

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-386/S-019 and 029**

**Medical Review(s)**



Douglas C. Throckmorton, M.D.  
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
Tel (301) 594-5365, FAX (301) 594-5494

### Memorandum

**DATE:** 10.21.02

**FROM:** Douglas C. Throckmorton, M.D., Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

**SUBJECT:** NDA 21-386/SE5-029,  
**NAME OF DRUG:** Cozaar (losartan hydrochloride)  
**SPONSOR:** Merck and Company

**DOCUMENTS USED FOR MEMO:**

1. Medical Review, including draft labeling, by Avi Karkowsky, M.D., dated 9.27.02.
2. Statistical Review by Jasmine Choi, Ph.D., dated 4.8.02.
3. Clinical Pharmacology and Biopharmaceutics Review by Elena Mishina, dated 9.19.02.
4. Chemistry Review by Ram Mittal, Ph.D., dated 10.18.02.

**CONCLUSIONS**

This memorandum constitutes the secondary Medical review for the named supplement as well as the Divisional memorandum for the approvability of losartan for the treatment of hypertension in children. The present database includes a robust demonstration of the antihypertensive efficacy of losartan in children at the two upper doses studied, and these data should be reflected in labeling. Additionally, the extemporaneous formulation developed by the sponsor should be described in labeling, both as an aid to the use of losartan in children but also potentially for adults who cannot swallow pills. Labeling should not, however, discuss any pharmacokinetics in children in whom no blood pressure effects of losartan have been demonstrated. Such language inappropriately suggests to physicians that such efficacy has been established.

**BACKGROUND**

What follows is a summary of the reviews submitted for the supplement.

**CHEMISTRY**

The Chemistry review by Dr. Mittal focused his attention on the extemporaneous formulation produced the sponsor to allow for a liquid formulation for children who could not swallow pills. He concluded that the sponsor had adequately demonstrated that the procedure for formulation, the materials used in the preparation, and the stability of losartan in the formulation were adequate, and that the proposed labeling describing the formulation is acceptable. This includes a statement that the formulation is stable for up to 4 weeks at 2-8 degrees Centigrade. The Environmental Assessment was reviewed by Dr. Zelinski and viewed as acceptable on 5.20.02.

He recommends that the labeling \_\_\_\_\_ The proposed label includes a clear description of the extemporaneous formulation in the Dosage and Administration section; I am not sure what he means by \_\_\_\_\_ and see no need for modification to the sponsor's proposal. Similarly, the suggestion \_\_\_\_\_ is not necessary. The approved product for \_\_\_\_\_ is the tablet, as reflected on the container. The extemporaneous formulation is included in label for those patients (pediatric and potentially adult) who cannot swallow pills. The two recommended changes are not necessary and should not be conveyed to the sponsor.

#### PHARMACOLOGY TOXICOLOGY

There was no Pharmacology Toxicology review of this supplement and no issues identified.

#### CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The conclusions for the Biopharmaceutics review rely on both the formal review by Dr. Mishina, where the reader is referred for details. Her review is based on the results of three studies:

- 1) Protocol 216 comparing the PK profile of losartan suspension (an extemporaneous formulation) and the losartan 50-mg tablet. For the parent compound, the C<sub>max</sub> for the suspension was 20% higher than for the tablet, but the AUC was considered equivalent. For the active metabolite, both formulations were bioequivalent for both C<sub>max</sub> and AUC.
- 2) Protocol 225 examined the pharmacokinetics of losartan and its active metabolite using urine and plasma in children from infants to adolescents. Overall, the pharmacokinetics of losartan in the children resembled those of adults, although there is a 'moderately high variability' for the values in both groups. Dr. Mishina and Gobburu recommended that this variability be more accurately reflected in the approved labeling for losartan.
- 3) Study 227 assessed the effects of losartan on blood pressure in children >6 years old (see Dr. Karkowsky's and Choi's reviews as well). There was no attempt at PK-PD modeling attempted given the complex interaction between the free parent drug and the active metabolite.

Her recommendations regarding the pediatric labeling are in her review and should be incorporated into the labeling by and large.

#### MEDICAL/STATISTICAL REVIEW

##### Efficacy

Both Dr. Karkowsky and Dr. Choi concluded that losartan demonstrated antihypertensive efficacy in the population of children studied, and the reader is referred there for details. Their conclusions were based first on the greater antihypertensive effect of the two higher doses of losartan (25 to 100 mg, depending on their body weight) relative to the lower dose (2.5 or 5.0 mg). Indeed, the lowest doses had not evident antihypertensive effect at all. Overall, the two higher doses in each weight cohort lowered sitting diastolic blood pressure (DBP) by 5-6 mm Hg more than the 2.5 mg dose (see Dr. Karkowsky's review, page 15). Efficacy was also demonstrated during the randomized withdrawal phase, where the trough sitting DBP rose in patients randomized to placebo by between 5 and 7 mm Hg more than patients randomized to continuing either of the two top doses (see Dr. Karkowsky's review page 17). Again, these data suggested that the lowest dose (2.5 or 5.0 mg) had no antihypertensive efficacy. Analysis of the BP data normalized for weight confirmed the antihypertensive effects of losartan, and suggested that the maximal BP reduction expected with losartan in this population would be around 11% from baseline (fairly close to the change observed for the 50 mg dose).

Dr. Choi examined the antihypertensive effects of losartan in a variety of demographic subgroups (see page 16 of her review for details). There was a consistent qualitative antihypertensive effect seen when grouped according to gender, race and age (<, >12), but the slope for BP reduction for the non-White populations is quite a bit smaller than the White population, and the number of Blacks is quite small (n=20). During the withdrawal phase there was a large increase in the BP in the Blacks, supporting an effect of losartan on BP in this group.

The labeling recommendations of Dr. Karkowsky about the efficacy of losartan are in his review. While some of them \_\_\_\_\_ do not belong in the label. His removal of all mention of the use of losartan in children <6 is appropriate, as discussed below.

### Safety

The safety review from this study revealed no new safety concerns for diltiazem (see Dr. Karkowsky's review, pages 28-36). Other sponsors have raised the issue of the safety of administering blockers of the ACE system (ACE-Inhibitors, Angiotensin Receptor Blockers) to children <2 years of age, whose kidneys have not yet finished developing. No adverse renal consequences of losartan administration in these children were reported in this supplement. Dr. Karkowsky has raised the issue of potential renal toxicity of losartan, based largely on two cases of renal failure. I find these cases unconvincing given their other problems and find no rationale for describing such cases in the label.

### SUMMARY

This is a substantial antihypertensive development program, one whose strengths should be reflected appropriately strong language in labeling. The development of an extemporaneous formulation is to be applauded, and has potential use not only in children but in adults who cannot swallow pills as well.

One issue that merits discussion is the pharmacokinetic (PK) data the sponsor has collected. These data are not matched to any demonstration of antihypertensive efficacy, and cannot be included in labeling. The Division has experience with drugs whose PK parameters do not differ significantly from those of adults, and yet the drug had no demonstrated antihypertensive effects in children. The reasons for this failure are unclear (*i.e.*, either the drugs didn't work or the trials failed to detect such an effect). With this lack of consistent relationship between PK and antihypertensive effect, the Division must insist on clinical data for any PK data to be included in label. The inclusion of such PK language would falsely imply such efficacy exists.

Another issue that bears a comment is the assertion by the Clinical Pharmacologist that the extemporaneous formulation and the approved tablet are not bioequivalent, as the C<sub>max</sub> for the parent compound differs between the two preparations by 20%. I disagree with this conclusion, given the following:

1. The flat dose-response curve for this drug and
2. The low frequency of dose-dependent side-effects
3. The equivalent AUC for the parent and the equivalent C<sub>max</sub> and AUC for the active metabolite (see Dr. Mishina's review page 10).

### LABELING

The sponsor has proposed changes to the approved losartan labeling. Several comments are necessary, aside from those made above during the summaries of the individual reviews.

- First, the [redacted] should be moved to the *Pharmacodynamics and Clinical Effects* section of the labeling under a heading identifying [redacted]. A heading for adult hypertension will need to be added. The description proposed by the sponsor should be augmented to more fully describe the antihypertensive effects seen.
- Second, the inclusion of [redacted] no clinical data on antihypertensive efficacy exist is not supportable (see above). Any mention of losartan's use in children <6 years old should be removed from the proposed label.
- Third, the extemporaneous formulation should be included in labeling as proposed by the sponsor. The two recommendations of the Chemists are not acceptable and should not be conveyed to the sponsor.
- Fourth, the variability of the adult PK for losartan, as per the recommendation of the Clinical Pharmacology staff, should more accurately be reflected in the label.

To be placed in *Pharmacodynamics and Clinical Effects* (with removal of similar language from the *Pharmacokinetics* section):

**Pediatric Hypertension**

The antihypertensive effect of losartan was studied in one trial enrolling 177 hypertensive pediatric patients aged 6 to 16 years old. Children who weighed <50 kg received 2.5, 25 or 50 mg of losartan daily and patients who weighed  $\geq$ 50 kg received 5, 50 or 100 mg of losartan daily. Children \_\_\_\_\_ were given losartan in a suspension formulation (see *Dosage and Administration, Preparation of Suspension*). The majority of the children had hypertension associated with kidney and urogenital disease,

L

J

APPEARS THIS WAY  
ON ORIGINAL

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Doug Throckmorton  
10/21/02 03:20:18 PM  
MEDICAL OFFICER

## Cover page

Division of Cardio-Renal Drug Products  
Medical Officer Review

NDA: 20-386

Name of Drug: Cozaar® Losartan potassium Tablets

Sponsor: Merck Research Laboratory

Date of Submission: December 21, 2001

Type of Submission: Pediatric Studies

Reviewer: Abraham M. Karkowsky, M.D., Ph.D.

**APPEARS THIS WAY  
ON ORIGINAL**

## Table of Contents

COVER PAGE.....	1
TABLE OF CONTENTS .....	2
EXECUTIVE SUMMARY: .....	5
RECOMMENDATIONS: .....	5
SUMMARY OF CLINICAL FINDINGS: .....	5
CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS: .....	6
DESCRIPTION OF CLINICAL DATA SOURCES: .....	6
HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS: .....	6
CLINICAL REVIEW METHODS: .....	6
INTEGRATED REVIEW OF EFFICACY:.....	6
INTEGRATED SUMMARY OF SAFETY: .....	6
LABELING: .....	7
1. STUDY # 227:.....	8
<b>TITLE OF STUDY: A DOUBLE-BLIND, RANDOMIZED DOSE-RESPONSE STUDY OF LOSARTAN IN CHILDREN WITH HYPERTENSION.</b> .....	8
INVESTIGATORS AND SITES: .....	8
FORMULATIONS: .....	9
STUDY DATES: .....	9
INCLUSION CRITERIA:.....	9
EXCLUSION CRITERIA: .....	10
DOSING: .....	10
PROCEDURES:.....	10
STATISTICS: .....	10
<i>Sample-size calculations:</i> .....	12
RESULTS:.....	12
DISPOSITION:.....	12
RANDOMIZED WITHDRAWAL PHASE DROPOUTS: .....	13
DEMOGRAPHICS:.....	13
BLOOD PRESSURE EFFECT: .....	14

<i>Slope Analysis:</i> .....	15
<i>Subgroups:</i> .....	15
<i>Additional Analyses:</i> .....	16
<b>SAFETY:</b> .....	19
<b>DISPOSITION/ DEMOGRAPHICS/DURATION OF EXPOSURE:</b> .....	19
<b>DEATHS/DROPOUTS/SERIOUS EVENTS/EVENTS LISTED AS “SEVERE” IN INTENSITY: ..</b>	20
<b>LONG-TERM EXTENSION SAFETY:</b> .....	20
<b>ADVERSE EVENTS:</b> .....	22
<b>HEART RATE:</b> .....	22
<b>TABLE 1.20 SITTING TROUGH HEART RATE.....</b>	22
<b>LABORATORY:</b> .....	23
<b>2. STUDY # P216:</b> .....	24
<b><u>TITLE OF STUDY:</u> AN OPEN-LABELED, RANDOMIZED, TWO-PERIOD, CROSSOVER STUDY TO DETERMINE THE RELATIVE BIOAVAILABILITY OF LOSARTAN 50-MG SUSPENSION AND LOSARTAN 50-MG TABLET ADMINISTERED ORALLY AS SINGLE DOSES.</b> .....	24
<b>INVESTIGATOR AND SITES:</b> .....	24
<b>PROTOCOL:</b> .....	24
<b>INCLUSION CRITERIA:</b> .....	24
<b>EXCLUSION CRITERIA:</b> .....	24
<b>DOSES:</b> .....	24
<b>PROCEDURES:</b> .....	24
<b>SAFETY:</b> .....	25
<b>3. STUDY P225</b> .....	26
<b><u>TITLE OF STUDY:</u> MULTICENTER STUDY: AN OPEN-LABEL STUDY TO INVESTIGATE THE PHARMACOKINETICS OF LOSARTAN IN HYPERTENSIVE CHILDREN AND INFANTS.</b> .....	26
<b>INVESTIGATOR AND SITES:</b> .....	26
<b>DOSES AND FORMULATIONS:</b> .....	26
<b>INCLUSION CRITERIA:</b> .....	27
<b>EXCLUSION CRITERIA:</b> .....	27
<b>RESULTS:</b> .....	27
<b>SAFETY:</b> .....	28

**OVERALL ADVERSE EVENTS: ..... 28**

**LABORATORY ADVERSE EVENTS:..... 29**

**VITAL SIGNS: ..... 30**

**CONCLUSION: ..... 31**

**1. SAFETY FROM CLINICAL STUDIES: ..... 32**

**2. CHART REVIEW. .... 32**

**3. THE SUMMARY OF THE WORLDWIDE ADVERSE EVENT SYSTEM (WAES) ..... 33**

**4. PUBLICATIONS:..... 35**

**OVERALL SAFETY CONCLUSIONS: ..... 35**

**APPENDIX 1-TENTATIVE LABELING ..... 36**

**APPEARS THIS WAY  
ON ORIGINAL**

**Executive Summary:**

**Recommendations:**

Based on the results of this submission, losartan at a dose of 25-50 mg daily for children aged 6-16 years old who weigh less than 50 kg and a dose range of 50-100 mg for those who weigh greater than 50 kg is a useful treatment for pediatric primary hypertension. No phase IV studies are recommended.

**Summary of Clinical Findings:**

This submission contains a dose-ranging study of losartan in pediatric patients aged 6-16 years old. The results demonstrate a dose related blood pressure effect over a dose range of 5-100 mg for those who weigh over 50 kg and 2.5-50 mg for those who weigh less than 50 kg. This observation is supported both by the significant slope of treatment versus blood pressure effect during a three-week treatment phase as well as the reversal of the blood pressure effect for the two highest dose groups upon a two-week randomized withdrawal period.

Those who received the lowest dose of losartan received the drug as a suspension. All others received losartan as a tablet. The pharmacokinetic properties of the losartan suspension was tested against tablets (study #216) at a dose of 50 mg. The suspension and tablets were apparently bioequivalent with respect to AUC for losartan and active metabolite (E-3174).  $C_{max}$  was higher for losartan as a suspension when compared to losartan as a tablet for parent compound and bioequivalent (or nearly bioequivalent) for the active metabolite E-3174.

A pharmacokinetic study was performed in hypertensive infants and children (study #225). Concentrations of losartan and its metabolite E-3174 were greatest for the adolescents when compared to younger children and infants.

With respect to safety, the database includes: a short-term double blind clinical study with an optional 6-month extension, a review of charts from the Children's Hospital of Pittsburgh of children who were treated with losartan, a summary of adverse events captured by the worldwide adverse event system (WAES) and a literature review.

Safety, in general, for losartan in a pediatric population was not that dissimilar from the safety of losartan in adults but the frequency or intensity of adverse events may be different in a pediatric population when compared to adults.

With respect to losartan's adverse events, two subjects (see page 21 of this review) developed ARF or CRF during a 6-month open label extension of study 225. There was one additional subject who had a rise in serum creatinine during the double-blind portion of the study (from a baseline value of 76.9 mmol/L at baseline to 109.6 mmol/L at the end of the double-blind period). During the 7-day treatment pharmacokinetic study, there were 5 subjects who had elevations in their serum creatinine. Unfortunately, there were no follow-up retests to determine if these abnormal values returned to normal. In the chart review of the 86 patients of the Pittsburgh Children's Hospital who were treated

with losartan, there were 3 Children, all with underlying renal disease whose renal function rapidly deteriorated. Lastly, among the adverse events captured in the WAES system for those under 18 years old, there were two subjects, neither apparently with underlying renal disease, who developed renal failure or worsening of creatinine during losartan treatment.

**Clinically relevant findings from chemistry, animal pharmacology and toxicology, microbiology, biopharmaceutics, statistics and/or other consultant Reviews:**

The only relevant review is that of the biopharmaceutics. Please refer to that review by Drs. Mishina and Gobburu for additional information.

**Description of clinical data sources:**

Sources used for review were the primary submission dated 12.21.02 as well as responses dated 6.28.02 and 7.19.02. All submissions were available as electronic submissions on the EDR.

**Human Pharmacokinetics and Pharmacodynamics:**

Drs. Mishina and Gobburu reviewed the pharmacokinetic studies for losartan in pediatrics. At the time of the writing of this review, the biopharmaceutic review was not yet finalized. From discussions with these reviewers, the only major complicating factor is the variability of the pharmacokinetic parameters in children which differ from the widely variable parameters observed in adults. None of the pharmacokinetic concerns will alter the approvability recommendations, but they will impact the overall labeling of the pharmacokinetic section.

**Clinical review methods:**

This reviewer utilized the tables and figures as supplied by the sponsor. This reviewer also asked for several additional analyses from the sponsor, which were supplied in the submissions of 6.28.02 and 7.19.02.

**Integrated Review of Efficacy:**

This submission contains a dose-ranging study in children aged 6-16 years old. The results of the single efficacy study demonstrate an antihypertensive effect of losartan as assessed by a positive slope in the dose range of 2.5 to 50 mg for subjects weighing less than 50 kg and 2.5 to 100 mg for those weighing more than 50 kg. The results are confirmed by a randomized withdrawal among those treated particularly with doses of 25 and 40 mg for those weighing less than 50 kg and 50 and 100 mg for those weighing greater than 50 kg.

**Integrated summary of safety:**

Safety, in general, for losartan in a pediatric population was not that dissimilar from the safety of losartan in adults but the frequency of adverse events may be different in a pediatric population when compared to adults (see above).

**Labeling:**

Tentative labeling changes are included in the markup labeling (See Appendix 1). The biopharmaceutical review not yet been finalized and the labeling will likely change upon completion of that review.

APPEARS THIS WAY  
ON ORIGINAL

APPEARS THIS WAY  
ON ORIGINAL

**1. Study # 227:**

**Title of Study: A double-blind, randomized dose-response study of losartan in children with hypertension.**

**Investigators and sites:**

The investigator, sites and number of subjects enrolled are shown in Table 1.1

Table 1.1. The investigator, sites and number of Subjects enrolled

Site number (227-), Investigator and Location	# subjects
(003) Achtel, Robert, M.D.; Sutter North Medical Foundation, Marysville, CA	3
(037) Alexandrov, Alexander, Prof.; National Research Center for Preventive Medicine, Petroverigsky, Moscow, Russia	8
(030) Arbus, Gerald, M.D.; Hospital for Sick Children; Toronto, Ontario	2
(053) Bartosh, Sharon, M.D.; University of Wisconsin Children's Hospital; Madison, WI	0
(004) Blumer, Jeffrey, L, M.D., Ph.D.; University Hospitals of Cleveland; Cleveland, OH	4
(036) Briazgounov, Igor, Prof.; Pediatric Research Institute, Moscow, Russia	12
(052) Campos, Alfonso, M.D.; University of So. Florida, Tampa, FL	2
(032) Cano, Francisco, M.D.; Hospital Calvo Mackenna; Santiago, Chile	16
(035) Capelli, Horacia, M.D.; Hospital Pediatria Juan P. Garrahan, Buenos Aires, Argentina	6
(031) Cote, Jean-Marc, M.D.; CHUQ, Quebec, Canada	2
(025) Cranswick, Noel, M.D.; Royal Children's Hospital, Melbourne, Australia	0
(006) Cunningham, Robert, M.D.; Cleveland Clinic Foundation; Cleveland, OH	0
(049) Daniels, Stephen, M.D., Ph.D.; Children's Hospital Medical Center; Cincinnati, OH	1
(064) de Almeida burdmann, Emmanuel, M.D.; Hospital de Base de Sao Jose de Rio Preto; Sap Paulo, Brazil	4
(061) de Cea-Crespo Jose M, M.D.; Hospital Severo Ochoa, Madrid, Spain	1
(007) Eissa, Mona, M.D., Ph.D.; University of Texas Medical School, Houston, TX	4
(008) Falkner, Bonita, M.D.; Jefferson Medical School, Philadelphia, PA	2
(043) Feber, Janusz, M.D.; Clinic Prague/University Hospital Motol, Czech Republic	2
(063) Garcia de la Puente, Silvestre, M.D.; Instituto Nacional de Pediatric, D.F., Mexico	8
(051) Gitomer, Jeremy J, M.D.; Marshfield Clinic, Marshfield, WI	2
(062) Hernandez Rodriguez, Oscar Adolpho, M.D.; Instituto Naciona Del Rinon, Bogata, Columbia	4
(010) Hogg, Ronald J., M.D.; Medical City Dallas Hospital; Dallas TX	0
(042) Holmberg, Christer, M.D.; Helsinki University Hospital; Helsinki Finland	5
(011) Hunley, Tracy E., M.D.; Division of Pediatric Nephrology, Vanderbilt University, Nashville, TN	0
(033) Koch, Vera, M.D.; Instituto de Crianco-UPS; Sao Paulo, Brazil	8
(044) Kolsky, Alexander, M.D.; Clinic Prague/ Thomayer University Hospital; Czech Republic	3
(001) Loza, Reyner, M.D.; Hospital Base Cayetano Heredia; Lima, Peru	5
(026) Lurbe, Empar, Prof.; Hospital La Fe, Valencia, Spain	1
(038) McKinney Ross E., Jr., M.D.; Duke Pediatric Clinical Research Program; Durham, NC	0
(027) Machado Hernandez, Livia Thais, M.D.; Clinica Santa Sofia, Edf Torre Alfa Piso, Caracas, Venezuela	5
(029) Martins, Maymone Fernando, M.D.; Hospital de Santa Cruz, Carnaxide, Portugal	1
(013) Meyers, Kevin, M.D.; Children's Hospital of Philadelphia, Philadelphia, PA	1
(041) Milford, David, M.D.; Birmingham Children's Hospital, Birmingham, UK	0
(014) Miller, Kenneth, M.D.; Nephrology & Hypertension; Park Ridge, IL	8
(054) Molina, Carmen, M.D.; Amedica Research Institute, Hialeah, FL	2
(048) Norwood, Victoria Fay, M.D.; University of Virginia, Charlottesville, VA	1
(056) Podracka, Ludmila, M.D.; Safrak University of Kosice, Kosice, Slovakia	5
(046) Proesmans, Wilhem Christiaan Jozef Jan, M.D.; Ph.D.; U.Z. Gasthuisberg, Leuven, Belgium	2
(040) Rayner, Brian, M.D.; Groote Schuur Hospital, Capetown, So. Africa	8
(058) Rokicki, Wladyslaw, M.D.; Katebra I Klinika Kardiologii Dzieciecej; Katowice, Poland	2
(045) Rucki, Stepan, M.D.; Department of Pediatrics City Hospital Trinec, Trinec, Czech Republic	3
(050) Sakihara Asata, Graciela, M.D.; Instituto de Salud del Nino; Lima, Peru	6
(016) Schwartz, George, M.D.; University of Rochester, Children's Hospital of Strong; Rochester, NY	3
(018) Siegel, Norman J., M.D.; Yale University School of Medicine, New Haven, CT	0
(034) Simsolo, Rosa, M.D.; Hosp. Ninos Ricardo Gutierrez; Buenos Aires, Argentina	4
(017) Sullivan, Janice, M.D.; Children & Youth Projects; Louisville, KY	0
(019) Tenney, Frank, M.D.; Louisiana State University Medical Center, Shreveport, LA	0
(039) Thomson, Peter, M.D.; Johannesburg General Hospital, Parktown, South Africa	7
(057) Toro-Domenech Maria Isabel, M.D.; Hopsital General Universitaria, Valencia, Spain	2
(021) Valenti, Rudolph, M.D.; Children's Hospital of Michigan, Detroit, MI	1
(065) Van De Walle, Johan, M.D.; U.Z. Gent Dienst Nefrologie/Pediatrie; Gent, Belgium	6
(020) Verega, Marcela, M.D.; Schneider Children's Hospital; New Hyde Park NY	0
(022) Wells, Thomas G., M.D.; Arkansas Children's Hospital, Little Rock, AR	0
(002) Wroblewska-Kaluzewska, Maria, M.D.; Instytut Kardiologii Klinika Nadcisnienia, Waszawa, Poland	5

The enrolling sites included both domestic and foreign (European and South American) sites.

#### Formulations:

The formulations during the study are shown below.

Table 1.2: Formulations: The following formulations were used during this study:

Dose	Control #	Formulation Number
25 mg	WP-H272, WP-H275, WP-H306, WP-H698, WP-H697	0954, FCT, 013B, 001
25 mg	WP-H340, WP-H278, WP-H343, WP-H352, WP-H352D	E927
Placebo 25 mg	WP-H272, WP-H275, WP-H306, WP-H698, WP-H697	P0954, FCT, 014B, 001
Placebo 25 mg	WP-H340, WP-H278, WP-H343, WP-H352, WP-H352C	E-9578
Losartan 50 mg	WP-H272, WP-H275, WP-H306, WP-H698, WP-H697	0954, FCT, 061C, 001
Losartan 50 mg	WP-H340, WP-H278, WP-H343, WP-H352, WP-H352D	E9671
Placebo 50 mg	WP-H272, WP-H275, WP-H306, WP-H698, WP-H697	P0954, FCT, 005T, 001
Placebo 50 mg	WP-H272, WP-H275, WP-H306, WP-H698, WP-H697	P0954, FCT, 062C, 001
Placebo 50 mg	WP-H340, WP-H343, WP-H278, WP-H352, WP-H352E	E-9706
Placebo 50 mg	WP-H340, WP-H278, WP-H343, WP-H352, WP-H352A	P0954, FCT, 006T, 001
An oral suspension of losartan was prepared as follows		
Add two tablets to PET bottle	2 x 50 mg losartan tablets or placebo tablets	
Add sterile water	2 ml	
Shake for three minutes, allow to sit for 20 minutes, shake to disperse for 1 minute		
Separately prepare 40 ml of a 50/50 volumetric mixture of Ora-Sweet SF™/Ora-Plus™ and mix well		
Add Ora-Sweet SF/ Ora-Plus mixture	38 ml	
Shake the resulting suspension to disperse. Store the suspension 2 to 8 °C and shake prior to dosing.		

#### Study dates:

Initial Protocol: 28 February 2000

Amendment #1: 14 April 2000- This amendment changed the sample size from 156 to 160. It also reworded the secondary hypothesis for clarity. The waiting period for enrollment after an investigational drug was changed from 4 to 2 weeks.

Amendment #2: 30 August 2000- This amendment was written for the Czech republic to allow rescue if a pre-specified blood pressure is reached. Home measurements would not be considered as last measurements for the assessment of efficacy.

Amendment #3: 16 May 2001- The number of subjects to be enrolled was changed to 150.

First patient enrolled: 13 July 2000.

Last patient completed: 31 August 2001.

Date blind broken: 3 October 2001.

#### Inclusion criteria:

- Those enrolled will be of either gender > 20 kg between 6-16 years old.
- Subjects are to be > 95<sup>th</sup> percentile for sitting diastolic blood pressure at the end of the washout period, based on gender, height and age.
- Patients would have a GFR of > 30 mL/min/1.73 M<sup>2</sup> at baseline, as calculated by the formula

$$\text{GFR} = \frac{0.55 \times \text{Height (in cm)}}{\text{Scr (in mg/dL)}}$$

- Patients must be able to swallow tablets

- Approximately 10 –30% will be black approximately 25-50% will be female and > 50% will either be between 6-12 years or > Tanner 3.

**Exclusion criteria:**

- History of severe hypertension (i.e. hypertensive crisis) within a year.
- Patients who require > 2 medications to control blood pressures.
- History of heart failure.
- History of obstructive valvular disease.
- Other significant neurologic, respiratory, gastrointestinal, hepatobiliary or hematologic disease, coarctation of the aorta, bilateral renal artery stenosis or stenosis with a single kidney, nephrotic patients.
- Patients post organ transplant.

**Dosing:**

Subjects were randomized to receive low, medium or high dose losartan. The low dose was formulated as a suspension, the others doses received tablets. Dosing was carried out as a double-dummy design. Children who weigh more than 50 kg received 5, 50 or 100 mg daily; children weighing less than 50-kg received half this dose. For those who received the 100-mg losartan dose, the dose was titrated to this dose after two days at 50 mg/day. At day 21, subjects were re- randomized to continue on therapy or to be withdrawn to placebo.

**Procedures:**

Patients were washed out from previous hypertensive medications on day -7. Blood pressure was monitored during the washout period with rescue medication pre-specified, if necessary, for large blood pressure increases. Randomization was to occur after two sets of measurements, at least one hour apart, indicate that the patient is > 95<sup>th</sup> percentile based on gender, age and weight for sitting diastolic blood pressure.

Patients were dosed as described above. Subjects in the high dose group were titrated to the goal dose at day 3.

Pivotal blood pressure measurements were to be taken at trough. However, when the dose was up-titrated (i.e. first dose and escalation dose on day 3) additional measurements were collected approximately 4 hours post dose.

A long-term visit is only scheduled at the 6-month time point.

The specifics of the procedures are shown in Table 1.3.

**Statistics:**

The study population that is to form the primary analysis is the intent-to-treat population. A last value measured carried forward analysis was planned for those with missing data. Baseline was defined as the average of two sets of measurements performed

and separated by at least one-hour. The key metric was derived from the double-blind portion of the study. The vital signs, which were collected during the randomized withdrawal phase of the study, were utilized as the secondary analysis. A stratified simple linear regression model was used for slope analysis, with weight group factor as the stratified intercepts and dose ratio

Table 1.3- Procedures and timing.

	PBO washout	Double-Blind					Randomized Washout		Open-Label
Visit number	1	2	3	4	5	6	7	8	9
Visit day	-7	1	3	7	15	22	29	36 <sup>(a)</sup>	Month 6
Informed consent/ D/C BP meds./med history/ PE									
Blood pressure/ heart rate	X <sup>a</sup>	X <sup>(b,c)</sup>	X <sup>(c)</sup>	X	X	X	X	X	X
ECG	X								
Laboratory evaluation <sup>d</sup>	X	X						X	X
Pregnancy test <sup>e</sup>									
Prepare/dispense study drug <sup>f</sup>	X	X				X		X	
Titrate study drug <sup>g</sup>			X						
Return study drug									
Adverse experience assessed		X	X	X	X	X	X	X	X
a -During the baseline washout period the child's parent will monitor blood pressure daily. Short acting nifedipine would be dispensed if necessary for rescue. b- Two sets of measurements of mean sitting diastolic blood pressure with each measurement indicating the subject > 95 <sup>th</sup> percentile for age, gender and height. c- Measure BP four hour post dose after titration- not necessarily at clinic d- On day 1- only chemistry. On other days labs will include chemistry, hematology and urinalysis e- For females at start and end of double -blind period and monthly during open-label period				f- Patients will receive either low medium or high dose losartan or placebo. The dose is dependent on weight < or > 50 Kg. Those under 50 Kg will receive half the dose of those > 50 kg. The low, medium and high dose losartan groups for those > 50 kg is 5, 50 or 100 mg. Those under 50 kg receive half the dose. Those in the high dose group will receive half the dose for two days then titrated to the indicated dose on day 3. On day 21 subjects will be randomized withdrawal to continued therapy or placebo					

(high, mid and low) as the continuous covariate. In addition a distribution-free test procedure for ordered alternatives, called the Jonckheere-Terpstra test is conducted when the assumptions underlying the regression model were violated.

Three supportive analyses were performed.

- A per protocol analysis- protocol violators were identified in a blinded manner and their data were excluded.
- Mixed model: Blood pressure measurements on days 3, 5 and 22 were used for this model. The stratified mixed linear regression model included terms for weight stratum and dose ratio.
- The following sub-groups were analyzed:
  - Age (> 12 and ≤ 12).

- Tanner stage ( $> 3$  and  $\leq 3$ ).
- Gender.
- Race (White, black, and Hispanic).
- Country (USA , Non-USA).

**Sample-size calculations:**

Based on an assumed difference of 4-mm Hg and a SD of 8 mm Hg, the study size of 156 children would have an 80% power to detect differences.

The secondary analysis consisted of the sitting diastolic blood pressure measurements during the randomized withdrawal study. This portion of the study is only relevant if the slope of the dose-ranging portion of the study is not significant. The primary analysis is to show the existence of an increase of mean change in trough sitting DBP when comparing the two-week post withdrawal measurement to the measurement at the end of double blind period. Patients will remain on their losartan dose or switched to placebo. The change in DBP will be analyzed by an ANOVA with weight stratum and include a factor for six treatment groups (low-low, low-PBO, mid-mid, mid-PBO, high-high, high-PBO).

When any of the assumptions underlying the ANOVA is violated the data will be analyzed by a distribution-free test procedure (Wilcoxon-Mann-Whitney test).

The following additional supportive analyses were performed for the randomized withdrawal data.

- Per-protocol analysis.
- Mixed model- A mixed ANOVA model utilizing the last and penultimate effects during the randomized withdrawal phase when compared to the last double-blind measurement during the dose-ranging phase. Only measurements obtained during the withdrawal phase will be carried forward in this analysis.
- Longitudinal model- This model will utilize the data from the double-blind dose-ranging as well as the randomized withdrawal phases.

**Results:**

A total of 177 subjects were entered into this study. Subjects were randomized in a 2:1:2 ratio to low: mid: high doses of losartan, respectively. There were no placebo-treated patients during this phase of the study.

**Disposition:**

Approximately 93% of those enrolled completed the study. The most common reason for discontinuation was lack of efficacy, equally distributed among the three treatment groups. The disposition of subjects is shown below:

Table 1.4. Disposition of subjects in study 227.

	Low Dose	Mid Dose	High Dose	Total
Entered	70	41	66	177
Completed	68	36	60	164
Discontinued*	2	5	6	13
Clinical adverse event	0	0	1	1
Laboratory adverse event	0	0	0	0
Lost to follow-up	1	0	0	1
Deviation from protocol	0	2	1	3
Patient withdrew	0	1	2	3
Lack of efficacy	1	2	2	5

\* See table 1.18 for specifics.

Three patients were excluded from the intent-to treat analysis. These subjects are:

- (# 1205 227-032- Spilled medication re-randomized as # 1207).
- (#1215- 227-056 -Discontinued due to protocol dosing deviations. Re-randomized as # 1220).
- (# 1317- 227-065 Lost to follow up on day 3).

Ten additional subjects were excluded from the per-protocol analysis (total of 13).

**Randomized withdrawal phase dropouts:**

There were 13 patients who were not evaluable for the randomized withdrawal portion of the study.

- #1205; 227-032. The study suspension was spilled. No measurements were available.
- #1215; 227-056. This subject deviated from the protocol dosing. No blood pressure measurements were used.
- #1317; 227-065. This subject was lost to follow-up.
- #1371; 227-063 This subject was discontinued on day 7 during double-blind phase due to lack of efficacy.
- #1433; 227-040 This subject was discontinued on day 18 due to an adverse event.
- #1441; 227-039. This subject was discontinued day 22 due to lack of efficacy.
- # 1443; 227-039. This subject was discontinued on day 15 due to lack of efficacy.
- # 1445; 227-039. This subject was discontinued on day 5 due to a protocol deviation.
- # 2019; 227-004. This subject was discontinued on day 22 due to lack of efficacy.
- # 2050; 227-054. This subject was discontinued on day 5 and lost to follow-up.
- # 2060; 227-052. This subject was discontinued on day 15 due to lack of efficacy.
- # 2241; 227-050. This subject was discontinued on day 2 due to lack of efficacy.
- # 2351; 227-033. Patient withdrew consent on day 6.

Five additional subjects were excluded from the per-protocol analysis.

**Demographics:**

The demographics among those who enrolled are shown below:

Table 1.5. Demographics of those of enrolled in study 227

	Low-dose (N=70)	Mid-dose (N=41)	High-dose (N=66)
Gender (male/female) (%/%)	38/32 (54%/46%)	24/17 (59%/41%)	37/29 (56%/44%)
Race (white/Hispanic/black/other)	34/13/12/11 (49%/19%/17%/16%)	22/9/3/7 (54%/22%/7%/17%)	42/16/5/3 (64%/24%/8%/5%)
Age (years) mean + SD [range]	12.3 + 3.2 [6-16]	12.1 + 3.2 [5-16]	11.6 + 2.9 [5-16]
Duration of Hypertension (years) (mean + SD) [range]	2.1 + 2.6 [0.08-13.8]	2.6 + 3.6 [0.08-16.8]	2.4 + 2.9 [0.08-16.8]
Weight (Kg) (mean + SD)	58.5 + 24.3	57.2 + 29.6	59.8 + 27.1
Tanner stage ≤ 3/ > 3 (%/%)	38/32 (54%/46%)	24/16 (60%/40%)	41/23 (64%/36%)
Sitting DBP mm Hg (mean + SD)	88 + 6	89 + 8	89 + 7
Sitting SBP mm Hg (mean + SD)	130 + 12	132 + 16	130 + 13
Selected medical conditions:			
Cardiovascular	17 (24%)	7 (17%)	17 (26%)
LVH	6 (9%)	2 (5%)	4 (6%)
Murmur	4 (6%)	1 (2%)	4 (6%)
Valvular	1 (1%)	1 (2%)	4 (6%)
Hematologic	9 (13%)	11 (27%)	8 (12%)
Anemia	8 (11%)	6 (15%)	4 (6%)
Metabolic/nutritional	30 (43%)	18 (44%)	36 (55%)
Obesity	20 (29%)	12 (29%)	25 (38%)
Musculoskeletal disorder	13 (19%)	6 (15%)	15 (23%)
SLE	4 (6%)	2 (5%)	0
Urogenital disorders	39 (56%)	21 (51%)	38 (58%)
Urogenital anomaly	4 (6%)	0	4 (6%)
Kidney biopsy	8 (11%)	2 (5%)	6 (9%)
Cystic kidney	3 (4%)	3 (7%)	6 (9%)
Glomerulonephritis	4 (6%)	4 (10%)	2 (3%)
Hematuria	5 (7%)	0	3 (5%)
Hydronephrosis	0	4 (10%)	0
Infection urinary tract	9 (13%)	5 (12%)	8 (12%)
Kidney disorder	4 (6%)	1 (2%)	4 (6%)
Nephrotic syndrome	6 (9%)	1 (2%)	6 (9%)
Proteinuria	4 (6%)	0	1 (2%)
Vesicoureteral reflux	6 (9%)	2 (5%)	3 (5%)
Chronic renal insufficiency	3 (4%)	4 (10%)	4 (6%)
Renal sclerosis	0	0	4 (6%)
Selected concomitant medications:			
Autonomic drugs	5 (7%)	2 (5%)	0
Cardiovascular drugs	6 (9%)	2 (5%)	3 (5%)
Central nervous system	11 (16%)	5 (12%)	17 (26%)
Hormones and synthetic	13 (19%)	5 (12%)	12 (18%)
Prednisone	8 (11%)	4 (10%)	6 (9%)

*Comments: This is a population that has a high frequency of underlying diseases, particularly renal/urogenital disease. Those on steroids were to be on stable doses for at least 1 month.*

**Blood pressure effect:**

The effect of losartan treatment on trough sitting diastolic blood pressure is shown below.

Table 1.6. Sitting diastolic blood pressures and blood pressure change (95% CI)

Dose	N	Day			Change + SD	
		1	15	22	Day 15-Day 1	Day 22-Day 1 (95% CI)
Low	70	87.9	80.8	81.9	-7.1 + 6.6	-6.0 + 7.6 (-7.8, -4.2)
Mid	40	89.4	78.4	77.7	-11.0 + 8.7	-11.7 + 9.1 (-14.6, -8.8)
High	64	88.8	78.6	76.6	-10.2 + 9.1	-12.2 + 8.9 (-14.4, -10.0)

The analysis of the sitting diastolic blood pressure response by weight stratum is shown below. The high and middle dose groups in each weight stratum had a greater blood pressure effect when compared to the low dose.

Table 1.7. Sitting diastolic blood pressure response based on weight categories.

	< 50 kg			> 50 kg		
	Low	Mid	High	Low	Mid	High
Dose	2.5 mg	25 mg	50 mg	5 mg	50 mg	100 mg
N	34	19	28	36	21	36
Mean Change +SD	-5.2 + 8.7	-9.8 + 11.2	-10.4 + 8.4	-6.8 + 6.4	-13.3 + 6.6	-13.6 + 9.1

**Slope Analysis:**

The analysis of the slope of blood pressure versus dose stratum is the primary metric of interest. The results of this analysis are shown below (see the statistical section for the methodology). Because the assumptions of normality (based in the Shapiro-Wilk test for normality) may not be justified, a non-parametric analysis, the Jonckheere-Terpstra non-parametric test was also performed. The p-values for this analysis are also shown below. The p-value indicate a positive dose response with and without weight stratum.

A supplemental analysis defining the slope effect on day 15 (2 weeks) and day 22 (3 weeks) indicates a dose-related slope for either time point. The slope is greater on day 22. This is not surprising since the effect in the low dose group was greater at 15 days and the effect for the higher doses somewhat less at three weeks. The net result is a flattened slope at week 2 than week 3.

Table 1.8. Slope analysis and corresponding statistics for trough sitting diastolic blood pressure.

	Value of slope	p-value
Primary slope analysis Day 22 or LOCF - baseline	-0.32 ± 0.08	<0.0001
Day 15	-0.16 ± 0.07	0.037
Non-parametric Jonckheere-Terpstra combined weight stratum		<0.0001
Non-parametric Jonckheere-Terpstra without weight stratum		<0.0001
Non-parametric Jonckheere-Terpstra stratum < 50 kg		0.156
Non-parametric Jonckheere-Terpstra stratum > 50 kg		0.0004

**Subgroups:**

The sponsor submits subgroup analyses. These are shown below.

Table 1.9. Subgroup analysis of slope for trough sitting diastolic blood pressure.

Parameter	Categorical	N	Slope	SE	95% CI
Age	≤ 12 years	80	-0.33	0.13	-0.59, -0.07
	> 12 years	94	-0.30	0.09	-0.48, -0.11
Tanner	≤ 3	103	-0.29	0.01	-0.50, -0.09
	> 3	71	-0.35	0.11	-0.58, -0.13
Country	USA	34	-0.25	0.16	-0.57, 0.07
	Other	140	-0.32	0.09	-0.49, -0.15
Race	White	96	-0.49	0.12	-0.73, -0.25
	Black	20	-0.13	0.17	-0.48, 0.22
	Hispanic	37	-0.22	0.11	-0.44, -0.00
	Asian/ mixed/American Indian	21	-0.04	0.24	-0.54, 0.46

There appears to be little difference in slope in considering those greater than and younger than 12 years old or those more or less advanced in their pubertal status than Tanner stage 3. The magnitude of effect in the US and non-US sites are similar. The predominant benefit appears to be in Caucasians. The current labeling of Cozaar® indicates a lesser effect in blacks in an adult population. The results from this analysis for blacks, however, are not entirely consistent with the randomized withdrawal phase (see below under withdrawal). The number of blacks in each of the 6 withdrawal groups is likely to be too small to comfortably draw any conclusion.

**Additional Analyses:**

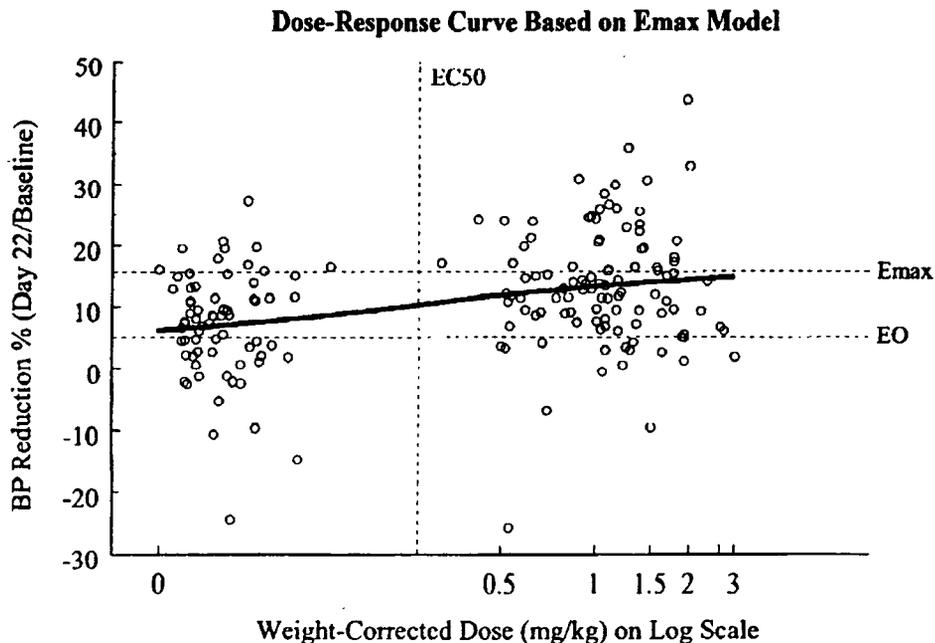
The sponsor analyzed the data normalizing for weight, by three models, an  $E_{max}$  model, a linear model and a log-linear model. The best fit parameters are shown below. The parameters below are ratios of end of treatment (day 22) divided by baseline values.

The  $E_{max}$  model suggests the drift in blood pressure is approximately 5% from baseline ( $E_o$ ). The maximal diastolic blood pressure effect of losartan ( $E_{max}$ ) is a 10.7% decrease from baseline (this is a reasonable way to express the data since baseline measurements defining hypertension were based on gender, age and weight normalized values). The scatter plots for the  $E_{max}$ , linear and log linear models are shown below. None of the models appear to fit the data any better than the others.

Table 1.10 . Weight corrected blood pressure dose response (ITT-approach)

Model	parameter	Estimate + SD	P-value
Emax model	$E_o$ =Baseline	0.95 + 0.028	<0.001
	$EC_{50}$ (mg/kg)	0.287 + 0.399	0.236
	$E_{max}$	-0.107 + 0.024	<0.001
Linear Model	Slope ( $\beta$ )	-0.039 + 0.011	<0.001
Log Linear Model	Slope ( $\beta$ )	-0.022 + 0.005	<0.001

Figure 1.1



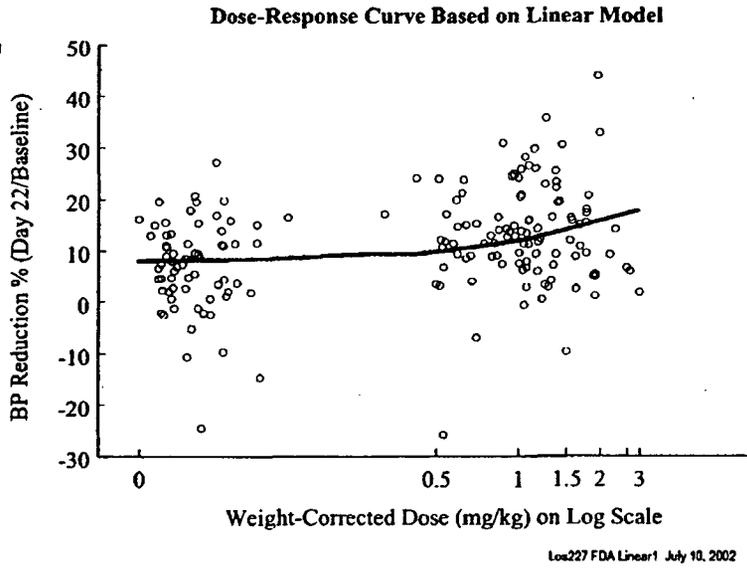


Figure 4: Dose-Response Curve Based on Log-Linear Model

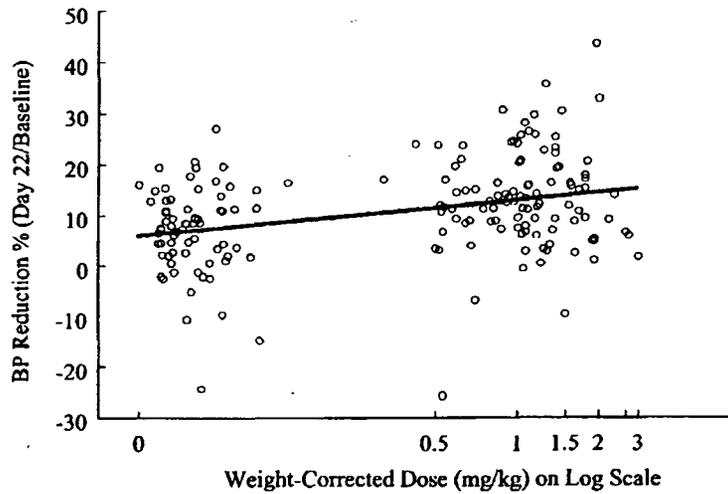


Figure 1. 2 and Figure 1.3

**Randomized withdrawal portion of the study:**

The effect of the randomized withdrawal phase is shown below. A total of 164 of the 177 subjects who entered the study participated in the randomized withdrawal study. For each of the treatments, those who were withdrawn to placebo had elevations in blood pressures.

Table 1.11 Effect on trough sitting diastolic blood pressure during randomized withdrawal period

Initial treatment	Low		Mid		High	
Randomized withdrawal period	Low	PBO	Mid	PBO	High	PBO
N=	33	35	15	21	29	31
Day 22 BP (Baseline) mm Hg	82.3	81.3	74.9	78.4	74.9	77.4
End of Withdrawal BP mm Hg	84.7	84.6	77.5	87.8	77.5	85.3
Change + SD	2.4 + 9.7	3.3 + 7.5	2.7 + 8.3	9.4 + 9.5	2.6 + 9.0	7.9 + 11.2
PBO subtracted	0.9 + 2.1		6.7 + 3.0		5.3 + 2.6	
Confidence intervals	-3.3, 5.1		0.8, 12.6		0.1, 10.4	

The overall dose response was determined by the significance of the F-test. This test has three degrees of freedom in the numerator (the three contrasts). The contrast also allows for the estimate of the treatment effect within a dose. The overall withdrawal effect was significant. The significance was driven by the responses of the two higher dose levels.

Table 1.12 Randomized withdrawal effect based on dose for sitting diastolic blood pressure at trough.

	Estimate	SE	Degrees of freedom	p-value
Overall treatment effect			3	0.02
Difference versus PBO				
low dose	1.1	2.3	1	0.6
mid dose	6.7	3.2	1	0.04
high dose	5.4	2.4	1	0.03
Weight stratum	-1.1	1.5	1	0.5

As a supplemental analysis, the slope of effect versus dose for those maintained on their fixed dose (not the group as a whole) was also analyzed. This model includes terms for the weight stratum, the subject's dose ratio and the period. An unstructured covariance matrix was used for the correlation of changes from baseline to day 22 in period 1 and the last measured blood pressure measurement during the randomized withdrawal phase. There were 77 subjects eligible for this analysis. The slope of the change from the end of period 1 (day 22) to the end of period 2 was non-significant (slope (mean ± SE) = 0.02 ± 0.12, p=0.9). These results suggest little splay in the blood pressure over the time of the withdrawal study for those who were maintained on their dose, although the variability was quite large.

Table 1.13. Subgroup of withdrawal portion of trough sitting diastolic blood pressure of study 227.

	N*= Low	Low			Mid			High		
		Low	PBO	Δ**	Mid	PBO	Δ**	High	PBO	Δ**
Gender										
Male	74	4.38	5.74	-1.35	1.75	14.83	-13.08	2.0	9.81	-7.81
Female	90	1.05	0.31	0.7	3.71	7.20	-3.49	3.06	5.80	-2.74
Tanner										
≤ 3	103	1.18	3.27	-2.08	3.25	10.36	-7.11	3.65	8.24	-4.59
> 3	71	4.73	3.25	1.48	2.00	7.43	-5.43	0.33	7.43	-7.10
Race										
White	96	1.47	-0.64	2.12	4.63	8.82	-4.19	3.57	9.41	-5.84
Black	20	-4.67	4.25	-8.92	-8.00	15.00	-23.00	0.50	8.00	-7.50
Hispanic	37	3.33	7.00	-3.67	3.50	8.00	-4.5	-0.25	5.60	-5.85
Others	21	8.80	6.67	2.13	-1.5	10.00	-11.5	0.00	6.67	-
Country										
US	34	-3.71	4.00	-7.71	-3.00	16.33	-19.33	2.20	5.14	-2.94
Non-US	140	4.00	3.04	0.96	3.07	8.22	-5.15	2.71	8.67	-5.96
Age										
≤ 12 years	80	-0.17	2.83	-3.00	4.00	8.30	-4.30	4.33	8.29	-3.95
> 12 years	94	5.40	3.48	1.92	2.00	10.36	-8.36	-0.18	-0.18	-7.71

\*The number of subjects across all 6 groups.

\*\* The Δ is the double delta, that is the change from day 22 and the differences between placebo and treatment.

I did not have the distribution for each of the dose subgroups. But the number of subjects is now distributed over 6 subgroups (The three doses x maintained or placebo withdrawn). It should be noted that the number of overall subjects in the mid-dose group was approximately 1/2 of those in the other two treatment or placebo groups. Of note, is

the large withdrawal effect observed in all black subjects, in contrast to the minimal slope effect observed during the initial 3-week randomized portion of the study.

**Other Blood Pressure Measurements:**

***Sitting Systolic Blood Pressure Effect:***

The effect on systolic blood pressure is shown below. The dose related slope is not submitted. The subgroup analyses was also not submitted. The sponsor’s analysis for the first period data is shown below. The effects of the two high doses are greater than that of the lowest dose.

Table 1.14 Trough sitting systolic blood pressure effect

	N=	Day 1	Day 22	Change ± SD (95% CI)
Low Dose	70	129.8	125.4	-4.4 ± 7.6 (-6.2, -2.6)
Mid Dose	40	132.2	122.2	-10.0 ± 9.2 (-12.9, -7.1)
High Dose	64	128.0	119.4	-8.6 ± 9.5 (-11.0, -6.3)

The effect on sitting systolic blood pressure after randomized withdrawal is shown below. Withdrawal to placebo is associated with an increase in sitting systolic blood pressure.

Table 1.15 Sitting trough systolic blood pressure randomized withdrawal phase.

	Low		Mid		High	
	Low	PBO	Mid	PBO	High	PBO
N	33	35	15	21	29	31
Day 22	125.3	124.5	118.3	123.2	120.1	118.1
Last Dose	126.8	125.2	120.0	130.2	118.9	126.9
Mean Change	1.4 ± 11.2	0.7 ± 9.3	1.7 ± 9.8	7.0 ± 8.0	-1.2 ± 8.2	8.1 ± 12.5
Difference ± SE (CI)	-0.8 ± 2.5 (-5.7, 4.2)		5.3 ± 3.1 (-0.8, 11.3)		9.3 ± 2.7 (4.0, 14.7)	

***Standing Diastolic/Systolic blood pressure:***

The effect of treatment in standing diastolic (Table 1.16) and standing systolic (Table 1.17) blood pressure measurements are shown below.

Table 1.16 Standing diastolic blood pressure (ITT group) phase 1.

Dose	N	Day 1	Day 22	Change Means ± SD
Low	70	90.6	85.0	-5.6 ± 7.1
Mid	40	91.7	81.5	-10.1 ± 9.8
High	62	90.9	81.7	-9.2 ± 7.9

Table 1.17 Standing Systolic blood (ITT group) phase I

Dose	N	Day 1	Day 22	Change Means ± SD
Low	70	130.3	124.9	-5.5 ± 8.0
Mid	40	132.3	122.6	-9.7 ± 9.3
High	62	128.5	120.1	-8.4 ± 9.0

The effects are not inconsistent with other measurements of blood pressure effect.

**Safety:**

**Disposition/ Demographics/Duration of Exposure:**

The disposition of patients is shown in Table 1.4 and the demographics characteristics are shown in Table 1.5. The duration considered by the safety assessment

spans the double-blind and the phase II withdrawal studies. The safety should be interpreted in the context that approximately 40% of those enrolled were patients treated with placebo-equivalent doses of losartan (2.5 or 5 mg) and that approximately 50% of those enrolled received placebo during the washout phase.

**Deaths/dropouts/serious events/events listed as “severe” in intensity:**

There were no deaths during the study. A tabular listing of those who did not complete the study is shown below. None of those who discontinued had laboratory abnormalities.

Table 1.18 . List of those who did not complete the study.

Pt ID	Demographics (Dose-level)	Reason	Comments:
52-2060	16y/o-M-Asian-(Mid)	Patients withdrew	Baseline BP 131/82- End 126/81
54-2050	16 y/o-M-Black- (Low)	Lost to follow-up	Baseline 139/89 - End 146/69
32-1205	5 y/o-M-Hispanic- (High)	Protocol violation	Baseline Tachycardia; BP (pulse)= 141/98 (136); End =127/83 (86)
63-1371	16 y/o-M-Hispanic- High	Lack of efficacy	Baseline Tachycardia; Initial BP 134/102 (102); End 129/98 (97)
50-2241	14 y/o-F-Mixed- (Mid)	Lack of efficacy	Baseline 142/80 End 140/77
56-1215	8 y/o-F- White- (Mid)	Protocol violation	Baseline 138/93 to 123/82
65-1317	7 y/o- M- White-(High)	Patient withdrew	No on-treatment values
40-1433	8 y/o-F-White-(Mid)	Adverse event	D/C symptomatic hypotension approximately 2 weeks into study. BP (pulse) at day of discontinuation sitting 109/71(88); standing 109/72 (96). Complaints of headache and dizziness.
39-1441	15 y/o-M-White (Mid)	Lack of efficacy	Baseline 145/83; End 144/106
39-1443	10 y/o -M-White (High)	Lack of efficacy	Baseline 136/99; End 128/91
39-1445	12y/o-F-White (Mid)	Protocol violation	Baseline 124/81; End 118/74
4-2019	14 y/o-M- White (Low)	Lack of efficacy	Baseline 138/91; End 131/98
33-2351	13 y/o- M-White (High)	Patient withdrew	Baseline 121/66; End 111/66

The sponsor lists the following children as having a serious adverse experience: #50-1243- A 7-year old mixed race, female (low dose) with SLE treated who received cyclophosphamide had her hospitalization prolonged due to bronchitis.

# 16-2059- An 11-year old, black male (low dose) broke a clavicle while bicycle riding and was hospitalized for an orthopedic procedure.

Two subjects had adverse events listed as “severe” in intensity. Patient # 64-1357 a 9 y/o Black female treated with the low dose group had numbness of tongue (angioedema???) with an intensity listed as “severe”, but apparently completed the study. Patient # 36-1411 a 13-y/o white male also treated with low dose had acute sinusitis with the intensity listed as “severe”.

**Long-term extension safety:**

There were provisions for subjects to enter a long-tem extension treatment phase. The number of such subjects who entered this phase of the study is unclear. The complete study report is scheduled for submission later this year. Aside from a 6-month visit, there was little information supplied on the dosing algorithm and other information captured. There were six subjects who discontinued during this portion of the study. Capsular summaries were supplied.

Patient # 34-1331, a 16-y/o white female developed increase blood pressure and abdominal pain after 52 days during open label study. She was diagnosed with biliary lithiasis. She was continued on losartan therapy.

Patient # 02-1381, a 11-y/o white female was hospitalized for progressive obesity, a karyotype indicated Turner's syndrome.

Patient # 01-1236, is a 15-y/o female of mixed race with SLE and among other conditions glomerulonephritis who completed the double-blind portion of losartan study. The subject was hospitalized after 2 months and 9 days for worsening lupus but had bronchitis and infected bronchiectasis. The subject was treated with cyclophosphamide. Approximately 1 month after a cyclophosphamide dose the subject was hospitalized due to a generalized seizure (there was no statement of a history seizure disorder at baseline). Blood pressure was elevated (magnitude not stated) at the time of the seizure (was this a hypertensive emergency?). The dose of losartan was raised. Five months into the study she was again hospitalized for a lobectomy of the infected bronchiectatic lobe.

Patient # 50-1243, 7-y/o female of mixed race and SLE developed worsening of her SLE and eventual acute renal failure that required dialysis after 12 days during the open-label phase. The subject was discontinued from losartan and was eventually started on enalapril and nifedipine. Renal function apparently did not recover.

Patient # 02-2381, a 15-y/o white female entered the open-label extension phase. She was hospitalized due to diarrhea and developed acute renal insufficiency. The sponsor notes that the renal insufficiency as well as the gastro-intestinal symptoms resolved.

Patient # 29-2401, 17-y/o black male with a history of hydrocephalus and seizure disorder sustained a seizure (I don't know what the frequency of seizures was before treatment) after approximately 3 ½ months on treatment during the open-label phase of the study

*[Comments: There were two subjects who developed renal failure in this database. Subject # 50-1243 and #02-2381 both developed acute renal failure. The role of losartan in exacerbating the renal disease is not clear. It is rare for kids in developed countries to progress to ARF during the course of a gastrointestinal episode (# 02-2381, the study site was in Poland). It is also not common for an exacerbation of SLE in pediatrics to result in ARF and CRF (the study site was in Peru).*

There were two subjects who developed seizures. # 28-2401 and #01-1236. The relationship of losartan to these events is unclear.]

**Adverse Events:**

Table 1.19 Adverse events with > 2 subjects in any group.

	Low (N=70)		Mid (N=41)		High (N=66)	
# subjects with ≥ 1 AE	33 (47%)		21 (51%)		33 (50%)	
Body as a whole	5 (7%)		4 (10%)		3 (5%)	
Asthenia/fatigue	2 (3%)	0	1 (2%)			
Fever	2 (3%)	0	1 (2%)			
Pain, abdominal	1 (1%)	2 (5%)	0			
Digestive system	8 (11%)		2 (5%)		6 (9%)	
Diarrhea	1 (1%)	2 (5%)	2 (3%)			
Dyspepsia	2 (3%)	0	1 (2%)			
Nausea	0	0	3 (5%)			
Musculoskeletal system	2 (3%)		2 (5%)		117 (2%)	
Nervous system and psychiatric	15 (21%)		5 (12%)		17 (26%)	
Dizziness	2 (3%)	0	2 (3%)			
Falling	2 (3%)	0	0			
Headache	7 (10%)	3 (7%)	13 (20%)			
Respiratory system	17 (24%)		15 (37%)		13 (20%)	
Asthma	2 (3%)	0	0			
Bronchitis	2 (3%)	0	1 (2%)			
Epistaxis	1 (1%)	0	2 (3%)			
Infection, respiratory	0	3 (7%)	0			
Infection, respiratory, upper	6 (9%)	3 (7%)	7 (11%)			
Influenza	3 (4%)	3 (7%)	0			
Pharyngitis	2 (3%)	1 (2%)	0			
Rhinitis	0	2 (5%)	0			
Skin and appendage	6 (9%)		3 (7%)		6 (9%)	
Sweating	0	0	2 (3%)			
Special senses	3 (4%)		0		3 (5%)	
Pain ear	2 (3%)	0	0			

There was no apparent dose relationship to adverse events. The most common event was headache.

**Heart Rate:**

The effect on sitting heart rate, both during the double blind period and during the withdrawal period, is shown below. Note that these measurements were not performed at peak drug effect.

Table 1.20 Sitting trough heart rate

Dose	N	Day 1	Day 22	Change ± SD
Low	70	85.8	83.5	-2.26 ± 10.11
Mid	40	84.7	85.4	0.70 ± 8.99
High	64	89.2	86.8	-2.4 ± 9.75

Table 1.21 Standing trough heart rate

Dose	N	Day 1	Day 22	Change ± SD
Low	70	92.0	90.1	-1.89 ± 10.2
Mid	40	93.5	92.3	-1.21 ± 12.2
High	62	94.5	94.1	-0.4 ± 10.4

Table 1.22 Sitting heart rate during withdrawal (day 36-Day 22)

Low			Mid			High		
Low	PBO	Δ*	Mid	PBO	Δ*	High	PBO	Δ*
-0.2	0.9	1.1	-5.8	0.8	6.6	0.9	0.0	-0.9

\*Δ = PBO-maintained on dose

Table 1.23 Standing heart rate during withdrawal (day 36-Day 22)

Low			Mid			High		
Low	PBO	Δ*	Middle	PBO	Δ*	High	PBO	Δ*
0.8	3.9	3.1	-0.3	-0.7	-0.4	-2.2	-0.1	2.3

\*Δ = PBO-maintained on dose

Trough heart rate, both sitting and standing are inconsistently changed, but do not apparently increase while on treatment.

**Laboratory:**

Laboratory measurements were collected at placebo washout, day 1 and end of study. There were no subjects who discontinued due to a laboratory event. There were 8 subjects who had laboratory events listed as adverse events. These are listed below. There does not appear to be a pattern to these events.

Table 1.24 Laboratory values listed as adverse events

Pt ID	Demographics	Tx	Event
02-1381	10-y/o W/F	Low	ALT =103 at baseline ALT= 90 double-blind
02-2201	14-y/o Hisp/F	Low	K <sup>+</sup> = 4.5 meq/l K <sup>+</sup> =5.3 meq/l double-blind
34-2331	11y./o W/M	Low	ALT=37 baseline ALT=51 double-blind
36-2430	14-y/o W/M	High	ALT=25 baseline ALT=49 double-blind
37-2415	13-y/o/W /F	Mid	Bili =18 umol/L baseline Bili =29 umol/L double-blind
64-1355	9-y/o/W/F	High	Ca <sup>+2</sup> = 2.171 at baseline Ca <sup>+2</sup> = 1.771 double blind Cl <sup>-</sup> = 101 meq/L at baseline Cl <sup>-</sup> = 118 meq/L double-blind
64-1357	9-y/o/B/F	Low	Cl <sup>-</sup> = 103 at baseline Cl <sup>-</sup> = 118 double-blind
65-2317	15-y/o W/M	Mid	SCr= 76.9 mmol/L at baseline SCr= 109.6 mmol/L double -Blind

**ECG:**

ECGs were only recorded at baseline.

APPEARS THIS WAY  
ON ORIGINAL

**2. Study # P216:**

**Title of Study:** An open-labeled, randomized, two-period, crossover study to determine the relative bioavailability of losartan 50-mg suspension and losartan 50-mg tablet administered orally as single doses.

**Investigator and Sites:**

**Protocol:**

This was a two-period, crossover study in which 16 subjects (8-per treatment) received either losartan suspension (see below) or losartan tablets.

**Inclusion Criteria:**

Subjects of either gender between the ages of 18 and 45 years within 20% of ideal body weight and if female non-pregnant were eligible.

**Exclusion criteria:**

Subjects were excluded if they had any illnesses or reproducible laboratory abnormality, which would confound the study. Subjects who recently donated blood or who had a history of bleeding disorder are excluded. Subjects who use controlled drugs, who smoke, consume > 4 cups of coffee daily or are taking vasoactive medications were also excluded. Subjects with a history of angioedema or a hypersensitivity to losartan are excluded.

**Doses:**

For losartan Tablet and suspension:

Table 2.1 losartan Tablet Clinical Lot number [Formulation #] and Instructions for preparing a solution

50 mg	WP-G370 [094FCT061C001]; WP-G370A [094FCT061C001]; WP-G371 [094FCT061C001]; WP-G371A [094FCT061C001];
50 mg suspension	40 mg of 2.5-mg/mL solution were prepared as follows:  2 x 50-mg losartan tablets were placed in 2 ml of sterile water into a polyethylene bottle. Shake vigorously for three minutes and allow to sit for an additional 20 minutes.  20 ml of OraSweet SF mixed with 20 mL OraPlus were separately mixed.  38 ml of the OraSweet SF/OraPlus were mixed with the losartan and shaken to disperse.  The suspension was stored at 2-8 degrees and shaken prior to administration.

**Procedures:**

Subjects received the initial dose after an overnight fast. Subjects could be discharged from the CRU after 24-hours, but they were to return for 30- and 36-hour blood draws. After a one-week washout period the crossover treatment was administered. The times of pharmacokinetic sampling was: 0, 1/4, 1/2, 3/4, 1, 1 1/4, 1 1/2, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 30 and 36 hours. Blood samples were analyzed for parent losartan and the active metabolite L-15864 [E-3174]. Log transformed data were used for the calculations.

**Results:**

The sponsor's tabulated results are shown below. Please refer to the biopharmaceutical review for additional descriptions and analyses.

Table 2.2 Pharmacokinetic constants for parent and active metabolite (L-158641).

	losartan			L-158641 [E-3174]		
	Suspension	Tablet	Mean Ratio (CI) <sup>1</sup>	Suspension	Tablet	Mean Ratio (CI) <sup>1</sup>
AUC <sub>0-∞</sub> ng*hr/mL	366	395	0.92 (0.82-1.06) <sup>1</sup>	1814	1787	1.02 (0.89-1.16) <sup>1</sup>
AUC <sub>0-t</sub> ng*hr/mL	358	388	0.92 (0.81-1.05) <sup>1</sup>	1781	1756	1.01 (0.90-1.16) <sup>1</sup>
Cmax (ng/mL)	208	174	1.20 (0.94-1.51) <sup>1</sup>	219	211	1.04 (0.88- 1.22) <sup>1</sup>
Tmax (hr) mean	0.6	1.5	-0.91 (-1.63 to -0.25) <sup>2</sup>	3.9	4.6	-0.6 (-2.0 to 0.5) <sup>2</sup>
<sup>1</sup> Geometric Mean Ratio		<sup>2</sup> Arithmetic Mean Difference				

The two formulations are bioequivalent with respect to AUC. Cmax and Tmax are higher and occur earlier with the solution for both losartan and E-3174.

**Safety:**

One subject had an asymptomatic blood pressure drop of 97/54 mm Hg at 4 hours and 96/51 at 24 hours. No adverse events were noted.

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

### 3. Study P225

**Title of Study:** Multicenter study: an open-label study to investigate the pharmacokinetics of losartan in hypertensive children and infants.

**Investigator and Sites:**

4 USA investigators, 1 investigator in each of the following countries: Brazil, Columbia, Israel and Mexico, The distribution of children and the site is shown as Table 1.

**Doses and formulations:**

Losartan is to be administered for seven days. The dose for group I (age 1 to 24 months) and group II (age 2 to 6 years) was 0.7 mg/kg/day, as a losartan suspension. For group III (age 6 < 12) the dose is to be 12.5 mg/day if they are able to swallow tablets and were ≤ 25 kg. Those > 25 and < 50 kg received 25 mg/day, and those ≥ 50 kg the dose is to be 50 mg/day. For those unable to swallow tablets, the dose was 0.7 mg/kg/day as the suspension. For group IV subjects (age ≥ 12 to 16) the dose was a 25-mg losartan tablet for those < 50 kg and 50 mg for those ≥ 50 kg.

Table 3.2 . Formulations: Clinical LOT # [Formulation #]

Strength	
12.5 mg	WP-H254 {E9284}; WP-H289 [E-9284]; WP-H295 [E-9284]; WP-H301 [E-9284]; WP-H333[E-9284]
25 mg	WP-H2555[0954-FCT01J3B001]; WP-H290 [0954-FCT01J3B001]; WP-H296 [E-9287]; WP-H302 [0954-FCT01J3B001]; WP-H3334 [E-9287]
50 mg	WLP-H253 [0954-FCT061C001]; WP-H256 [0954-FCT061C001]; WP-H288 [0954-FCT061C001]; WP-H291[0954-FCT061C001]; WP-H294[E-9671]; WP-H297 [E-9671]; WP-H300 [0954-FCT061C001]; WP-H303 [0954-FCT061C001]; WP-H322 [E-9671]; WP-H335 [E-9671]

The losartan suspension was prepared as follows:

2 losartan 50-mg tablets were placed in a PET bottle.

2 ml of sterile water was added and allowed to sit for 20 minutes, then shaken and dispersed for 1-minute.

20 ml of OraSweet SF and 20 ml of OraPlus were combined and mixed in a separate container.

38 ml of the OraSweet and OraPlus was added to the 2-ml of losartan containing suspension.

The suspension was shaken and stored at 2-8° C. The suspension was shaken prior to administration.

**Inclusion criteria:**

A total of 32 subjects were to be enrolled. These subjects are to be between the ages of > 1 month to < 16 years. Eight patients were enrolled in each of the following age groups:

- infants and toddlers (age 1-24 months; Group I);
- preschool aged children (age 2-6 years; group II);
- school aged children (> 6-12 years; Group III); and
- adolescents (> aged 12-16; Group IV),

These subjects are to have a documented history of hypertension, their parent must be willing to sign an informed consent and where appropriate, the child is to grant assent for the study. Patients are to have a GFR as determined by the Schwartz formula of  $\geq 30$  ml/min.

$$\text{GFR} = 0.55 * \text{Height (in cm)} / \text{Serum creatinine (in mg/dL)}$$

**Exclusion criteria:**

Subjects are to be excluded for:

- A recent (within 1 year) episode of severe hypertension.
- A history of heart failure.
- Clinically significant neurologic, respiratory, gastro-intestinal, hepato-biliary or hematologic disease or clinically relevant laboratory values.
- Cardiovascular disease, such as conductance disturbances, LBBB, sick sinus syndrome, heart failure.
- Post transplant.
- Recent use of losartan (7 days) or a history of sensitivity to AII blockers or a history of angioneurotic edema.

**Results:**

The description of those enrolled is shown below:

Table 3.3 Distribution of ages in study 225.

	Group I Infants and toddlers	Group II Preschool children	Group III School-aged children	Group IV Adolescents
Entered	11	13	12	14
Gender:				
Male, N (Age Range)	8 (3-23 months)	8 (2-5 years)	8 (6-11 years)	9 (12-15 years)
Female N (Age Range)	3 (10-23 months)	5 (2-5 years)	4 (7-8 years)	5 (12-15 years)

All subjects completed the study. Kinetic parameters, however, were collected on only 46 of the 50 subjects treated.

For more details about the pharmacokinetic results see the biopharmaceutical review.

A summary of the results for losartan and E-3174 (the main metabolite) are shown below. Note, the results need to be interpreted based on the differences in mean

doses. The results below are both those uncorrected and corrected for the difference in dose on mg/kg basis.

Table 3.4 Pharmacokinetic results

	Group I	Group II	Group III	Group IV
Number enrolled	11	13	12	14
Number with data	9	13*	11	14
Mean age (years)	1.14	3.66	8.96	14.75
Mean Dose (mg/Kg)	0.7	0.7	0.77	0.54
Losartan Parameters-Geometric mean (95% CI)				
AUC 0-24 (ng*hr/ml)	244.5 (162-368)	314.5 (239-414)	251 (142-445) 233 <sup>n</sup>	303.1 (253-363) 405 <sup>n</sup>
Cmax (ng/ml)	66.6 (41-108)	89.8 (59-137)	98.7 (64-153) 91 <sup>n</sup>	105 (71-155) 141 <sup>n</sup>
Median Tmax	1.05 (0.8-2.5)	1.07 (0.8-2.5)	2.0 (1.0-3.5)	1.5 (1.5-2.0)
Harmonic mean half-life (h)	1.93 (1.6-2.4)	2.37 (2.0-3.0)	2.2 (1.8-2.7)	2.41 (2.0-3.0)
Steady State Plasma E-3174				
AUC 0-24 (ng*hr/ml)	1456 (988-2146)	951 (680-1330)	1164 (819-1652) 1078 <sup>n</sup>	1590 (1165-2170) 2127 <sup>n</sup>
Cmax	147 (97-223)	91.5 (64-131)	139 (95-203) 129 <sup>n</sup>	188 (135-263) 252 <sup>n</sup>
Median T <sub>max</sub>	5.5 (3.7-7.8)	6.01 (5.0-7.0)	4.5 (3.0-6.0)	5.0 (4.0-5.1)
Harmonic mean half-life (h)	4.8 (4.3-5.5)	5.6 (5.0-6.4)	5.4 (4.8-6.2)	5.7 (5.1-6.5)
* One subject received a higher than planned dose and was excluded from these calculations				
<sup>n</sup> Normalized to 0.7 mg/kg dose				

The C<sub>max</sub> and AUC for the older group, particularly when corrected for differences in dose, were greater for both losartan and metabolite.

#### Safety:

There were no deaths, dropouts or serious adverse events.

One subject who enrolled into the extension phase of the study of the study had a serious adverse event.

“ Study 225-006/AN 4006. This was an 11-month old white female with VATER syndrome and a history of bowel surgery for imperforate anus and a left nephrectomy due to vesicourethral reflux. She was hospitalized on day 26 due to perianal abscess/fistula. She was discharged on antibiotic therapy. She was hospitalized on day 44 for bowel obstruction and dehydration.

#### Overall Adverse events:

Overall adverse events are listed below.

Table 3.5 Overall adverse events study # 225

Patient #	Gender	Age	Race	Dose	Day	Event
225-001; 4071	M	4 y	His	---	-5	Rhinitis
225-001;6022	M	6 y	His	25 mg	1	Pain, back
225-001; 6023	M	11 y	Hisp	---	-6	Upper respiratory infection
				25 mg	7	Rash
225-003; 4093	F	3 y	W	8 mg	2	Excoriation
				8 mg	5	Bronchitis
225-003; 4096	M	5 y	W	13.02 mg	6	Infection, upper respiratory
225-003; 4097	M	15 mo	W	7.5 mg	3	Trauma

225-005; 4007	M	23 mo	W	9.59 mg 9.59 mg	1 4	Vomiting Vomiting
225-005; 4008	M	2 y	W	12.32 mg 12.32 mg 12.32 mg	1 4 7	Diarrhea Muscle cramp Muscle cramp
225-005; 4009	M	18 mo	W	8.34 mg 8.12 mg	2 9	Diarrhea Diarrhea
225-005; 6010	F	15 y	W	50 mg	2	Asthenia, fatigue
225-006; 4006	F	10 mo	W	7 mg	16	Genital pain
225-007; 5009	F	8 y	B	25 mg --- --- --- --- ---	6 7 7 8 8 16	Flatulence Headache Neck pain Anorexia Abdominal pain Constipation
225-008; 6001	F	15 y	W	50 mg 50 mg 50 mg 50 mg	2 2 2 6	Malaise Asthenia/fatigue Anorexia Irritability
225-008; 6016	M	12 y	W	---	8	Diarrhea
225-010; 6044	M	14 y	W	50 mg 50 mg 50 mg	3 4 4	Respiratory infection Headache Pharyngitis
225-010; 6045	M	14 y	M	50 mg	3	Respiratory infection

None of these adverse events led to discontinuation.

**Laboratory Adverse events:**

Five subjects had six adverse events related to laboratory abnormalities. All subjects with adverse events were randomized from a single study center. All of these subjects had elevated serum creatinine values. All subjects were less than 4 years old. One subject, in addition, had a decrease in WBC (as well as ANC). There were no submitted follow-up values.

Table 3.6. Adverse laboratory abnormalities study #225

Study #	Pt #	Gender/Age/Race	Dose	Lab	Baseline	Post
225-003	4091	M/5 mo/W	5.75 mg	Scr	0.45 mg/dL	0.81 mg/dL
	4092	M/2 y/W	6.75 mg	Scr	0.23 mg/dL	0.7 mg/dL
	4093	F/3 y/W	8 mg	Scr	0.45 mg/dL	0.7 mg/dL
	4094	F/4 y/W	12 mg	Scr	0.6 mg/dL	0.9 mg/dL
	4095	M/ 8 mo/W	4.75 mg	Scr WBC ANC	0.55 mg/dL 12.4 x10 <sup>9</sup> /L 5084 x10 <sup>9</sup> /L	0.7 mg/dL 4.55 x10 <sup>9</sup> /L 591 x10 <sup>9</sup> /L

**Laboratory:**

The group means for hematology and chemistry values are shown below.

Table 3.7. Group mean changes in laboratory parameters study #225.

	Group I			Group II			Group III			Group IV		
	N	Change	SD	N	Change	SD	N	Change	SD	N	Change	SD
Hemoglobin (gm/dL)	11	-0.32	0.6	13	-0.09	0.7	11	0.06	0.7	14	-0.54	0.4
Hematocrit (%)	11	-0.733	1.7	13	-0.12	2.3	11	0.07	2.6	14	-1.2	1.1
Creatinine (mg/dL)	11	0.05	0.2	13	0.08	0.2	12	0.04	0.2	14	0.04	0.1
Uric Acid (mg/dl)	10	-0.20	1.3	13	-0.42	0.5	12	-0.21	0.7	13	-1.3	1.3
Sodium (mEq/L)	11	0.74	2.6	13	0.23	2.1	12	-2.2	3.01	14	0.5	2.8
Potassium (mEq/L)	11	-0.02	4	13	-0.01	0.3	12	0.05	0.6	14	-0.01	0.6

There were small and consistent increases in serum creatinine, but given the degree of variability in measurement, all values overlap the no-effect range.

**Vital signs:**

Vital signs were collected pre-dose, the first four hours after a dose and for 36 hours after the last dose. Supine measurements were performed for the lowest age group and sitting for the three older groups. There was an apparent drop in supine diastolic blood pressure relative to the single baseline measurement for the youngest group (Group I), for the other groups, the effect on sitting diastolic blood pressure does not appear different from the single baseline measurement. The effect on sitting systolic blood pressure is similar to that of diastolic although the youngest group demonstrated an attenuated effect. There was no consist effect on supine (group I) or sitting (Groups II-IV) pulse. The sponsor did not submit a pharmacokinetic/pharmacokinetic model for this database.

Table 3.8 Change in blood pressure study #225 relative to single baseline measurement.

Group			Hour											
			0	0.5	1	2	3	4	6	8	12	24	36	
I	Day I	Supine DBP	---		-8.8	-11.0	-5.6	-4.8						
		SD			8.9	11.2	12.0	12.8						
		N	9		8	8	7	6						
	End	Supine DBP	-4.8	-6.5	-7.5	-8.3		-7.4	-7.3	-7.3	-6.1	-4.1	-5.5	
		SD	9.6	8.9	10.0	13.1		10.5	10.2	9.6	10.5	10.0	13.8	
		N	9	8	8	6		8	6	8	8	8	8	
II	Day I	Sitting DBP	---		-5.4	-5.4	-2.1	-4.3						
		SD			8.1	8.3	7.0	7.5						
		N	12		10	9	8	8						
	End	Sitting DBP	-2.0	-3.7	-3.9	-1.5		-2.0	-4.0	-1.1	-0.9	-0.8	0.3	
		SD	8.5	9.1	7.5	7.6		11.3	10.9	11.5	5.9	6.5	7.8	
		N	12	11	12	11		12	11	12	11	12	12	
III	Day I	Sitting DBP	---		-0.4	-1.6	-1.0	2.0						
		SD	5.3		2.7	3.2								
		N	12		5	5	1	1						
	End	Sitting DBP	1.4	1.5	1.6	-0.8		-2.4	-1.7	0.3	1.9	2.1	5.0	
		SD	8.8	5.7	7.0	5.5		7.8	10.2	6.3	10.6	6.8	8.2	
		N	12	11	12	12		10	11	12	10	12	11	
IV	Day I	Sitting DBP	---		-0.4			4.1						
		SD	9.7		26			5.9						
		N	14		5.7			2						
	End	DBP	4.1	1.6	3.4	2.1		0.5	-4.1	-1.7	1.1	3.5	5.0	
		SD	5.9	8.2	8.2	8.0		9.8	9.0	10.8	10.8	11.5	99	
		N	14	14	14	14		14	14	14	14	14	14	

**Conclusion:**

This was a pharmacokinetic study in children of different age groups. Each child received one week of therapy. For the younger age groups, infants/ toddlers, (Group I) and preschoolers (Group II) the dose was 0.7 mg/kg/day by an extemporaneous formulation (the instructions for its preparations are supplied). For school aged children, age 6 < 12 (Group III) the dose was 12.5 mg/day if they are able to swallow tablets and were < 25 kg; 25 mg/day for those > 25 and < 50 kg and 50 mg for those  $\geq$  50 kg the dose is to be 50 mg/day. For those unable to swallow tablets, the dose was 0.7 mg/kg/day via suspension. For group IV subjects (age  $\geq$  12 to 16) the dose was a 25-mg losartan tablet for those < 50 kg, and 50 mg for those  $\geq$  50 kg.

The pharmacokinetic parameters of both losartan and its active metabolite, E33174 were, in general, similar across age groups. The oldest group, when the dose was corrected for differences in dose (assuming linearity of dose and AUC and Cmax) had somewhat higher exposure of both losartan and E-3174 than the younger groups.

There were no unusual safety issues. Only small increases in creatinine were noted.

APPEARS THIS WAY  
ON ORIGINAL

## Overall Safety:

The safety of losartan in children is derived from four sources.

- The safety as derived from the randomized clinical and pharmacokinetic studies, and include long-term extension information.
- A chart review of those under 18 years old treated at a pediatric nephrology clinic at the Children's Hospital of Pittsburgh, Pittsburgh, PA who received losartan. The database consists of a total of 89 patients.
- A summary of adverse experience reports is reported in children under 18 years old as reported from the Worldwide Adverse Experience Reports (WAES). There were 30 subjects with 32 adverse events captured by this system
- A literature search of the use of losartan in children, two publications were submitted.

### 1. Safety from clinical studies:

The safety profile, as derived from the randomized database is reviewed in conjunction with each of the individual studies.

### 2. Chart review.

The review consisted of a total of 89 subjects into three age categories < 6 years (n=5), 6 to < 12 (n=31) and 12 to < 18 (n=51). The majority of those captured by the chart review were Caucasian (81%) followed by blacks (18%). Approximately 51% were male. The mean duration of treatment was 1 year and 219 days, and ranged in duration from 25 days to 5 years. The mean starting dose of losartan was approximately 0.76 mg/kg (range 0.28-1.67 mg/kg/day).

Based on the chart review, the most common adverse events that potentially could be attributed to losartan was dizziness (16%). Other attributed events include headache (8%), asthenia/ fatigue (7%), blurred vision (4%), hypotension (4%), syncope (4%), and abdominal pain (3%) and hyperkalemia (3%).

There were no deaths in this database. One patient with membranoproliferative glomerulonephritis and baseline chronic renal insufficiency was hospitalized with presumed septic shock, acute renal failure and hyperkalemia.

The population culled from the chart review was a sick population. There were 11 subjects who had severe chronic renal disease (Cr clearance <25 mL/min/1.73 M<sup>2</sup>). Nine of these patients eventually began dialysis or were transplanted. Two additional patients progressed to severe renal disease during losartan treatment. There were a total of 3 subjects who progressed to end stage renal disease while on losartan.

Patient #121- This was a 17.8 year old white female who began treatment with losartan on March 18, 1998. This subject had a history of rapidly progressive glomerular nephritis due to IgA nephropathy. She was proteinuric (4.5g/day). In July, 1998 the dose of losartan was halved as her creatinine increased to 2.0 mg/dl. She began dialysis on

Patient #162- This was a 13.4 year old black male with focal segmental glomerular sclerosis. The subject began treatment on May 7, 1998 with an initial serum creatinine of 1.8 mg/dL. On September 8, 1998 the creatinine was 2.7 mg/dL. The subject eventually progressed to end-stage renal disease.

Patient # 181- This was a 14.9 year old white male with a history of proteinuria and focal segmental glomerular sclerosis. Treatment with losartan was started on February 5, 1998. The initial creatinine was 1.0 mg/dL. On \_\_\_\_\_ the creatinine rose to 1.4-1.5 mg/dL. The medication was discontinued at that time. While off medication the creatinine rose to 2.2 mg/dL on \_\_\_\_\_. Losartan was subsequently re-started. After an episode of pneumonia on \_\_\_\_\_ the creatinine rose to 6.8 mg/dL and hemodialysis was started.

*(Comment: These three cases are of concern. Although it is possible that the steep and rapid decline of renal function was independent of losartan therapy, and related to the natural course of the disease, it is also possible that the use of losartan contributed to this decline.)*

According to the sponsor, the percentile for weight, height and BMI were essentially unchanged for those > 6 years. For the small number of children < 6 years, there was a decrease in weight and BMI percentiles. The authors of the document attribute the loss of weight to two patients. One patient with nephrotic syndrome lost 4.7 kg in 5 weeks (was this due to loss of edema?) and a second subject who had a liver and small bowel transplant lost 2.9 kg in 19 weeks. Height was apparently spared for these patients.

**3. The summary of the Worldwide Adverse Event System (WAES)**

The summary of the WAES reporting system for those ≤16 years old for losartan are tabulated below. There were 32 such events captured. Of interest, two patients (#2 and 16) had marked elevations of creatinine in conjunction during losartan therapy. Patients #s 3, 8, 10, 13 had adverse events with a component of hypotension. Patients # (1, 5, 7, 9, 10, 18, 22, 23, 26, 27, 28, 29, 31 and 32) had accidental or purposeful overdoses (# 22, 23, 27 had suicide attempts). The table below contains line summaries of the adverse events.

Table 4.1 Line-listings for adverse events from WAES database.

	WAES #	AGE	Gender	Comments
1	00026055	3 y	M	Single pill ingestion
2	00080401	12 y	F	History of ventricular dysfunction and Fontan procedure. Concomitant medications included digoxin, furosemide, spironolactone and trichlormethiazide. She developed acute renal failure (maximum creatinine 3.2 mg/dL). The patient recovered over 2 weeks with a discharge creatinine of 0.81 mg/dL; .K+ values not supplied.
3	00122098	8 y	F	History of hypocalcemia and tricuspid atresia . Concomitant medications included spironolactone. She developed hypotension BP 50/20 approximately 3 hours after a losartan dose (41.5-mg). Dopamine was instituted. The patient recovered.

4	00125141	9 y	M	Subject with history of hypertension and membranoproliferative glomerulonephritis. The subject developed hyperacusis, hyperesthesia and visual disturbances. Concomitant medication included Zyrtec. The losartan was discontinued and the subject recovered. It is unclear how the discontinuation of treatment and cessation of the event was related.
5	01015199	4 y	M	Accidentally ingested 1 tablet.
6	01019453	15 y	F	This child was enrolled in the clinical trial (see page 21 of this review).
7	01019852	28 m	M	Subject enrolled into clinical study received approximately 2.5 times the specified dose. No hypotension was noted.
8	01029452	15 y	F	Child was enrolled into clinical study (see page 21 of this review). She had a history of SLE and anxiety disorder. She was enrolled into the open -label phase of the study. The dose of losartan was increased due to poor blood pressure control. She was hospitalized with a general seizure.
9	01037291	7 y	F	Subject was to take one 50-mg tablet of losartan daily. She received a dose of 200 mg of losartan and was hospitalized for observation. No hypotension was noted.
10	01037292	2 y	M	This subject accidentally ingested 7 losartan tablets. He was hospitalized for hypotension (90/60). Note : this is not hypotensive for a two-year old
11	01039803	11 y	F	This was a patient included in the clinical trial database. She developed obesity but was subsequently diagnosed with Turner's syndrome (see page 21 of this review).
12	01040570	11 m	F	This child with VATER syndrome had dehydration and infected anal fistula and was hospitalized for perianal fistula and later for bowel obstruction (see page 21 of this review).
13	01041758	8 y	F	This was a child who had life-threatening hypotension. (Comment: The report seems similar to WAES '00122098).
14	01049454	15 y	F	This report appears to be patient WAES # 01019543 with an adverse event of bronchitis.
15	01050970	16 y	?	This patient, with a history of nephritis, was treated with losartan 25-mg daily. The subject complained of asthenia/fatigue and somnolence. Blood pressure measurements indicated a BP of 151/59 with a repeat of 150/70. Losartan was discontinued.
16	01059808	15 y	F	This patient was enrolled into the clinical studies. Patient developed vomiting and diarrhea (secondary to presumed rotavirus infection). The patient developed elevated creatinine (2.1 mg/dL). She received intravenous fluids, antibiotics and nifedipine. The renal function recovered (last creatinine was 0.6 mg/dL)
17	01065508	8 y	M	This child was receiving dialysis. He developed bone marrow suppression (no values submitted) while on losartan. The results of a de-challenge test from other medications have not yet been submitted.
18	92050669	3 y	F	This was a possible ingestion, subsequently verified by serum measurements of losartan and E3174. Values not stated and therefore number of pills ingested is unclear. Child hospitalized for 24-hours. Blood pressure and heart rate were normal.
19	96023196	7 mo	M	Child treated with losartan for hypertension with treatment discontinued due to cough.
20	96121527	35 m	F	This child had Down's syndrome and endocarditis. The subject had a history of Steven's Johnson syndrome while on captopril, which was discontinued. The child's hand turned blue with sloughing of skin which may have begun with the start of losartan therapy. Concomitant medications included prednisone, albumin, diphenhydramine HCl, ciprofloxacin HCl, bumetanide, calcium carbonate, nystatin and nalbuphine HCl/sodium metabisulfite.
21	97013730	9 wk	M	This child with congestive heart failure was treated with losartan for hypertension developed transpiration(?).
22	97026049	11 y	F	Polypharmacy suicide attempt with parent's medication including losartan. Apparently, no sequelae to ingestion.
23	98035611	15 y	F	Suicide attempt with losartan/HCTX 1400/350mg. Aside from bradycardia (heart rate 52) the other vital signs were within normal range.
24	98105545	12 y	F	Child placed on losartan, but developed hair loss.
25	98105546	8 y	M	Child placed on losartan, but developed hair loss.
26	99038404	4 wk	M	Child breast fed by mother who was treated with amlodipine, atorvastatin and losartan developed rash. After discontinuation of each of the above the rash resolved.

27	99075559	16 y	F	Poly-pharmacy suicide attempt with parent's medication including losartan/HCTZ, 1250/312.5 mg, trandolapril/verapamil 140/12600 mg and sotalol 1600mg. She developed cardiovascular insufficiency and A-V block. She was intubated and required vascular support. She subsequently developed anemia.
28	99080938	?? y	F	Apparent ingestion of 30 50-mg losartan tablets. No additional outcome data supplied.
29	99110689	19 m	M	Ingestion, no sequelae.
30	01062533	11 y	M	Fell from bike and fell from bike and fractured clavicle
31	95060291	36 m	M	Possible ingestion but later discounted.
32	97026053	8 y	F	Child with asthenia/fatigue after three days of accidental mistreatment with losartan.

#### 4. Publications:

Two publications were supplied:

- A. Cachat, F.Guignard J-P "Successful treatment of post-renal transplant erythrocytosis with losartan" *Pediatr Nephrol*; 1999; 13 (8):718-9.

This is a case report of a single patient who had post transplant erythrocytosis, the excess in hemoglobin and elevated erythropoietin levels returned towards the normal range after treatment with losartan.

- B. Donati-Genet P, Bianchetti MG "Modulation of the renin-angiotensin-aldosterone system and cough in childhood" *Pediatr Nephrol* 1996; 10 (4) 545-6.

This publication consists of two case-reports of children with hypertension who developed cough on enalapril (0.3 mg/kg/day) as part of their regimen to control hypertension. The cough subsided when losartan (2-3 mg/kg/day) was substituted for enalapril.

#### Overall safety conclusions:

The database that supports safety is derived from multiple sources. In general, the safety appears no different than the safety of losartan in adults. The only concern that appears from this database is the number of pediatric patients who had evidence of acute renal failure in concert with losartan therapy or whose renal failure rapidly declined during therapy. It is impossible for this reviewer to determine if the decline was due to the disease process alone or was exacerbated by the concurrent use of losartan. Since there were no randomized concurrent controls, the overall interpretation is somewhat subjective. The observation, however, that renal function alterations as judged by increases in serum creatinine levels as well as frank onset of acute renal failure cannot be easily disregarded as random events.

## **APPENDIX 1-Tentative Labeling**

10 pages redacted from this section of  
the approval package consisted of draft labeling.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Abraham Karkowsky  
9/27/02 01:18:36 PM  
MEDICAL OFFICER