatment (end of initial treatment Period B) with low, medium, or high doses of fosinopril in children and adolescents age 6-16 years who at baseline have SeSBP or seated diastolic blood pressure (SeDBP) ≥ 90th percentile for age, gender, and height.
The secondary objectives included:

1. To evaluate the change from the end of the initial treatment period (Period B) to the end of the withdrawal period (Period C) in trough SeSBP for fosinopril (all three levels combined) vs. placebo. This was to be the first secondary objective in the event the primary analysis failed to show a statistically significant dose-response relationship.
2. To evaluate the dose-response relationship in change from baseline in trough SeDBP at the end of the initial treatment period (Period B).
3. To evaluate the change from the end of the initial treatment period (Period B) to the end of the withdrawal period (Period C) in trough SeDBP for fosinopril (all three levels combined) vs. placebo.
4. To evaluate the percentage of subjects who reach a target BP of < 90th percentile for systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the end of the initial treatment period (Period B).
5. To assess the safety and tolerability of fosinopril in the pediatric population.

Methodology: This multinational, multicenter, randomized, double-blind, dose-ranging and parallel group study evaluated the safety and effectiveness of a range of daily doses of fosinopril in the treatment of children and adolescents with hypertension (HTN) or high-normal blood pressure (BP) and either diabetes mellitus, or family history of hypertension, or any other condition for which, in the opinion of the investigator, the reduction of BP would be in the best interest of the child or adolescent. Hypertension and high-normal BP were defined as SeSBP or SeDBP ≥ 95th percentile and SeSBP or SeDBP ≥ 90th percentile and < 95th percentile, respectively, for gender, age, and height, on at least 3 sequential occasions.[3] Patients were excluded from the study is they had, among others, a history of hypersensitivity or intolerance to ACE inhibitors or idiopathic angioedema, malignant hypertension, severe HTN not controlled by ACE inhibitors, obesity that would limit BP measurement, bilateral renal stenosis, known solitary kidney with renal artery stenosis, marked coartation of the aorta, and clinically important abnormal laboratory findings.

Doses[4] **And Treatment Regimen:**

- Maximum 10 day lead-in (Period A) - All subjects received a single test-dose of fosinopril 0.1 mg/kg.
- Four-week double-blind initial treatment (Period B) - All subjects titrated up to the assigned target dose (0.1 mg/kg, 0.3 mg/kg, and 0.6 mg/kg) after one week of fosinopril therapy.

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[2] See Appendix, Table 5.8A.
[3] At all visits during the study, BP measurements were obtained using the Device for Indirect Noninvasive Automatic Mean Arterial Pressure (DINAMAP).
[4] The fosinopril doses that were used in this dose-ranging study were selected by determining the per kilogram dose of fosinopril for a 70 kg adult for both the lowest and highest doses approved for the treatment of hypertension. For fosinopril, the range of approved doses for the treatment of hypertension in adults is 10 mg to 40 mg.

- Maximum two-week double-blind withdrawal phase (Period C) - Subjects at each dose level were randomly allocated to receive placebo, or continue on the assigned target dose of fosinopril taken during Period B.
- Fifty-two weeks open-label therapy (Period D) - Open-label extension of fosinopril therapy (0.1 mg/kg, 0.3 mg/kg, and 0.6 mg/kg). All subjects were reintroduced to fosinopril at the 0.1 mg/kg dose. To achieve BP control, fosinopril could be titrated to 0.3 mg/kg and then to 0.6 mg/kg. The use of adjunctive antihypertensive therapy to control BP was permitted only during Period D. Period D is ongoing.

Maximum fosinopril dose was not to exceed the adult dose of 40 mg regardless of the subject's body weight (see APPENDIX, Table 5.5.1). The study used a tablet formulation of fosinopril with the following strengths: 1.25, 2.5, 5, 10, and 20 mg.

Antihypertensive therapy other than the study drug was not permitted during the randomized, double blind treatment periods (Period B and Period C). Before the subject could participate in the study, current antihypertensive medication was withdrawn at the enrollment visit according to the recommended washout times specified in the protocol and the judgment of the investigator. The use of adjunctive antihypertensive agents to control BP was allowed only during the open-label, long-term extension period (Period D) at the discretion of the investigator.

Subjects who tolerated the test dose and satisfied the inclusion and exclusion criteria were eligible to enter the 4-week, randomized, double blind treatment period (Period B). Subjects were randomly assigned to one of three fosinopril regimens and study medication was titrated up to the assigned target dose after the first week of study treatment as shown below.[5]

Table 1. Fosinopril Randomized Dosing Regimens during Double-Blind Therapy (Period B)

Visit	Randomized Dosing Regimen		
	Low-Dose	Medium-Dose	High-Dose
Randomization visit	0.1 mg/kg	0.1 mg/kg	0.3 mg/kg
First week of Rx visit	0.1 mg/kg	0.3 mg/kg	0.6 mg/kg

[NDA 19-915, Protocol CV118028]

All subjects were closely monitored for clinical signs and symptoms of uncontrolled hypertension. Subjects were discontinued from Period C, with the option to enter directly into Period D, i.e., 52-week open-label extension period, if:

1. The investigator felt that continuing in Period C was no longer in the best interest of the subject,
2. The subject experienced an increase in BP
3. The subject showed clinical signs or symptoms of uncontrolled hypertension.

Criteria For Evaluation

Primary Efficacy Outcome Measure: Change from baseline in trough SeSBPs for low, medium, and high dose fosinopril-treated subjects after 4 weeks double-blind treatment (Period B).

Secondary Efficacy Outcome Measures:

1. Difference at the end of the withdrawal period (Period C) in change from the end of the initial treatment period (Period B) in trough SeSBP for fosinopril (all three levels combined) vs. placebo (from all three levels combined)
2. Change from baseline in trough SeDBPs for low, medium, and high dose fosinopril-treated subjects after 4 weeks double-blind treatment (Period B)
3. Difference at the end of the withdrawal period (Period C) in change from the end of the initial treatment period (Period B) in trough SeDBP for fosinopril (all three levels combined) vs. placebo (from all three levels combined)
4. Percent of subjects with both SeSBP and SeDBP < 90th percentile at the end of 4 weeks treatment with double-blind study medication (Period B)

Safety: Evaluation of AEs and laboratory abnormalities.

[5] Subjects who were unable to tolerate titration to the assigned target dose were eligible to directly enter open-label therapy (Period D).

Pharmacokinetic And Pharmacodynamic Variables: No pharmacokinetic or pharmacodynamics evaluations were performed in this protocol.

Statistical Methods: All randomized subjects[6] were included in the efficacy analyses. Comparisons among regimen groups (Period B) and treatment groups (Period C) were carried out for SeSBP and SeDBP. The variables analyzed in all cases were change from baseline for Period B, and change from the final week of Period B for Period C. For Period B a trend test for possible dose-response relationship among the three regimens was carried out in the intended final relative doses of 0.1, 0.3, and 0.6 mg/kg. In accordance with prior plan the analyses in Period C compared the two combined treatment groups of any placebo and any fosinopril.
Safety analyses included all subjects who received at least one dose of study drug. The incidence of clinical and laboratory AEs (number [%] of subjects experiencing AEs) are presented for the overall AEs, by system organ class, and by preferred term. Laboratory analyses included the evaluation of marked abnormalities.

RESULTS
Protocol Deviations/Violations: Significant protocol violations, defined as those that could affect the primary efficacy assessment, are shown in the Appendix, Table S.7.3B.

Interim Monitoring and Analyses: No interim analyses were planned or conducted.

Unblinding: In the course of routine monitoring as well as during a formal site audit, irregularities in dispensing Period B study drug that may have compromised the blind in 2 subjects were identified at Site #0085. There was no evidence to suggest that the site personnel were aware of the blinded information. Both subjects continued in the study.

Changes in the Conduct of the Study: Five (5) amendments were issued to Protocol CV118028 after study initiation. These included the addition of a inclusion criterion, and several exclusion criteria. Other changes addressed minor clarifications or modifications to existing protocol procedures, administrative changes, and typographical corrections.

Study Population
Disposition of Subjects: A total of 376 subjects were enrolled into the study at 78 study sites located in U.S (62 sites), Russia (12 sites), and Israel (4 sites). Of these, 255 received the fosinopril test dose. Two hundred fifty-three (253) subjects were assigned to randomized, double-blind therapy with fosinopril in Period B. A total of 235 subjects were enrolled into the randomized, double-blind, placebo withdrawal period (Period C). Two hundred nine (209) continued into the open-label, long-term extension phase, Period D. The first subject was enrolled on 05 April 2001 and the last subject completed the short-term, double-blind study phase on 01 April 2002. The disposition of subjects for the different study periods is summarized in Tables 2 and 3.

[6] The sample size was based on the primary comparison, which is the trend test for low, medium, and high dose regimens of fosinopril with respect to changes in trough SeSBP after 4 weeks of once-daily treatment administration in the double-blind Period B of the study. Change in trough SeSBP from baseline at the end of week 4 was the primary response variable, assessed for trend with dose by means of a contrast test in an analysis of covariance (ANCOVA) model. A sample size of 62 subjects per dose level was estimated to provide 80% power to detect a trend across the three dose regimens in the primary response variable. A two-sided contrast test at the 0.05 level was assumed. It was also assumed that the true response in SeSBP is linear in relative dose and differs by 6.0 mmHg between the high and low dose regimens. Contrast coefficients linear in the relative doses, i.e., coefficients of -7, -1, +8, were to be used, corresponding to the relative doses of 0.1, 0.3, and 0.6 mg/kg respectively.

Table 2: Summary of Subjects Who Discontinued During Double-Blind Period B and Reasons for Discontinuation

	Fosinopril 0.1/0.1 mg/kg	Fosinopril 0.1/0.3 mg/kg	Fosinopril 0.3/0.6 mg/kg
No. of Subjects Randomized	83[a]	87	83
No. of Subjects Treated	82[a]	87	83
No. of Subjects Discontinued Period B and Enrolled into Period D	3	0	0
No. of Subjects Discontinued Period B Completely (Not Enrolled in Period D)	6	1	4
Reason for Discontinuation			
Withdrew consent	4[a]	0	2
Non-compliance	0	1	0
Lost to follow-up	1	0	1
Adverse event	0	0	1
Other	1[b]	0	0
No. of Subjects Completing Period B	74	86	79

[Sponsor's analysis, MDA 19-915, Protocol CV118028, Table 8.1.2. [a] Subject 0069/005 was randomized but study medication was not dispensed. Parent withdrew consent after randomization. [b] Subject 0133/006 discontinued due to unspecified laboratory abnormalities. [c] Two subjects (0010/008 and 0069/001) completed Period B and were enrolled directly into Period D. [d] Two subjects (0017/001 and 0119/003) completed Period B but did not continue in the study.]

Table 3: Summary of Subjects Who Discontinued During Withdrawal Period C and Reasons for Discontinuation

	Placebo	Fosinopril 0.1 mg/kg	Fosinopril 0.3 mg/kg	Fosinopril 0.6 mg/kg
No. of Subjects Randomized	127	38	34	36
No. of Subjects Treated	127	38	34	36
No. of Subjects Discontinued Period C and Enrolled into Period D	5	0	1	0
No. of Subjects Discontinued Period C Completely (Not Enrolled in Period D)	6	0	1	0
Reason for Discontinuation				
Withdrew consent	1	0	0	0
BP≥ 90th percentile	1	0	0	0
Adverse event	1	0	0	0
Other	3	0	1	0
No. of Subjects Completing Period C	116	38	32	36

[Sponsor's analysis, MDA 19-915, Protocol CV118028, Table 8.1.3.]

Demographic characteristics: Demographic characteristics of all randomized subjects are presented in table 4.

Table 4. Baseline Demographic Characteristics

Demographic Characteristic	Fosinopril 0.1/0.1 mg/kg N = 83	Fosinopril 0.1/0.3 mg/kg N = 87	Fosinopril 0.3/0.6 mg/kg N = 83
Age (years)			
Mean (SD)	12.0 (2.8)	12.0 (2.6)	12.3 (2.5)
Range	6 - 16	7 - 16	6 - 16
Age Group: n (%)			
6 - 12 years	46 (55.4)	47 (54.0)	47 (56.6)
13 - 16 years	37 (44.6)	40 (46.0)	36 (43.4)

Gender: n (%)			
Male	51 (61.4)	63 (72.4)	52 (62.7)
Female	32 (38.6)	24 (27.6)	31 (37.3)
Race; n (%)			
White	49 (59.0)	53 (60.9)	50 (60.2)
Black	12 (14.5)	20 (23.0)	20 (24.1)
Asian	2 (2.4)	1 (1.1)	2 (2.4)
Hispanic	17 (20.5)	9 (10.3)	9 (10.8)
Native American	1 (1.2)	0	0
Other	2 (2.4)	4 (4.6)	2 (2.4)
Height (cm)			
Mean (SD)	156.0 (17.4)	157.4 (16.5)	158.9 (15.8)
Range	103.0 - 193.5	117.0 - 186.7	112.3 - 189.0
Weight (kg)			
Mean (SD)	71.1 (30.4)	75.8 (32.9)	73.8 (28.5)
Range	22.2 - 178.8	24.3 - 168.6	18.0 - 165.4
Hypertensive Status: n (%)			
High-normal BP	12 (14.5)	15 (17.2)	9 (10.8)
Hypertension	71 (85.5)	72 (82.8)	74 (89.2)
Hypertension Duration (months)			
Mean (SD)	15.3 (25.9)	18.4 (29.0)	18.4 (28.9)
Range	0.1 - 168.3	0.2 - 142.2	0.4 - 152.1
Region: n (%)			
North America	52 (62.7)	61 (70.1)	55 (66.3)
Europe	31 (37.3)	26 (29.9)	28 (33.7)

[NDA 19-915, Protocol CV118028, Table 8.3A.]

According to the sponsor, a total of 91 (36.0%) randomized subjects had received antihypertensive therapy prior to study entry. The percentage of subjects who received antihypertensive agents prior to study entry was similar across the fosinopril treatment regimens. The most frequent classes of antihypertensive agents reported at enrollment were ACE-I (19.8%) and dihydropyridine derivatives (14.6%).

Extent of Exposure: In Period B the overall mean duration of exposure to fosinopril was 26.9 days and was similar across the fosinopril treatment regimens. The mean days of exposure to Period C study drug was the same in the placebo and the combined fosinopril dose groups, i.e., 13.9 days and was also similar across the fosinopril treatment regimens.

Treatment Compliance: Subject 0065/007 discontinue during Period B and Subject 0017/001 discontinued the study after completing Period B because of non-compliance.

Concomitant Therapy: Class and frequency of concomitant medications use during Period A, the 4-week double-blind treatment period (Period B), and the 2-week double-blind, placebo withdrawal period (Period C) were similar among the groups.[7]

Efficacy Results

Mean Changes from Baseline in Trough SeDBP and SeSBP at Week 4 of Period B: The primary endpoint was change in SeSBP from baseline. Results for the primary (observed case instead of intent-to-treat analysis) analysis of SeSBP and the corresponding analysis of SeDBP for change from baseline to Week 4 of Period B, appear in Table 5. The results for the intent-to-treat analysis using last observation carried forward were similar to the observed case analysis.[8]

[7] NDA 19-915, Protocol CV118028, Appendix 9.4.
[8] See the statistical Review by Dr. John Lawrence, FDA, HFD-710.

According to the sponsor, for SeSBP, the adjusted mean changes from baseline are -10.9, -11.3, and -11.9 mmHg for the low, medium, and high-dose fosinopril treatment regimens, respectively. Thus the three regimen groups show adjusted mean decreases from baseline which are similar. The test for trend across these regimen groups reveals no evidence of a dose-response relationship (p = 0.53). For SeDBP, the adjusted mean changes from baseline are -4.5, -4.2, and -5.1 mmHg for the low, medium, and high-dose fosinopril treatment regimens, respectively. Thus again the three regimen groups show adjusted mean decreases from baseline which are similar. And again, the test for trend across these regimen groups reveals no evidence of a dose-response relationship (p = 0.52).

Table 5. Mean Changes from Baseline in Trough SeDBP and SeSBP at Week 4 of Period B: Randomized Subjects (observed case analysis)

	Fosinopril 0.1/0.1 mg/kg N = 83	**Fosinopril 0.1/0.3 mg/kg N = 87**	**Fosinopril 0.3/0.6 mg/kg N = 83**
Trough SeSBP (mmHg)			
n	73	86	79
Baseline Mean (SD)	134.3 (11.1)	133.1 (12.0)	133.7 (10.6)
Adj. Mean On-Therapy Change from Baseline (SE)	-10.9 (1.2)	-11.3 (1.1)	-11.9 (1.1)
95% Confidence Interval	(-13.2, -8.6)	(-13.4, -9.1)	(-14.2, -9.7)
P-value for the overall trend test			0.5266
Trough SeDBP (mmHg)			
n	73	86	79
Baseline Mean (SD)	71.1 (11.3)	70.8 (9.4)	72.7 (9.2)
Adj. Mean On-Therapy Change from Baseline (SE)	-4.5 (0.8)	-4.2 (0.7)	-5.1 (0.8)
95% Confidence Interval	(-6.0, -3.0)	(-5.7, -2.8)	(-6.6, -3.6)
P-value for the overall trend test			0.5158

[NDA 19-915, Protocol CV118028, Table 10.1.1.]

Therapeutic Response During Period B: The sponsor also calculated, for each visit during Period B, the frequency and proportion of subjects reaching target BP, that is SeSBP and SeDBP less than the 90th percentile based on age, gender, and height.
In keeping with results of the mean changes from baseline, the proportion of subjects reaching target BP show on indication of a dose-response relationship. Of note, at Week 4 nearly half the subjects in each regimen group had reached target BP, 45% for 0.1 mg/kg, 47% for 0.3 mg/kg, and 42% for 0.6 mg/kg.[9]

Mean Changes from Week 4 of Period B to Week 2 of Period C: Without evidence of a dose-response relationship, the withdrawal phase provides the opportunity to establish that there is a positive drug effect and thus to assess the interpretability of the study.
There were relatively small mean increases for both SeSBP and SeDBP from Week 4 of Period B to Week 2 of Period C in the group of patients remaining on fosinopril (any dose regimen of Fosinopril). However, greater increases in BP were observed in the withdrawal group receiving Placebo. In the placebo group, the adjusted mean change for SeSBP represents a statistically significant (p = 0.013) withdrawal effect from the end of Period B, which is 3.7 mmHg greater than the mean change in the fosinopril group. The adjusted mean change for SeDBP was 1.6 mmHg higher for the placebo group than for the fosinopril group, a not statistically significant difference (p = 0.104).[10] The results of the last-observation-carried forward analysis were similar to the observed case results. In the Placebo group, the adjusted mean increase in SeSBP from the end of Period B, after subtracting Monopril, was a statistically significant 3.9 mmHg (p=0.007). For SeDBP, the adjusted increase was a non-significant 1.7 mmHg (p=0.066).[11]

[9] See NDA 19-915, Protocol CV118028, Table 10.1.3.
[10] See Appendix, Figures 10.2.2A and 10.2.2B.
[11] See the statistical Review by Dr. John Lawrence, FDA, HFD-710.

Therefore, based on the Pediatric Written Request this trial is interpretable and has the following interpretation: "line flat, withdrawal slower on active treatment."

Table 6. Mean Changes from Week 4 of Period B in Trough SeSBP and SeDBP at Week 2 of Period C (observed case analysis)

	Any Placebo N = 127	**Any Fosinopril N = 108**
Trough SeSBP (mmHg)		
n	115	116
Baseline Mean (SD)	122.3 (11.1)	120.6 (12.6)
Adj. Mean On-Therapy Change from Baseline (SE)	5.2 (1.0)	1.5 (1.1)
Est. Difference between treatment and placebo with 95 % CI		-3.7 (-6.6, -0.8)
P-value for the difference between treatment and placebo		0.0132
Trough SeDBP (mmHg)		
n	115	116
Baseline Mean (SD)	67.1 (8.1)	66.2 (7.1)
Adj. Mean On-Therapy Change from Baseline (SE)	1.7 (0.7)	0.1 (0.7)
Est. Difference between treatment and placebo with 95 % CI		-1.6 (-3.5, 0.3)
P-value for the difference between treatment and placebo		0.1036

[NDA 19-915, Protocol CV118028, Table 10.2.1.]

Because the aforementioned results are derived from the statistical analysis of pool data, i.e., pools all patients in Period C into two groups regardless of which dose they were receiving in Period B, Dr. John Lawrence analyzed the BP data in Period C within the three cohorts defined by the doses given in Period B. According to his analyses, " For the patients randomized to the low dose in Period B, the adjusted mean changes in Period C were 5.34 (Placebo) and 5.07 (Monopril) and the adjusted p-value is 0.99. For the patients randomized to the middle dose in Period B, the adjusted mean changes in Period C were 5.46 (Placebo) and –0.47 (Monopril) and the adjusted p-value 0.08. For the patients randomized to the high dose in Period B, the adjusted mean changes in Period C were 4.91 (Placebo) and –0.41 (Monopril) and the adjusted p-value is 0.09."
These results indicate that the effect on BP of any of the tested doses of Monopril is not statistically different from Placebo in the randomized withdrawal phase.

Safety Results
The safety and tolerability of fosinopril in this study population was evaluated based on clinical and laboratory AEs, evaluation of laboratory marked abnormalities, changes from baseline in standard safety laboratory analytes, and changes in physical examinations. The analysis of safety includes data from all subjects who received at least one dose of study medication (treated subjects) and participated in the short-term and long-tern portions of the study.
A total of 24 (9.4%) experienced an adverse event, 1 (0.4%) patient had a serious AE, "pupils unequal", which also led to discontinuation following the test dose. Another patient was discontinued from the study because of hypotension, a decrease in BP ≥ 20 mmHg. Thus of the 255 patients that received the fosinopril test dose, 253 patients were randomized, The most frequently reported AEs following the fosinopril test dose were hypotension (15 subjects, 5.9%), cough (2 subjects, 0.8%) and headache (2 subjects, 0.8%). Table 7 summarizes clinical adverse events, serious adverse events, deaths and discontinuations due to adverse events for Period B, the randomized, double-blind treatment period. One patient receiving fosinopril 0.3 mg/kg was discontinued because of blood potassium increased (6.6 mmol/L). Another patient had a serious adverse event that was reported as torticollis.

Table 7. Summary of Clinical Adverse Events During Double-Blind Therapy - Period B

Event	Number (%) of Subjects		
	Fosinopril 0.1/0.1 mg/kg N = 82	**Fosinopril 0.1/0.3 mg/kg N = 87**	**Fosinopril 0.3/0.6 mg/kg N = 83**
Adverse Event	29 (35.4)	47 (54.0)	37 (44.6)
Serious Adverse Event	1 (1.2)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations due to AE[a]	1 (1.2)	0 (0.0)	1 (1.2)

[NDA 19-915, Protocol CV118028, Table 12.1.2. [a]Subject 0133/006 in the low dose group was discontinued because of unspecified laboratory abnormalities that were not reported as adverse events.]

The incidence of clinical and laboratory adverse events, as reported in ≥ 3% of subjects in any treatment regimen during randomized, double-blind therapy (Period B), is presented in Table 8. Headache (13.9%), hypotension (4.8%), cough (3.6%) and elevated blood potassium or hyperkalemia (3.6%) were the most frequently reported adverse events during Period B. The incidence of the aforementioned adverse events appears dose dependent. According to the sponsor, "during Period B, seven subjects had elevations in creatine kinase greater than 3 times the ULN. Of these, 4 subjects had baseline creatine kinase values above ULN. Most subjects had single elevations and experienced no symptoms. One subject had a substantially elevated baseline value (5610 U/L) that decreased throughout Periods B and C (range: 720-1178 U/L). Three (3) subjects continued to experience markedly abnormal creatine kinase levels during Period C."

Table 8. Summary of Clinical and Laboratory Adverse Events as Reported in ≥ 3% of Subjects During Double-Blind Therapy - Period B

Event	Number (%) of Subjects		
	Fosinopril 0.1/0.1 mg/kg N = 82	**Fosinopril 0.1/0.3 mg/kg N = 87**	**Fosinopril 0.3/0.6 mg/kg N = 83**
Headache	7 (8.5)	16 (18.4)	12 (14.5)
Hypotension	3 (3.7)	5 (5.7)	4 (4.8)
Cough	0 (0.0)	4 (4.6)	5 (6.0)
Blood Potassium↑/Hyperkalemia	1 (1.2)	4 (4.6)	4 (4.8)
URI	1 (1.2)	4(4.6)	1 (1.2)
Pharyngitis	2 (2.4)	1 (1.1)	3 (3.6)
Vomiting	3 (3.7)	1 (1.1)	2 (2.4)
Epistaxis	1 (1.2)	3 (3.4)	1 (1.2)
Pyrexia	0 (0.0)	1 (1.1)	3 (3.6)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	3 (3.4)	0 (0.0)

[NDA 19-915, Protocol CV118028, Table 12.1.2.2.]

To reiterate, a total of 235 subjects entered Period C, the randomized, double-blind, placebo withdrawal period, and were re-assigned to either placebo (127 subjects) or to continue fosinopril (108 subjects) at the target dose assigned during Period B. A summary of the incidence of adverse events for Period C is presented in Table 9. The overall incident of adverse events during the two weeks of exposure to study drug in Period C was similar among the groups.
No deaths were reported during the study. No serious adverse events were reported during Period C. One patient was discontinued because of increase bilirubin during Period C.

Table 9. Summary of Clinical Adverse Events During Double-Blind Withdrawal Therapy - Period C

Event	Number (%) of Subjects				
	Placebo N = 127	**Fosinopril 0.1/0.1 mg/kg N = 38**	**Fosinopril 0.1/0.3 mg/kg N = 34**	**Fosinopril 0.3/0.6 mg/kg N = 36**	**Any Fosinopril N = 108**
Adverse Event	43 (33.9)	12 (31.6)	12 (35.3)	13 (36.1)	37 (34.3)
Serious Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations due to AE	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[NDA 19-915, Protocol CV118028, Table 12.1.3.]

Table 10 summarizes common adverse events reported in ≥ 3% of subjects in any treatment regimen during Period C. Headache was the most commonly reported adverse event occurring more frequently in subjects receiving any fosinopril than in the placebo group (14.8% versus 11.0%). However, the very short term exposure coupled with the small number of patients exposed to study drug prevent any valid conclusion as to the safety profile of fosinopril compared with placebo in the pediatric population.

Table 10. Summary of Clinical and Laboratory Adverse Events as Reported in ≥ 3% of Subjects During Double-Blind Withdrawal Therapy - Period C

Event	Number (%) of Subjects				
	Placebo N = 127	**Fosinopril 0.1/0.1 mg/kg N = 38**	**Fosinopril 0.1/0.3 mg/kg N = 34**	**Fosinopril 0.3/0.6 mg/kg N = 36**	**Any Fosinopril N = 108**
Headache	14 (11.0)	4 (10.5)	7 (20.6)	5 (13.9)	16 (14.8)
Back Pain	1 (0.8)	2 (5.3)	1 (2.9)	0 (0.0)	3 (2.8)
Dizziness	1 (0.8)	0 (0.0)	1 (2.9)	2 (5.6)	3 (2.8)
Nasal Congestion	1 (0.8)	0 (0.0)	0 (0.0)	2 (5.6)	2 (1.9)
Ear Infection	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)	2 (1.9)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.6)	2 (1.9)
Blood Potassium ↑ /Hyperkalemia	5 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[NDA 19-915, Protocol CV118028, Table 12.1.3.2.]

More patients receiving fosinopril, any dose, had increases in serum creatinine[12] than those patients receiving placebo, 5 subjects (4.1%) versus 9 subjects (8.9%).[13] During Period C, 11 subjects experienced markedly abnormal creatine kinase levels; 6 subjects in the placebo group and 5 subjects in the combined fosinopril group. In 4 of the 5 subjects randomized to fosinopril, baseline creatine kinase levels were above ULN. In 5 of the 6 placebo subjects, markedly abnormal creatine kinase levels appear to be new occurrences. There was no study discontinuations attributed to elevated creatine kinase levels. Finally, there were no clinically significant changes in body weight in any treatment regimen.

Long-Term Open-Label Extension-Period D:[14] Two hundred and nine subjects were enrolled into Period D and treated with open-label fosinopril, 50 subjects withdrew from the study, 4 subjects completed the study and 155 subjects remain in the study.

Table 11 provides a summary of subjects who discontinued and reasons for discontinuation.

[12] >1.33 times the baseline value.
[13] NDA 19-915, Protocol CV118028, Table 12.5.1.2.
[14] This section presents the study population, exposure, and safety results of Period D for all data received by 16 August 2002.

Table 11. Summary of Subjects Who Discontinued During Open Label Extension Period D and Reasons for Discontinuation

	Any Fosinopril N = 209
Number of Subjects Discontinued	50 (24%)
Reasons for Discontinuations	
Withdrew consent	19
Non-compliance	13
Uncontrolled BP	2
Lost to follow-up	4
Adverse event	4
Other	8

[NDA 19-915, Protocol CV118028, Table 13.1.1B. Uncontrolled BP defined as ≥ 90th percentiles for age gender and height**]**

Subjects entering Period D were reintroduced to fosinopril at 0.1 mg/kg. To achieve BP control (SeSBP and SeDBP < 90th percentile for age, gender, and height or as defined by the investigator), fosinopril could be titrated. Of the 209 subjects who received the initial dose of 0.1 mg/kg, 98 subjects were titrated up to 0.3 mg/kg dose and 33 subjects required titration to 0.6 mg/kg dose. The overall mean duration of exposure to any fosinopril dose was 166.9 days.[15]

No deaths were reported during Period D. A total of 146 subjects (69.9%) experienced at least one adverse event during open-label treatment with fosinopril. Six (2.9%) subjects experienced a serious adverse event and 4 subjects were discontinued due to an adverse event. Table 12 provides the incidence of the most common adverse events as reported by more than 3% of subjects treated with open-label fosinopril. The most frequently reported adverse events were headache (20.1%), nasopharyngitis (9.6%), and cough (9.1%). Hypotension was reported 11 (5.3%) subjects and hyperkalemia was reported in 3 subjects (1.4%).

Table 12. Most Common Clinical and Laboratory Adverse Events, as Reported by More Than 3 Percent of Subjects During Period D Therapy

Adverse Event (Preferred Term)	**Any Fosinopril (N = 209) n (%)**
Headache	42 (20.1)
Nasopharyngitis	20 (9.6)
Cough	19 (9.1)
Pharyngitis	18 (8.6)
Abdominal pain	13 (6.2)
Upper respiratory tract infection	12 (5.7)
Hypotension	11 (5.3)
Vomiting	11 (5.3)
Pyrexia	8 (3.8)
Arthralgia	7 (3.3)
Ear infection	7 (3.3)

[NDA 19-915, Protocol CV118028, Table 13.4.1.2.]

Six subjects reported a serious adverse event: 0008/003 osteotomy, 0010/001 headache, 0013/007 adenoidectomy and tonsillectomy, 0062/001 asthma, 0122/003 hypertension. And four subjects were discontinued due to adverse events: 0019/018 chest pain and Dyspnea, 0086/001 blood creatine kinase increase, 0086/005 blood creatine kinase increase, 0099/001 weight increase. Of note 28 (13.9%) subjects had markedly elevated serum creatinine.[16]

[15] See Appendix, Table 13.2.1.
[16] > 1.33 times the baseline value.

APPENDIX

Table 5.5.1: Fosinopril Target Dose Assignments for Children and Adolescents

Body Weight	Low (0.1 mg/kg)	Medium (0.3 mg/kg)	High (0.6 mg/kg)
≥ 20 kg to < 30 kg	2.5 mg	7.5 mg	20.0 mg
≥ 30 kg to < 40 kg	3.75 mg	10.0 mg	25.0 mg
≥ 40 kg to < 50 kg	5.0 mg	15.0 mg	30.0 mg
≥ 50 kg to < 60 kg	6.25 mg	20.0 mg	40.0 mg[a]
≥ 60 kg	10.0 mg	20.0 mg	40.0 mg[a]

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Source: Appendix 5.1A

[a] Maximum allowable dose

Table 5.8A: Treatment Times and Events Schedule: Periods A and B

	Lead-In Period A[a]		Double-Blind Period B[a]			
End Week		1		1	2	4
Visit Days	**Screen/Enroll[b,c,d]**	**AR[d,e]**	**B1[d,f,g]**	**B8[d,h]**	**B15[d,i]**	**B29[d]**
Consent & Age Appropriate Assent	X					
Medical History	X					
Full Physical Exam	X					X
BP and HR	X	X	X	X	X	X
Tanner Staging	X					
Adverse Events		X	X	X	X	X
Review Con Meds	X	X	X	X	X	X
Standard Safety Lab Tests	X			X[j]	X[j]	X
Serum/Urine Pregnancy Test		X[k]	X[k]			X
Test-dose		X[l]	X[l]			
Enrollment (IVRS)	X					
Randomize (IVRS)		X[m]	X[m,n]			
Titration Step				X		
Monitor 2 - 3 hr in Clinic		X	X	X		
Medication Dispensing		X	X	X		
Medication Count				X	X	X

CV118028

Source: Appendix 5.1A

[a] ± 3 days allowed for all Period A and Period B visits.

[b] Written informed consent and age-appropriate assent, obtained at the screening/enrollment visit prior to discontinuation of antihypertensive medication and prior to performing any other protocol – related procedure. Discontinuation of all previous antihypertensive medications was done at this visit according to the recommended

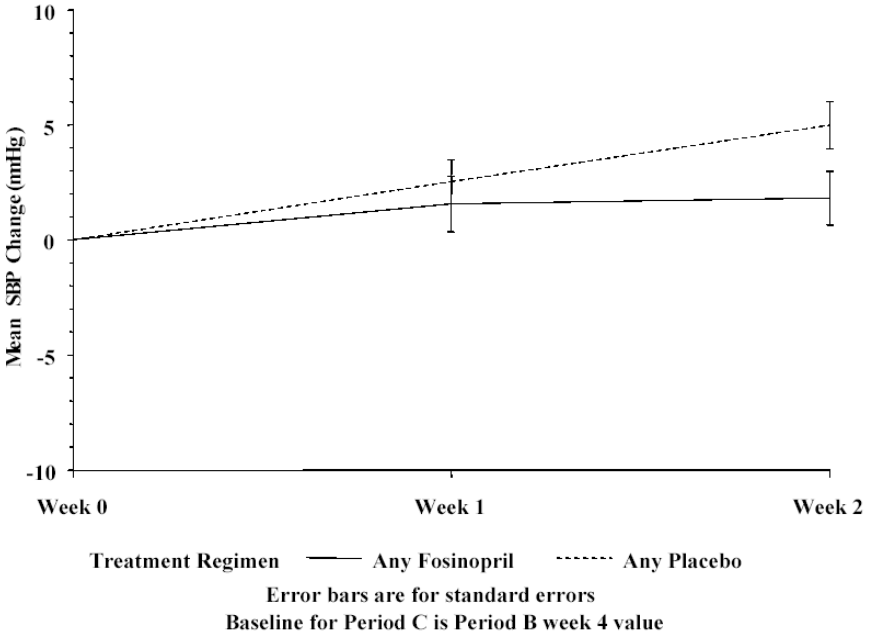
wash-out times listed in Appendix 6 of the Protocol. Withdrawal from any prohibited medication was done in accordance with the manufacturer.s recommendations for withdrawal.
[c] Subjects taking oral contraceptives, methylphenidate, or chronic bronchodilator therapy must have been on therapy at least one month prior to the screening/enrollment visit.
[d] Subjects were not permitted to use oral, intravenous, or subcutaneous bronchodilators 24 hours prior to a scheduled visit. Nebulizers, metered-dose bronchodilator inhalers, or nasal bronchoinhalers were not to be used 6 hours prior to a scheduled visit.
[e] For subjects not previously on antihypertensive therapy, this visit could occur 3 days from the screening/enrollment visit. All subjects withdrawn from antihypertensive therapy at the screening/enrollment visit could return for the Lead-in Period A AR visit according to the recommended wash-out times listed in Appendix 6 of the Protocol.
[f] Visit B1 occurred on the same day as the Lead-in Period A AR visit. Visit B1 occurred within 3 days of the AR visit, if the subject was not randomized at the AR visit.
[g] Each procedure was performed at this visit if not completed at the AR visit.
[h] Subjects unable to tolerate titration to the assigned target dose were to be discontinued from Period B.
[i] This visit could be conducted at home by qualified study staff.
[j] Standard Safety Laboratory Tests were drawn at either Visit B8 or Visit B15, at the investigator's discretion.
[k] Serum or urine pregnancy test was to be performed prior to test-dose administration.
[l] Test-dose was administered only once prior to randomization.
[m] Randomization occurred only if the test-dose was tolerated and all eligibility criteria were met.
[n] Randomization occurred at this visit if not completed at Visit AR during Period A.

Table S.7.3B
Listing of Significant Protocol Violations

Site	Subject	Visit	Visit Date	Visit/Patient Exclusion	Reason Exclude	Violation Reason
006	002	C15	12SEP2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
010	004	B29	02AUG2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
013	004	B29	24AUG2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
013	005	C15	20SEP2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
015	003	B29	01AUG2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
015	003	C15	15AUG2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
015	004	B29	03JAN2002	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
017	002	B29	23OCT2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
019	016	B29	13DEC2001	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours
019	020	B29	14MAR2002	Visit	V YES	Time since last dose (for all trough BP readings) is < 20 or > 28 hours

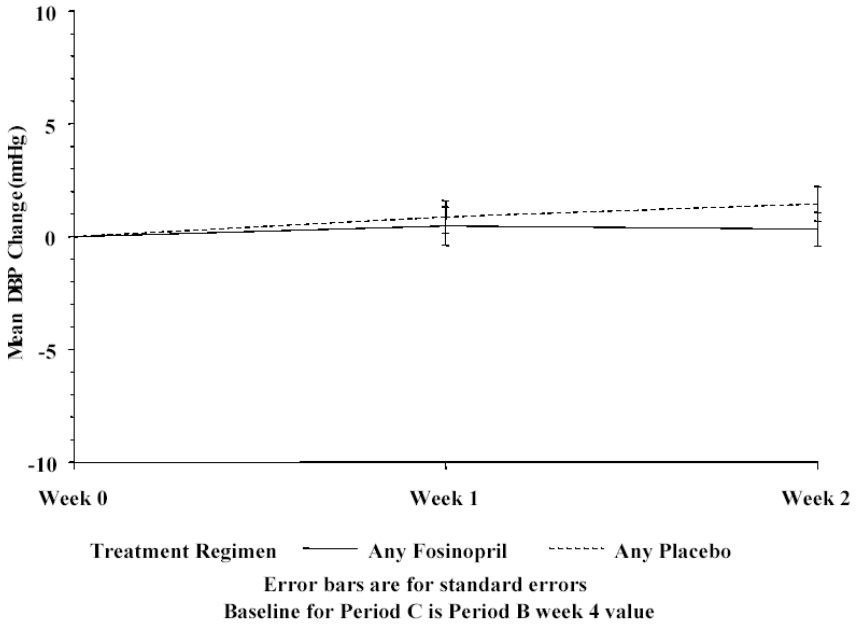
Program Source: /ct/bmspeds/tables/s_sign_protvio.sas Run Date: 20JUN2002

Figure 10.2.2A: Mean Changes from Week 4 of Period B in Trough SeSBP for All Visits in Period C



[NDA 19-915, Protocol CV118028.]

Figure 10.2.2B: Mean Changes from Week 4 of Period B in Trough SeDBP for All Visits in Period C



[NDA 19-915, Protocol CV118028.]

Table 13.2.1: Extent of Exposure to Study Drug During Open Label Extension Period D

	Low[a] N = 209	Medium[a] N = 98	High[a] N = 33	Any Fosinopril N = 209
Duration of Exposure				
1 - 30 days	93 (44.5%)	32 (32.7%)	1 (3.0%)	12 (5.7%)
31 - 60 days	3 (1.4%)	3 (3.1%)	4 (12.1%)	3 (1.4%)
61 - 120 days	15 (7.2%)	18 (18.4%)	10 (30.3%)	14 (6.7%)
121 - 180 days	54 (25.8%)	36 (36.7%)	14 (42.4%)	100 (47.8%)
181 - 270 days	35 (16.7%)	8 (8.2%)	3 (9.1%)	66 (31.6%)
271 - 365 days	9 (4.3%)	1 (1.0%)	1 (3.0%)	14 (6.7%)
> 365 days	0	0	0	0
Mean Days of Exposure	100.1	100.5	125.2	166.9
Total Dose (mg/kg)				
Mean	12.3	30.1	81.4	39.3
Range	0.1 - 55.3	0.3 - 99.4	16.4 - 216.5	0.2 - 232.9

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Reference: Supplemental table S.13.2.1A

[a] Low Dose: ≤ 0.20 mg/kg, Medium Dose: 0.21 - 0.45 mg/kg, High Dose: ≥ 0.46 mg/kg

Protocol No.: CV118027
Phase: I
Title Of Study: The Pharmacokinetics of Fosinopril in Children and Adolescents
Study Initiation Date: 22-Nov-1999
Study Completion Date: 06-Sep-2001
Investigators: 6
Study Centers: 6 (5 in the U.S., and 1 in Ukraine)

INVESTIGATIONAL PLAN
Objectives: The primary objective was to assess the single dose pharmacokinetics of fosinopril including Cmax, Tmax and AUC(INF) in children and adolescents. The secondary objective was to assess the safety of a single dose of fosinopril in this age group.

Dose Calculation And Dosing: The dose for each subject for this study was based on a 0.3 mg/kg dosing paradigm, approximating a 20 mg dose for a 70 kg adult. Doses were given orally as a solution in water with a flavoring added.

Study Design And Methodology:[17] This study was an open-label, multi-center, single-dose study in children of 4 age groups: (1) infants and toddlers, 1 month to 2 years; (2) preschoolers, > 2 years to 6 years; (3) school-age, > 6 years to 12 years; (4) adolescents, > 12 years to 16 years. Following screening procedures including a physical examination, clinical laboratory tests and fulfillment of inclusion and exclusion criteria, each subject was enrolled and received a single oral solution dose of 0.3 mg/kg of fosinopril. Pharmacokinetic samples were obtained at specified times for up to 48 hours after dosing.

Treatment Administration: Subjects received a single dose of 0.3 mg/kg fosinopril. Bottles containing 25 mg of fosinopril sodium powder were supplied for each subject. Prior to drug administration, the powder was dissolved by adding 15 mL of Purified Water USP or Water for Injection USP by syringe to the vial. After the powder was dissolved by shaking, the solution was diluted by adding 10 mL of Syrup, National Formulary (Simple Syrup, NDC 0395-2661-16, Humco, Texas) to the vial followed by shaking. The resulting solution contained 1 mg/mL of fosinopril sodium. Each dose was administered within 6 hours of preparation. A sufficient amount of drug solution was withdrawn with a syringe of appropriate size to provide the 0.3 mg/kg dose, and was administered to the subject orally by a study nurse using the syringe. Any antihypertensive therapy was suspended until 12 hours after the dose of fosinopril.

Inclusion Criteria: Hypertensive children as determined by blood pressure consistently above the 95th percentile as defined by the 1996 update of the 1987 Task Force Report on Blood Pressure Control in Children criteria or children with blood pressure consistently above the 90th percentile with other risk factors, such as family history of hypertension, renal disease, target organ damage, diabetes mellitus Type I or bronchopulmonary dysplasia (BPD).

- Children in four age groups
  - Infants and toddlers: 1 month to 2 years
  - Preschoolers: > 2 years to 6 years
  - School-age: > 6 years to 12 years
  - Adolescents: >12 years to 16 years
- Corrected creatinine clearance of ≥ 25 mL/min/1.73 m2 using the Schwartz formula.
- Serum albumin ≥ 2.5 mg/dL.
- Increase phosphorus and BUN.

Criteria For Evaluation
Efficacy: Not assessed in this single-dose study.

Safety, Tolerability: Safety assessments were based on review of adverse event reports and the results of vital sign measurements, electrocardiograms, physical examinations, and clinical laboratory tests. The incidence of adverse events was tabulated and reviewed for potential significance and clinical importance.

[17] See Appendix, Table 5.8.1.

Pharmacokinetics/Pharmacodynamics: Blood samples (0.8 mL) were obtained at specific time points[18] after dosing for analysis for fosinoprilat, the active metabolite of fosinopril. Sample analysis was performed using a validated assay method. Cmax, Tmax, AUC(INF), AUC(0-T) and T-HALF were calculated using a noncompartmental analysis.

Statistical Methods: Although the sample sizes for this study were not based on statistical power considerations, the data from 8 subjects within an age group would provide 95% confidence that the corresponding sample mean would be within 35% of the true population mean, for any pharmacokinetic parameter with a 45% or less coefficient of variation. Previous studies of fosinopril in healthy adult subjects have reported coefficients of variation for Cmax and AUC ranging from approximately 25% to 45%. Subject demographics, physical examinations, laboratory data, and vital signs were summarized. Incidence of adverse events was tabulated by body system and severity. The distributions of the pharmacokinetic variables were summarized by age group. All available data from all subjects who received study medication were included in the safety and pharmacokinetic summaries.

RESULTS
Study Population
Disposition/Number of Subjects: A total of 43 subjects were enrolled and given fosinopril oral solution. There were 10 subjects in the 1 month to 2 years and in the > 6 years to 12 years groups, 14 subjects in > 2 years to 6 years, and 9 subjects in the > 12 years to 16 years. All enrolled subjects completed the protocol as designed.

Demography and Patient Characteristics: The demographic characteristics of the enrolled subjects are summarized in the following table.

Table 12. Demographic Characteristics of Enrolled Subjects

Characteristic	Fosinopril Oral Solution 0.3 mg/kg			
	1 month to 2 years (N = 10)	> 2 years to 6 years (N = 14)	> 6 years to 12 years (N = 10)	> 12 years to 16 years (N = 9)
Age, years				
Mean	0.83	4.79	9.00	14.11
SD	0.23	0.70	1.83	0.93
Range	0.47-1	3 - 5	7 - 12	13 - 15
Gender, n (%)				
Male	6 (60)	9 (64)	6 (60)	5 (56)
Female	4 (40)	5 (36)	4 (40)	4 (44)
Race, n (%)				
White	10 (100)	13 (93)	2 (20)	3 (33)
Black	0 (0)	1 (7)	8 (80)	6 (67)
Weight, kg				
Mean	10.6[a]	21.2[b]	44.9	91.1
SD	3.82[a]	8.56[b]	26.08	24.0
Range	7.4 - 19.0[a]	16.0 - 46.7[b]	23 -100.0	55.9 - 134.5

[18] Pre-dose, 1, 2, 3, 4, 7, 10, 12, 24 and 36 hrs post-dose.

Height, cm				
Mean	77.8	113.0	137.3	169.9
SD	14.07	7.27	16.09	7.88
Range	60.0 - 98.0	102.0 - 127.0	115.0 - 164.0	160.5 - 184.2
Body Surface Area, m^2				
Mean	0.48[a]	0.81[b]	1.29	2.09
SD	0.123[a]	0.171[b]	0.450	0.319
Range	0.36 - 0.73[a]	0.69 - 1.31[b]	0.86 - 2.18	1.59 - 2.59

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Source: Appendix 8.3

[a] n = 9: The weight of one subject was not recorded at screening and is not included in this table. The weight was obtained on Day of Dosing (14.8 kg) and is within the range presented.

[b] n = 11: The weights of three subjects were not recorded at screening and are not included in this table. Their weights were obtained on Day of Dosing (22 kg, 24.5 kg, and 16.9 kg) and are within the range presented.

[NDA19915, Protocol CV118027, Table 8.3.]

The associated medical conditions and diagnoses were primarily those associated with hypertension.[19]

Extent of Exposure: All subjects received single doses of fosinopril 0.3 mg/kg. No subject discontinued the study.

Pharmacokinetic Results: Individual Cmax, AUC(INF) (0-T), Tmax, and T-Half are presented by age group in Table 14. Subjects 004/005, 006/004 and 006/018 had large variation in plasma concentrations in the terminal elimination, and therefore were excluded from the T-Half pharmacokinetics data set. In these subjects AUC(INF) extrapolation from the last measurable serum time point to infinity could not be performed, and they were also excluded from the AUC(INF) pharmacokinetic data set. Subjects 006/006 and 006/017 had inadequate plasma time data in the terminal phase and also were excluded from the T-Half pharmacokinetic data set. Cmax, and AUC increased with age (Table 13).[20] According to the sponsor there was a marked correlation between both Cmax and AUC and age, body weight and body surface area. Tmax and T-Half were not significantly affected by age.

Table 13. Summary Statistics for Fosinoprilat Pharmacokinetic Parameters

	Pharmacokinetic Parameter				
Age Group	**Cmax (ng/mL) Geom. Mean (C.V.%)**	**AUC(INF) (ng·h/mL) Geom. Mean (C.V.%)**	**AUC(0-T) (ng·h/mL) Geom. Mean (C.V.%)**	**Tmax (h) Median (min, max)**	**T-Half (h) Mean (S.D.)**
1 month to 2 years (n = 10)	70.11 (67%)	559.66[a] (63%)	523.57 (61%)	4.00 (2.00, 7.00)	10.17[b] (2.50)
> 2 years to 6 years (n = 14)	111.43 (66%)	919.92[c] (51%)	844.26 (52%)	3.00 (1.00, 7.00)	11.95[d] (6.08)

[19] NDA 19-915, Protocol CV118027.

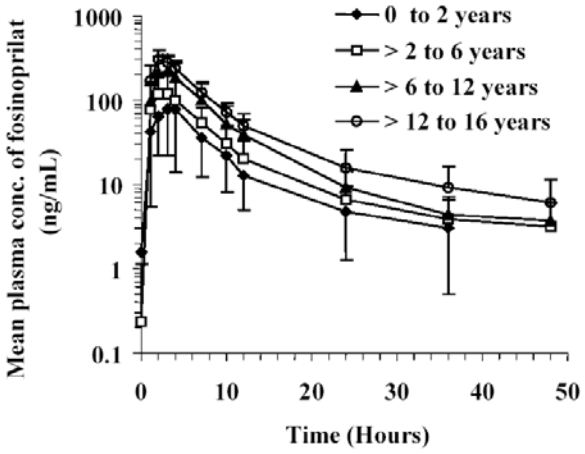
[20] Cmax and AUC (0-T) in adults after a single dose of fosinopril were 272-328 ng/mL and 2019-2630 ng.hr/mL.

> 6 years to 12 years (n = 10)	213.51 (49%)	1741.55[a] (44%)	1506.17 (51%)	3.00 (2.00, 4.00)	10.86[a] (4.04)
> 12 years to 16 years (n = 9)	303.08 (27%)	2475.80 (20%)	2335.56 (18%)	2.00 (2.00, 3.00)	11.81 (6.03)

CV118027
Source: Supplemental Table S.11.2.1C
[a]n = 9, [b]n = 8, [c]n = 13, [d]n = 12
[NDA 19-915, ProtocolCV118027, Table 11.2.1.]

Figure 1 depicts the fosinoprilat plasma concentrations over time for each age group.

Figure 1. Mean (±SD) Serum Concentration vs. Time Profiles of Fosinoprilat in Children and Adolescents



CV118027
Source: Appendix 11.2.1B
Note: To facilitate a concise presentation of the age groups, the "1 month up to 2 years" group was represented in this figure as "0 to 2 years" (i.e., in years only).
[NDA 19-915, Protocol CV118027, Figure 11.2.1A.]

Safety Results
A total of 11 treatment-emergent adverse events were reported in 9 subjects (Table 14). There were no deaths or serious adverse events reported in the study.

Table 14. Number (%) of Subjects with Treatment-Emergent Adverse Events by Age Group.

Body System Primary Term	Number (Percent) of Subjects			
	1 month to 2 years N = 10	> 2 years to 6 years N = 14	> 6 years to 12 years N = 10	>12 years to 16 years N = 9
Gastrointestinal				
Abdominal Pain	0	0	0	1 (11.1)
General				
Fever	1 (10.0)	2 (14.3)	1 (10.0)	0
Local Reaction Administration Site	0	0	0	1 (11.1)
Nervous				
Headache	0	0	0	1 (11.1)

Renal/Genito-urinary Urine Glucose Increase	0	0	0	1 (11.1)
Special Senses Taste Disturbance	0	0	1 (10.0)	2 (22.2)
Total Events[a]	1	2	2	6
Total Subjects	1 (10.0)	2 (14.3)	2 (20.0)	4 (44.4)

CV118027

Source: Appendix 12.1C

[a] Total events may exceed the total subjects or the sum of subjects with events in the age group because some subjects reported more than one event categorized under more than one body system and/or because a single subject may have reported more than one event within the same body system.

There were no significant drug-related changes reported for laboratory variables, vital signs, physical examination findings or ECG. Although, there was a trend for BP to decrease after administration of fosinopril, a consistent antihypertensive effect was not observed.

APPENDIX

Table 5.8.1: Time and Events Schedule

Event	Screening Phase	Study Day	
	Within 14 Days of Study Day 1	1	2
Sign Consent Form and Assent Form[a]	x		
Medical History	x		
Physical Examination	x[b]	x[b]	x
12-lead ECG	x[b]	x[b]	x
Clinical Laboratory Tests	x[b]	x[b]	x
Urine Pregnancy Test[c]	x	x	x
Vital Signs[d]	x	x	x
Study Drug Administration		x	
Serial Blood Pharmacokinetic Sampling		x	x
Monitor Adverse Events		x	x

CV118027

Source: Appendix 5.1A

[a] For age 7 and above.

[b] If the screening procedures were performed within 48 hours of dosing, they counted as both the screening and predose.

[c] Urine pregnancy tests were performed for all females of child bearing potential.

[d] Vital signs were performed every 30 minutes for the first 2 hours and hourly for the next 8 hours following dosing, and at the time of blood draws thereafter.

FINANCIAL DISCLOSURE INFORMATION

The sponsor provided financial disclosure information from the majority of Principal Investigators and Sub-Investigators for the only clinical study Protocol CV118-028. The sponsor was unable to obtain financial disclosure from a few Principal Investigators and Sub-Investigators despite due diligence, at least two attempts were made for each individual. Upon reviewing the financial disclosure information[21] provided by the sponsor on the participating Principal Investigators and Sub-Investigators does not appear to be any conflict of interest that could have led to investigator's bias.

[21] NDA 19-915, Financial Disclosure Information.

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/s/

Juan Carlos Pelayo
4/10/03 01:42:41 PM
MEDICAL OFFICER