Protocol 004: **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.104)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*

DATE ASSIGNED: *26-Jun-1997*
DATE COMPLETED *27-Jun-1997*

04.1 STUDY PROTOCOL

04.1.1 Title

A dose rising study to assess the safety and preliminary pharmacokinetics of single intravenous doses of SK&F 108566 in healthy male volunteers

04.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the safety and pharmacokinetics of eprosartan, an A-II AT_1 receptor antagonist, in single intravenous doses.

04.1.3 Objectives

1. To evaluate the single dose safety and tolerability of intravenous SK&F 108566 over the dose range of 0.1 to 50 mg, and
2. To obtain preliminary pharmacokinetic data for intravenous SK&F 108566 in humans.

04.1.4 Study design

The study was a single-blind, placebo-controlled, intravenous dose rising study. Subjects were to participate in 4 study sessions which were separated by at least one week. During each study period, subjects received, by random allocation, placebo (50 ml 0.9 % sodium chloride solution USP, Baxter Healthcare, Deerfield, IL) or one of the following single intravenous doses of SK&F 108566 injection (5 mg/ml in 125 mM phosphate buffer in 10 ml ampoules, Lot# U-92010): 0.1, 0.3, 1, 3, 5, 10, 20, 35 or 50 mg. (However, the maximum dose of SK&F 108566 was limited to 20 mg because the study was terminated early.)

The appropriate dose of SK&F 108566 was diluted to a final volume of 50 ml with 0.9% sodium chloride injection, USP. Study medications were infused over a period of 30 minutes using an electronic syringe pump (AutoSyringe®, Model AS20GH-2, Baxter Healthcare, Deerfield, IL).

No subject proceeded to a higher dose until the lower doses had been safely (based on clinical grounds) administered and their effects observed in at least 3 subjects.

04.1.5 Protocol Amendments

There were no protocol amendment to this study.

04.1.6 Population enrolled/analyzed

12 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: Subjects were administered the study medication intravenously in the clinical pharmacology unit under nursing supervision.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 2 week prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each pharmacokinetic study session.

04.1.7 Study procedures

Subjects report to the clinical pharmacology unit between 7:30 a.m. after a 10-hour overnight fast. A brief physical examination was done and baseline symptoms and signs were recorded at the first session, and blood and urine samples obtained for clinical laboratory studies. An intravenous catheter kept patent with heparin (100 U/ml) was inserted in one forearm vein for 12 hours for drawing blood samples. A second intravenous catheter was placed in the other arm for administration of the study medication.

A 12-lead ECG was obtained prior to dosing, and a single-led ECG was monitored continuously for 8 hours after dosing. Supine blood pressure and pulse rate were recorded at times -15, -10, -5, 0 (predose), 5, 10, 15, 20, 25, 30,

35 and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 hours following start of the infusion of study medication. Subjects remained recumbent for 4 hours following dosing except to void. From 4 to 8 hours post dose, subjects were allowed to sit in bed while undergoing continuous single lead ECG monitoring. After 8 hours, subjects were allowed to ambulate in the clinical pharmacology unit at will.

Subjects remained in the clinical pharmacology unit for 24 hours after dosing. Water, soft drinks with caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing, and meals were given at 5, 10 and 24 hours post dose. Blood samples (5 ml) for pharmacokinetic analysis were drawn at 0 (predose), 0.5 (end of infusion), 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours following the start of the infusion of study medication.

Blood (15 ml) and urine samples were collected at 24 hours after dosing to repeat safety clinical laboratory tests. A brief physical examination and 12-lead ECG were performed at 24 hours. Subjects were discharged after collection of the last blood and urine sample. Subjects returned 1 week following the last study session for safety laboratory tests.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

04.1.8 **Pharmacokinetic procedures:**
Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 3 months. Plasma concentrations of eprosartan were determined by reverse phase HPLC with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml for a 0.5 ml aliquot. Urine was collected and pooled for the interval 0-24 hours after administration of study medication, and immediately frozen and stored at -20°C to be used later for exploratory biotransformation work. (N.B. The urine specimens were inadvertently discarded by the laboratory.)

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain Cmax, Tmax, the apparent terminal elimination rate constant (λ), AUC(0-τ), $T_{1/2}$, AUC(0-∞), the extrapolated area under the first moment curve from time zero to infinity {AUMC(0-∞)}, plasma clearance (CL) calculated as dose/AUC(0-∞), and the volume of distribution at steady state (Vss).

04.1.9 **Endpoints:**
Although not defined by protocol at this early stage in the development of research program for eprosartan, AUC(0-τ), AUC(0-∞) and Cmax were presumed to be the primary endpoints. Tmax, plasma clearance (CL) and the volume of distribution of steady state (Vss), the safety data were presumed to be the secondary endpoints.

04.1.10 **Sample size:**
The numbers of subjects in study groups were based on feasibility. No statistical power calculations were done.

04.1.11 **Investigator , Center and Study Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center, Philadelphia, USA. Dates: 17-Jun-1992 to 14-Aug-1992.

04.2. **STUDY POPULATION**

04.2.1 **Subject disposition:**
12 healthy male subjects, 20-42 (mean = 24.4) years of age, weighing 63.1 to 86.1 (mean = 78.4) kg, and 169-194 (mean = 180) cm tall, were randomized. 83% were Caucasian, 8% were African-American, and 8% were "Others".

04.2.2 **Withdrawals:**
10 of 12 subjects were withdrawn prior to completing all 4 study sessions. Subject #433 was withdrawn after one study session at his own request because he no longer wished to participate. Subjects #413, #414, #416, #418, #422, #428, #431 and # 432 (who were assigned to receive doses of SK&F 108566 > 20 mg) were withdrawn by the investigator when the study was closed early to limit the maximum intravenous dose of SK&F 108566 so that systemic exposure to SK&F 108566 did not exceed the maximum values (approximately 2000 ng/ml) studied during 30-day repeated dose animal toxicology experiments. Thus, the maximum dose of SK&F 108566 studied was 20 mg rather than 50 mg as specified by the protocol.

04.2.3 **Protocol violations:**
Subjects #413, #414, #416, #418, #422, #428, #431 and # 432 (who were assigned to receive doses of SK&F 108566 > 20 mg) were withdrawn by the investigator when the study was closed early to limit the maximum

intravenous dose of SK&F 108566 so that systemic exposure to SK&F 108566 did not exceed the maximum values (approximately 2000 ng/ml) studied during 30-day repeated dose animal toxicology experiments. Thus, the maximum dose of SK&F 108566 studied was 20 mg rather than 50 mg as specified by the protocol.

04.3. SAFETY RESULTS

04.3.1 General considerations:

A total of 12 adverse experiences (AEs) were reported for 6 subjects, viz., 11 AEs in 6 subjects on SK&F 108566 and 1 AE in 1 subject given placebo.

04.3.2 **Deaths:** There were no deaths during this study.

04.3.3 **Withdrawals:** There were no subjects withdrawn from the study because of adverse experiences.

04.3.4 **Serious, Non-fatal Adverse Events:** There was no non-fatal adverse experience during this study.

04.3.5 **Adverse Events:** No dose-related AEs were noted following intravenous administration of SK&F 108566. All AEs were mild in nature. The most frequent was diarrhea (3 episodes reported by 2 subjects).

Placebo (1 AE):	Subject #420 reported epistaxis (after weight lifting);
0.1 mg intravenous SK&F (2 AEs):	Subject #413 reported bilateral temporal headache, #416 reported partial paresthesia of fingertips
0.3 mg intravenous SK&F (2 AEs):	Subject #431 reported flatulence and diarrhea;
1.0 mg intravenous SK&F (2 AEs):	Subject #431 reported flatulence and diarrhea;
3.0 mg intravenous SK&F (5 AEs):	Subject #414 reported soreness of left upper arm, palpitations and diarrhea; #418 reported arthralgia (aching of knuckles), and lightheadedness.

04.3.6 Laboratory findings, ECGs, Vital signs

3 subjects on placebo (#413, 414 and 420) and 5 subjects following administration of SK&F 108566 (#413, #414, #416, #424 and #432) had blood pressure changes. The changes in blood pressure were isolated occurrences, they were not sustained, were asymptomatic, were not associated with changes in heart rate, and did not appear to be dose-related.

There was a 9-13 mmHg decrease from baseline in mean supine systolic blood pressure, and a 3-10 mmHg decrease in mean supine diastolic blood pressure 3 to 5 hours after administration of 20 mg SK&F 108566. No other clinically-relevant changes in mean supine blood pressure or heart rate was observed following intravenous administration of SK&F 108566.

Screening ECGs were normal. There were no clinically relevant ECG changes in any subject.

Subjects #414, #420 and #424 were noted to have elevated CPK (attributed by sponsor to physical exertion), all of which returned within the reference range at subsequent laboratory examinations performed 5-8 days later.

04.4. PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

Plasma concentrations of eprosartan were not detectable or very low in the majority of subjects given intravenous doses of 0.1 and 0.3 mg (Table Epro-004-1). Plasma concentrations were measurable for 2 to 4 hours following 1, 3, and 5 mg doses, and up to 8-10 hours following 10 and 20 mg doses of eprosartan administered intravenously.

Median Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner over the 1 mg to 20 mg intravenous dose range. Median $T_{1/2}$ for the 1 to 20 mg intravenous doses of SK&F 108566 ranged from 1.05 to 2.34 hours (which is similar to that observed with oral administration of the solution or tablet formulations of eprosartan, Protocol 003).

Plasma clearance and volume of distribution at steady state were only calculated for the 3 to 20 mg doses (because the percent extrapolated area for AUC(0-∞) following administration of 0.3 and 1 mg doses was greater than 20%). The median plasma clearance was approximately 125 ml/min (range= 117 ml/min to 136 ml/min). The blood clearance of eprosartan, calculated based on a blood-to-plasma ratio of 0.62 for eprosartan, was approximately 200 ml/min. Assuming normal hepatic blood flow of 1500 ml/min and negligible renal clearance of eprosartan, the estimated hepatic extraction ratio of eprosartan is approximately 0.15, giving an absolute bioavailability of approximately 85% when eprosartan is administered by the intravenous route.

The median steady state volume of distribution (Vss) was about 13 liters (range= 12.4 L to 14.5 L), which approximates total extracellular water. This small Vss indicates minimal tissue distribution of eprosartan and is consistent with the polar nature of eprosartan and a high degree of plasma protein binding (approximately 98%).

Table Epro-004-1. Pharmacokinetic values for intravenous SK&F 10866 administered to healthy volunteers

Parameter	Cmax [ng/ml]	T1/2 [h]	AUC(0-t) [ng.h/ml]	AUC(0-∞) [ng.h/ml]	CL [ml.min] (Wt-adj CL)	Vss [L] (Wt-adj Vss)
0.1 mg (n=4)						
Mean	NC	NC	NC	NC	NC	NC
Median	NC	NC	NC	NC	NC	NC
S.D.	NC	NC	NC	NC	NC	NC
0.3 mg (n=4)						
Mean	38.9	NC	NC	NC	NC	NC
Median	36.3	NC	NC	NC	NC	NC
S.D.	10.8	NC	NC	NC	NC	NC
1 mg (n=4)						
Mean	120.7	1.23	110.3	130.7	NC	NC
Median	118.8	1.05	110.5	136.0	NC	NC
Range	34.5	0.53	46.7	46.1	NC	NC
3 mg (n=4)						
Mean	333.2	2.24	458.8	499.2	114.1 (1.5)	12.51 (0.16)
Median	333.2	1.45	377.3	409.4	122.4 (1.5)	12.49 (0.16)
S.D.	20.5	1.85	215.6	238.2	39.9 (0.7)	1.18 (0.03)
5 mg (n=4)						
Mean	555.6	1.79	595.1	628.8	147.4 (1.8)	13.99 (0.17)
Median	592.9	1.68	631.7	663.7	131.3 (1.6)	12.72 (0.16)
S.D.	159.0	0.60	223.5	218.2	58.0 (0.8)	4.21 (0.06)
10 mg (n=4)						
Mean	1313.2	2.10	1573.0	1602.1	112.1 (1.4)	11.98 (0.14)
Median	1173.3	2.05	1430.3	1459.1	116.9 (1.4)	12.42 (0.15)
S.D.	345.2	0.40	537.6	531.0	32.8 (0.4)	4.21 (0.05)
20 mg (n=4)						
Mean	2286.7	2.24	2448.9	2490.8	149.8 (1.9)	15.34 (0.19)
Median	2404.6	2.34	2452.7	2500.2	135.5 (1.7)	14.53 (0.18)
S.D.	734.1	0.32	895.0	901.3	61.1 (0.9)	5.75 (0.08)

04.5. CONCLUSION

Single oral doses of eprosartan up to 350 mg given to healthy volunteers were not associated with serious adverse experiences in this study. No dose related increase in adverse experience was observed. The study was terminated early so that systemic exposure to eprosartan (based on preliminary Cmax data) did not exceed the maximum value (approximately 2000 ng/ml) studied during 30-day repeated dose animal toxicology experiments.

Plasma concentrations of eprosartan were not detectable or very low in the majority of subjects given intravenous doses of 0.1 and 0.3 mg. Plasma concentrations were measurable for 2 to 4 hours following 1, 3, and 5 mg doses, and for up to 8-10 hours following 10 and 20 mg doses of eprosartan administered intravenously. Median Cmax, AUC(0-τ) and AUC(0-∞) increased in a dose proportional manner over the 1 mg to 20 mg intravenous dose range. Median $T_{1/2}$ for the 1 to 20 mg intravenous doses of SK&F 108566 ranged from 1.05 to 2.34 hours.

The median plasma clearance was approximately 125 ml/min (range= 117 ml/min to 136 ml/min). The blood clearance of eprosartan, calculated based on a blood-to-plasma ratio of 0.62 for eprosartan, was approximately 200 ml/min. Assuming normal hepatic blood flow of 1500 ml/min and negligible renal clearance of eprosartan, the estimated hepatic extraction ratio of eprosartan is approximately 0.15, giving an absolute bioavailability of approximately 85% when eprosartan was administered by the intravenous route.

The median steady state volume of distribution (Vss) was about 13 liters (range= 12.4 L to 14.5 L), which approximates total extracellular water. This small steady-state volume of distribution indicates minimal tissue distribution of eprosartan and is consistent with the polar nature of eprosartan and a high degree of plasma protein binding (approximately 98%).

Protocol 005: **NDA 20-738 Teveten™ (Eprosartan) Tablets** ***(Vol. 1.104)***

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *27-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *27-Jun-1997*

05.1. **STUDY PROTOCOL**

05.1.1 **Title** ***A study of the absolute bioavailability and effect of food on the final commercial formulation of eprosartan in healthy male volunteers***

05.1.2 **Rationale**

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and offer potential therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the effect of food on eprosartan pharmacokinetics following a 300 mg dose which is anticipated to be the final commercial formulation for the treatment of hypertension. Because eprosartan pharmacokinetics are not dose proportional at doses greater than 200 mg, the effect of food on the commercial formulation was investigated.

05.1.3 **Objectives**

1. To estimate the difference between the pharmacokinetics of a single oral doses of the final commercial formulation for eprosartan following a standard high fat meal and under fasting conditions in healthy male volunteers,
2. To estimate the absolute bioavailability of the final commercial formulation of eprosartan following administration of an immediate release tablet compared to an intravenous infusion, and
3. To evaluate the safety and tolerability of intravenous and oral eprosartan.

05.1.4 **Study design**

The study was a randomized, open-label, three-period, period balanced crossover study of three groups (A, B and C). Each subject participated in three study periods separated by ≥ 3 days from the last blood sample of the preceding study session. At each study session, subjects received a single oral dose of one of the following:

1. Regimen A: eprosartan 300 mg, (Lot# U94191, 100 mg tablet x 3) administered orally to fasted subjects,
2. Regimen B: eprosartan 300 mg, (Lot# U94191, 100 mg tablet x 3) administered orally following a standard high fat meal,
3. Regimen C: eprosartan 20 mg , (Lot# U92078, injection, Formula A) administered intravenously to fasted subjects.

05.1.5 **Protocol Amendments**

There were no amendments to the protocol.

05.1.6 **Population enrolled/analyzed**

20 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were screened.

Compliance: All study medication was administered at the testing site under the supervision of site personnel.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, and physical examination. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 1 week prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period.

05.1.7 **Study procedures**

After an overnight fast, patients reported to the clinical pharmacology unit at 7:00 am. Assessment of baseline symptoms and vital signs, and a brief physical examination were made. Blood (15 ml) and urine were obtained for clinical laboratory tests. The fed group was given a standard breakfast (2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 2 teaspoons (10 grams) of butter, 4 ounces (113 grams) of hash brown potatoes and 8 ounces (240 ml) of whole milk) equivalent to 1020 calories (58 g carbohydrate, 33 g protein, 58-75 g fat). The meal was given at 7:30 am, and completely consumed within 20 minutes. Subjects allocated to the fed or fasted groups were physically separated during the consumption of the breakfast.

At 8:00 am (within 20 minutes of fed subjects finishing the meal), all subjects were administered the study medication with 240 ml of tepid water. No food or drink was permitted for 5 hours after dosing. Subjects drank

240 ml water at 4 hours after dosing. Water, soft drinks with caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing, and lunch and dinner were given at 5 and 9-10 hours post dose, respectively. Subjects remained in the clinical pharmacology unit for 24 hours after dosing.

For subjects receiving intravenous eprosartan, a second intravenous catheter was inserted in the arm opposite the heparin lock. The intravenous dose of eprosartan (20 mg = 4 ml) was diluted with 46 ml of 0.9% sodium chloride injection; the total in infusate was 50 ml, administered by an electronic infusion pump over a 30 minute period, followed by an additional 20 ml of normal saline to flush the line. All timings for the blood samples related to the commencement of the infusion.

Prior to dosing and at 1 and 2 hours post-dose, sitting blood pressure and pulse rate were obtained. For subjects who had oral dosing, blood sample (5 ml) collections for pharmacokinetics were done pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours following dosing. For subjects assigned to intravenous dosing, blood sample (5 ml) collections for pharmacokinetics were done prior to starting the infusion, and at 0.25, 0.5 (immediately after termination of the infusion), 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours following the start of the infusion. Subjects were permitted to leave the center after the 24 hour pharmacokinetics sample was drawn. Subjects returned 1 week following the last study session for safety laboratory tests.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

05.1.8 **Pharmacokinetic procedures:**
Following collection, blood samples were centrifuged at 4°C, and plasma was transferred to polypropylene containers and frozen at -20°C, and were assayed within 3 months. Plasma concentrations of eprosartan were determined by a reversed-phase HPLC method with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml based on a 0.5 ml aliquot.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain Cmax, Tmax, the apparent terminal elimination rate constant (λ), AUC(0-τ), $T_{1/2}$, AUC(0-∞), and, for subjects given intravenous eprosartan, plasma clearance (CL) calculated as dose/AUC(0-∞), and the volume of distribution at steady state (Vss). Absolute bioavailability (F) of eprosartan was determined as the ratio of dose-normalized AUC(0-∞) for eprosartan after single oral (fasted state) and intravenous dose administration.

05.1.9 **Endpoints:**
Not defined in the protocol, but it could be assumed that AUC(0-τ) and Cmax were primary endpoints, and Tmax was the secondary endpoint, and that clinical monitoring and laboratory safety data were also secondary endpoints.

05.1.10 **Sample size:**
Based on an average within-subject coefficients of variation (CVw) for AUC and Cmax to be 23.8% and 20.8%, respectively, it was estimated that a sample size of 12 would provide at least 90% power, on a two-tailed procedure, with Type I error rate of 5% and a critical range symmetric on the ln-scale, to detect a difference of at least 30% between the fed and fasted regimens.

05.1.11 **Investigator , Center and Study Dates:**
Rita Hust, MD, Focus Clinical Drug Development GmbH, Neuss, Germany.
Study dates: 08-Mar-1995 to 03-May-1995.

05.2. **STUDY POPULATION**

05.2.1 **Subject disposition:**
20 healthy male volunteers were screened; 2 failed to meet entrance criteria. 18 male subjects, 24-38 (mean = 29) years of age, weighing 51.0 to 101.0 (mean = 77.3) kg, and 168-195 (mean = 181) cm tall, were screened and randomized. All were white. All subjects received at least one dose of study medication.

05.2.2 **Withdrawals:**
One subject (#009) was withdrawn after oral eprosartan 300 mg in the fed state because of an adverse experience.

05.2.3 **Protocol violations:**
No protocol violations were reported.

Figure Epro-005-1. Time course of plasma concentrations following a single oral dose of eprosartan in fed and fasted states and a single intravenous dose of eprosartan in the fasted state.

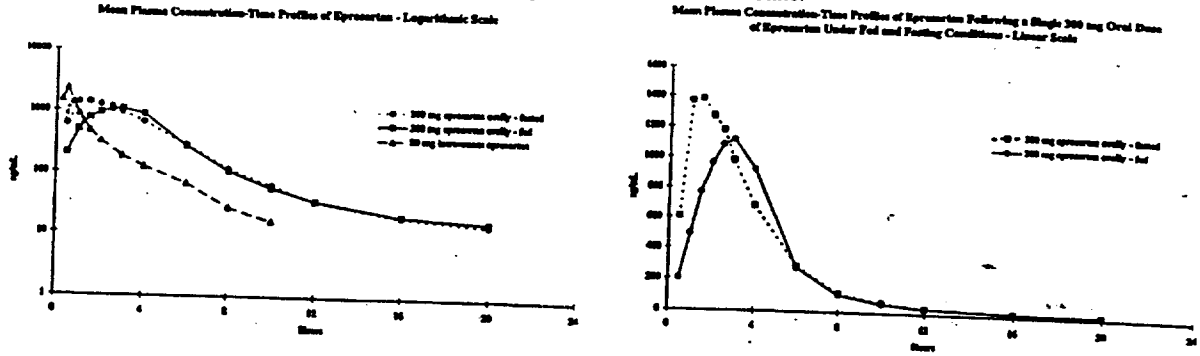


Table Epro-005-1. Pharmacokinetic values for eprosartan following single oral or i.v. doses of eprosartan in fed and fasted states

End Point	Eprosartan 300 mg fasted	Eprosartan 300 mg fed	Eprosartan i.v. 20 mg fasted
AUC(0-τ) (ng.h/ml)			
Mean	5657	4807	2631
Median	5547	4655	2746
S.D.	2694	1907	582
AUC(0-∞) (ng.h/ml)			
Geometric Mean	5107	4601	2605
Mean	5750	4950	2671
Median	5654	4719	2768
S.D.	2716	1884	576
Dose-normalized AUC(0-∞) (ng.h/ml)			
Geometric Mean	17.02		130.25
Mean	19.17		133.55
Median	18.85		138.38
S.D.	9.05		28.79
Cmax (ng/ml)			
Geometric Mean	1452	1102	2231
Mean	1612	1205	2246
Median	1675	1222	2255
S.D.	720	484	255
Tmax (hr)			
Mean	1.62	2.82	0.50
Median	1.50	3.00	0.50
S.D.	0.63	0.61	0.00
$T_{1/2}$ (hr)			
Mean	4.52	7.25	2.07
Median	3.91	6.24	1.87
S.D.	3.05	4.61	0.63

The high fat meal caused a delay in Tmax as the median difference between oral eprosartan in the fed state compared to the fasted state was 1.25 hours (Table Epro-005-2).

The above findings indicate that single oral doses of eprosartan following a high fat meal resulted in a similar extent of absorption but a decrease in the rate of absorption of eprosartan. The sponsor suggested that the clinically relevant efficacy parameter for control of blood pressure was likely to be AUC not Cmax, and that while Cmax may be different for eprosartan when administered with food, it is not clinically significant for efficacy, and therefore that eprosartan at a dose of 300 mg could be recommended to be given without regard to meal times. Also, in another study (protocol #007), the administration of a single 350 mg oral dose of eprosartan with a high fat meal resulted in an increase in mean AUC by 55% (7836 ng.h/ml fed vs 5041 ng.h/ml fasted) and Cmax by 80% (2259 ng/ml fed vs 1247 ng/ml fasted). In that study, a different formulation (direct compression formulation) of eprosartan was used (in

contrast to the commercial wet granulation formulation used in the current study) which may account for the differences in the food effect.

Table Epro-005-2. Point Estimates and 90% confidence intervals of comparisons of oral and i.v. eprosartan in fed and fasted states

Parameter	Comparison	Point Estimate	95% Confidence Interval
AUC(0-∞)†	B:A	0.89	(0.70, 1.13)
Cmax†	B:A	0.75	(0.58, 0.96)
Tmax§	B-A	1.25 h	(0.75 h, 1.75 h)
Absolute Bioavailability*	A:C	13.1%	(10.7%, 16.0%)

† Data presented as the ratio of the geometric means for oral eprosartan in regimen B (fed) : regimen A (fasted)
§ Data presented as the median difference of oral eprosartan in regimen B (fed) - regimen A (fasted) and 95% C.I.
* Data presented as the ratio of the geometric means of dose-normalized AUC(0-∞) after single oral (fasted) dose and intravenous (fasted) dose.

The mean plasma clearance (CL) of eprosartan after a 20 mg intravenous dose was 131.8 (±36.2) ml/min, and the mean volume of distribution at steady state was 12.6 (±2.6) Liters, the latter approximating total extracellular water. Absolute bioavailability of eprosartan, determined as the ratio of the geometric means of dose-normalized AUC(0-∞) after single oral (fasted state) and intravenous dose administration, was 13.1% (Table Epro-005-2) with a 95% confidence interval of (10.7% to 16.0%). Individual absolute bioavailability values of eprosartan ranged from 6.4% to 28.8%. The residual coefficient of variation for this comparison was 27.9%.

(Note: The residual coefficients of variation in this study for AUC(0-∞) and Cmax (single oral fasted vs single oral fed states) were 33.3% and 35%, respectively. These observed values were higher than those used for sample size estimation (23.8% and 20.8% for AUC and Cmax, respectively), indicating that 24 subjects would have been required to provide at least 90% power to detect a difference of at least 30% between the fed and fasted regimens.)

05.5 CONCLUSION

Single dose oral administration of 300 mg eprosartan in fed and fasted states and intravenous administration of 20 mg eprosartan in fasted state were not associated with serious adverse events in this study.

Following single oral doses of 300 mg of eprosartan, plasma concentrations peaked within 1 to 2.5 hours in the fasted state and within 2.5 to 4 hours in the fed state, and declined in a mono- or bi-exponential manner. Following intravenous dose of 20 mg eprosartan, plasma concentrations declined from peak in a bi-exponential manner.

The geometric mean for Cmax in the fed state was 25% lower than in the fasted state, with the ratio (point estimate) being 0.75. This is due to Cmax being decreased (by 23% to 65%) in 11 of 17 subjects and increased (by 3% to 67%) in 6 of 17 subjects in the fed state compared to the fasted state.

The geometric mean of AUC(0-∞) was decreased (by 9.9%) in the fed state compared to the fasted state, because AUC(0-∞) decreased (by 12% to 54%) in 10 of 17 subjects and increased (by 12% to 118%) in 6 of 17 subjects in the fed state compared to the fasted state; in one subject, there was no change.

The high fat meal caused a delay in Tmax as the median difference between oral eprosartan in the fed state compared to the fasted state was 1.25 hours.

These suggest that single oral doses of eprosartan following a high fat meal resulted in a similar extent of absorption but a decrease in the rate of absorption of eprosartan, and that a 300 mg dose of eprosartan can be given orally without regard to meal times.

The mean plasma clearance (CL) of eprosartan after a 20 mg intravenous dose was 131.8 (±36.2) ml/min, and the mean volume of distribution at steady state was 12.6 (±2.6) Liters, the latter approximating total extracellular water. Absolute bioavailability of eprosartan, determined as the ratio of the geometric means of dose-normalized AUC(0-∞) after single oral (fasted state) and intravenous dose administration, was 13.1% with a 95% confidence interval of (10.7% to 16.0%). Individual absolute bioavailability values of eprosartan ranged from 6.4% to 28.8%. The residual coefficient of variation for this comparison was 27.9%.

Protocol 006 NDA 20-738 Teveten™ (Eprosartan) Tablets *(Vol. 1.080)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *27-Jun-1997*
DATE COMPLETED *30-Jun-1997*

06.1 STUDY PROTOCOL

06.1.1 Title

A dose-response study to assess the pharmacokinetics and pharmacodynamics of single oral doses of SK&F 108566 in healthy male volunteers

06.1.2 Rationale

Angiotensin-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the effect of eprosartan, an A-II AT1 receptor antagonist, on angiotensin-II-induced decreases in effective renal plasma flow, and the relationship of this effect to plasma concentrations of eprosartan in healthy volunteers.

06.1.3 Objectives

1. To assess the onset of the inhibitory effect of SK&F 108566 on angiotensin-II-induced decreases in effective renal plasma flow (ERPF) (Part 1);
2. To assess the inhibitory effect of SK&F 108566 on angiotensin-II-induced decreases in (ERPF) at 24 hours after dosing (Part 1);
3. To establish the lack of agonist activity of SK&F 108566 as determined by the absence of a SK&F 108566-induced decrease in ERPF (Part 1);
4. To assess the dose-response profile of single oral doses of SK&F 108566 on SK&F 108566 pharmacokinetics and on inhibition of angiotensin-II-induced decreases in ERPF (Part 2);
5. To describe the relationship between plasma concentrations of SK&F 108566 and inhibition of angiotensin-II-induced decreases in ERPF (Part 2);
6. To assess the inhibitory effect of selected doses of SK&F 108566 on angiotensin-II-induced decreases in ERPF at 12 hours after dosing (Part 3).

06.1.4 Study design

The study was a double-blind, placebo-controlled, four-period, period-balanced crossover study conducted in 3 parts. An additional study session (Session 5) was added to Part 1 of the study to further investigate activity of SK&F 108566 at 12 hours, which was not blinded.

During 2 study sessions of Part 1, PAH alone (i.e., without angiotensin II administration) was administered to assess the angiotensin-II agonist effects of SK&F 108566 compared to placebo.

During the remainder of Part 1, and during Parts 2 and 3, PAH and angiotensin II were administered to assess changes in effective renal plasma flow (as measured by PAH clearance), blood pressure and pulse rate, and serum aldosterone concentrations at 0 to 3 hours, and 24 to 27 hours after dosing (Part 1, Sessions 1 to 4), at 0 to 3 hours after dosing (Part 2) and at 12 to 15 hours (Part 1, Session 5, and Part 3) following the administration of SK&F 108566 or placebo. Treatments (SK&F 108566 or placebo) were allocated in a random sequence. Study sessions were separated by an interval of 7 days.

Study medications used were SK&F 108566 oral tablets 10 mg (Lot# U-92054), 50 mg (Lot# U-92055) and matching placebo tablets (Lot# U-92053), Aminohippurate sodium (PAH) injection (Merck, Sharpe and Dohme Pharmaceuticals) 20%, 10 ml vials, and Angiotensin II (Hypertensin®, Ciba-Geigy Pharmaceuticals) for intravenous injection, 2.5 mg in ampoules.

06.1.5 Protocol Amendments

There were 3 amendments to the original protocol.

In Amendment 1, the maximum allowed systolic blood pressure was changed from >120 mmHg to >130 mmHg at screening, and from >128 to >138 at baseline; the restriction against use of medications was reduced from 2 weeks to 5 days prior to or during the study. Enrollment criteria were changed to restrict participation to Caucasian males only because black subjects were noted to have increased pressor response to angiotensin II infusions.

In Amendment 2, the maximum allowed increase in systolic/diastolic blood pressure during infusion of angiotensin II was revised from >30/20 mmHg to sustained blood pressure elevations of >35/30 mmHg for more than 1 hour.

In Amendment 3, the second planned PAH and angiotensin-II infusions (22 to 28 hours after administration of study) in part 2 of the study were deleted.

06.1.6 **Population enrolled/analyzed**

33 healthy Caucasian (by protocol amendment) male volunteers 18-45 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All study medication was administered by study personnel.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical history, 24-hour dietary history to estimate baseline sodium and potassium intake, physical examination, and 12-lead ECG. After resting supine for 15 minutes, 3 measurements of blood pressure and pulse rate were obtained at 2 minute intervals. Subjects then stood for 5 minutes following which 3 measurements of blood pressure and pulse rate were obtained at 2 minute intervals. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). A 24-hour urine specimen was also obtained for urine volume, creatinine, sodium and potassium excretion; instructions regarding dietary sodium supplements were based on the 24 hour urinary sodium and potassium excretion results.

Salt supplementation: Based upon the dietary history obtained at screening, subjects received instructions to take a 2500 calorie diet containing about 200 mEq sodium and 100 mEq potassium for at least 5 days prior to each study session. They were also given up to 3 g sodium chloride (1 g tablets, Eli Lilly & Co.) 2 times daily, and up to 30 mEq potassium chloride (10 mEq K-Dur® tablets, Key Pharmaceuticals) 2 times daily during the 5 days prior to and throughout the study. No salt supplementation was given during the PAH infusions. Each subject collected a 24-hour urine sample on the day before each admission to the clinical research unit and returned with the collection the next morning. The urine samples were analyzed for sodium, potassium, creatinine, and volume to evaluate sodium and potassium excretion (and electrolyte supplements were given based on the results, targeted sodium excretion being 200 mEq/day, and potassium 100 mEq/day).

06.1.7 **Study procedures**

Study sessions for Parts 1, 2 and 3 were conducted in a similar manner. Subjects were admitted at 4:00 pm on Day 1. Dinner was served. Blood and urine samples for safety laboratory studies were collected prior to dosing. A 12-lead ECG and brief physical examination were performed. At 5:15 am the following morning, the subject voided in the bathroom. Subjects then remained supine. An intravenous catheter was placed in both forearm veins. Blood specimens were obtained for pre-dose aldosterone and cortisol concentrations.

PAH clearance tests were performed on the morning of each study period. An iv loading dose of PAH (8 mg/kg) was given at 7.00 am followed by continuous intravenous infusions of maintenance doses of PAH for 6 hours. PAH maintenance infusions were started 1 hour (equilibrium) prior to initiation of the angiotensin-II infusions, continued during infusion of angiotensin-II, and were discontinued 1 hour following the discontinuation of the angiotensin-II infusions. Single-lead ECG was monitored continuously during infusion of PAH. Blood pressure and heart rate were measured every 15 minutes following initiation of the PAH infusions, and every 5 minutes during the last 15 minutes of the PAH equilibration period (prior to administration of angiotensin II). The "baseline blood pressure and heart rate" were defined as the average of the 4 readings taken immediately before the start of the angiotensin II infusion.

Angiotensin-II was reconstituted with sterile water for injection to make a stock concentration of 2.5 mg/ml, and further diluted with 5% dextrose in water to make a final concentration of 1000 ng/ml which was administered by continuous intravenous infusion using an electronic syringe pump. The infusion was started at a rate of 0.3 ng/kg/min and titrated as follows: 0.3 ng/kg/min for 5 minutes, 1 ng/kg/min for 5 minutes, 3 ng/kg/min for 5 minutes, and then 10 ng/kg/min for the remainder of the infusion period. Angiotensin-II infusions were started 1 hour after initiation of the PAH infusions and continued for a total of 4 hours. Angiotensin II infusion were not administered to subjects if their baseline systolic blood pressure exceeded 138 mmHg or their baseline diastolic blood pressure exceeded 84 mmHg. Angiotensin II infusions were to be terminated if the supine systolic blood pressure increased by >35 mmHg or the supine diastolic BP increased by >30 mmHg or if the supine pulse rate decreased to <40 bpm, and these changes were sustained for > 1 hour.

PAH and angiotensin II were administered at the same time of day during each study session. The time of administration of study medication was altered in order to assess ERPF at 0-3 hours and 24-27 hours, or at 12-15 hours following administration of SK&F 108566 or placebo. Study medications were administered at approximately 9:00 am on Day 2 of the study session (Part 1, Sessions 1 to 4, and Part 2) or 9:00 pm on Day 1 of the study session (Part 1, Session 5, and Part 3), with 200 ml of water. Study medication given on Day 2 was administered after a 10-hour overnight fast. Study medication given on Day 1 was administered at least 4 hours after the evening meal. Treatment regimens were allocated as shown in Table Epro-006-1:

Table Epro-006-1: Treatment Regimens

			PAH		Angiotensin-II	
Part	Session	Study Medication‡	Start* (hrs)	Stop* (hrs)	Start* (hrs)	Stop* (hrs)
1	1 - 4§	A, B	-2 22	4 28	-1 23	3 27
		C, D	-2 22	4 28	Not given	
	5	E	10	16	11	15
2	1 - 4§	A, B, C, D, E, F, G	-2	4	-1	3
3	1 - 4§	A, B, C, D	10	16	11	15

* Infusion start and stop times relative to time of dosing with study medication

‡ Study Medication: Part 1 - SKAF 108566 200 mg = A, C, E; Placebo = B, D
Part 2 - SKAF 108566: A= 10 mg, B= 30 mg, C= 50 mg, D= 70 mg, E= 100 mg, F= 200 mg; G = Placebo
Part 3 - SKAF 108566: A=50 mg, B=100 mg, C=350 mg; D = Placebo

§ Sequence of administration of study medication was double blind and randomized. Subjects received seven tablets, comprised of active drug and/or placebo, for each dose of study medication.

Sitting blood pressure and heart rate were measured in Part 1 (Sessions 1 to 4) at 6, 8, 12, 16 and 21 hours, Part 1 (Session 5) and Part 2 at 6, 8, and 12 hours, and Part 3 at 0.5, 1, 2, 3, 4 and 8 hours. Subjects were allowed to void spontaneously, but were not permitted to stand to void during angiotensin-II infusions. They remained supine during the infusions of PAH and angiotensin II. Water, soft drinks without caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing. For Parts 1 and 2, meals were served at 5, 11 and 28 hours following the dose of the study medication. For Part 3, subjects remained fasted except for sodium and potassium supplements and non-caffeinated beverages until 16 hours following the evening dose of the study medication.

Blood sample (5 ml) for PAH, cortisol and aldosterone were collected during Part 1 (sessions 1 to 4) at -1, 0 (predose), 1, 2, 3, 4 23, 24, 25, 26, 27 and 28 hours after the dose of study medication. During Part 2, samples were obtained at -1, 0 (predose), 1, 2 and 3 hours after dosing. During Part 1 (session 5) and Part 3, samples were obtained at 10.75, 11, 12, 13, 14, 15 and 16 hours following dosing. Blood samples (5 ml) for pharmacokinetic analysis were obtained in Parts 2 and 3 only. In Part 2, samples were drawn at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 15 and 24 hours following dosing. In Part 3, samples were drawn at 0 (predose), 0.5, 1, 1.5, 2, 3, 6, 10, 12, 15 and 20 hours following dosing.

A brief physical examination and 12-lead ECG were performed at 24 hours following medication, or, for Part 3 and Part 1 Session 5, 4 hours after the end of the infusion period. Blood and urine samples for safety laboratory tests were collected before discharge, or for Part 1 session 5 and Part 3 the following morning (36 hour). Subjects returned 4 - 7 days following the last study session, at which time safety laboratory tests were performed.

Adverse experiences (AEs) were elicited by spontaneous reporting by subjects, by nursing observation, physical examination findings, laboratory findings and 12-lead ECG data.

06.1.8 Assay Methodology

06.1.10 **Endpoints and Statistical Analyses:**

The Primary Endpoint for pharmacodynamic effect was CL_{PAH}, a measure of effective renal plasma flow

The Secondary Endpoints were urinary excretion rates and fractional excretion for Na^+, K^+ and Cl^-, plasma cortisol and aldosterone levels and pharmacokinetic parameters for SK&F 108566.

For Part 1, the onset of inhibitory activity of eprosartan on angiotensin-II induced decreases in ERPF and the inhibitory activity of eprosartan on angiotensin-II induced decreases in ERPF at 24 hours after dosing were determined by estimation of the difference (and associated 95% confidence intervals) in CL_{PAH}: (i) between Regimen A (350 mg eprosartan in the presence of angiotensin-II) and Regimen D (placebo, no angiotensin-II infusion); and (ii) between Regimen B (placebo in the presence of angiotensin-II) and Regimen D (placebo, no angiotensin-II infusion). The activity of eprosartan at 12 hours after dosing is obtained by the difference and associated 95% confidence intervals in CL_{PAH} between Regimen E (350 mg eprosartan in the presence of angiotensin-II) and Regimen D (placebo, no angiotensin-II infusion). The lack of agonist effect of eprosartan (defined as the absence of an eprosartan-induced decreased in ERPF) was examined by the estimation of the difference and associated 90% confidence intervals in CL_{PAH} between Regimen C (350 mg eprosartan, no angiotensin-II infusion) and Regimen D (placebo, no angiotensin-II infusion); lack of agonist activity was established when the 90% confidence interval for the difference in ERPF between Regimens C and D was contained within the equivalence range: (-22% of Regimen D, +22% of Regimen D).

For Part 2, the relationship between dose of eprosartan and the inhibitory activity of eprosartan on angiotensin-II-induced decreases in ERPF was examined by estimating all pairwise differences and associated 95% confidence intervals in CL_{PAH} between each of the seven doses (eprosartan 10, 30, 50, 70, 100 or 200 mg, or placebo).

For Part 3, the inhibitory effects of 3 doses of eprosartan (50, 100 and 350 mg) on angiotensin-II-induced decreases in ERPF at 12 and 15 hours after dosing were examined by the estimation of the difference and associated 95% confidence intervals in CL_{PAH} between the active regimens A, B and C and the placebo regimen D (A-D, B-D, C-D).

06.1.11 **Sample size:**

The numbers of subjects in study groups were based on feasibility. No statistical power calculations were done.

06.1.12 **Investigator , Center and Dates:**

Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center University of Pennsylvania Health System, Philadelphia, PA. Study Dates: 21-Aug-1992 to 22-Dec-1992.

06.2 **STUDY POPULATION**

06.2.1 **Subject disposition:**

Of 33 subjects screened, 2 subjects (#540 and #562) did not receive study medications. All were Caucasians, by protocol amendment. Demographic data are shown in Table Epro-006-2.

06.2.2 **Withdrawals:**

7 subjects withdrew early from the study. Subjects #540 (not treated), 546 (placebo) and 551 (placebo) were withdrawn at session 1 because of sinus arrhythmia (bradycardia). Subjects #541 (placebo), #553 (350 mg eprosartan during session 1, and placebo during session 2) and #562 (not treated) were withdrawn because of an exaggerated hypertensive blood pressure response to angiotensin-II infusions. Subject #550 was withdrawn because of an episode of ventricular tachycardia following the administration of placebo.

Table: Epro-006-2. Demographic data

DEMOGRAPHICS OF STUDY POPULATION
Mean (SD)
[Range]

Study Part	N*	Age (yrs)	Body Weight (kg)	Height (cm)
1	12	25 (6) [19-40]	76.0 (7.7) [64.8-89.0]	180.0 (7.0) [169.0-190.5]
2	14	27 (5) [20-39]	76.0 (7.5) [66.6-88.8]	176.0 (4.8) [168.0-184.0]
3	5	24 (4) [20-28]	68.0 (1.8) [67.4-71.6]	173.0 (3.1) [170.0-177.0]
Pooled	31	26 (5) [19-40]	74.9 (7.4) [64.8-89.0]	176.9 (6.0) [168.0-190.5]

*Does not include two subjects who were enrolled but did not receive study medication

06.2.3 **Protocol violations:**
Subject #549 received a 1-day course for acetaminophen for symptomatic relief during a viral syndrome. He continued in the study.

06.3 **SAFETY RESULTS**

06.3.1 **General considerations:**
Pre-existing baseline conditions were present in the following subjects:
Subject #540: Vomiting (attributed to protocol-specified sodium and potassium supplementation), and bradycardia with atrioventricular junctional rhythm;
Subject #552: Vomiting (attributed to protocol-specified sodium and potassium supplementation);
Subject #557: Vomiting (attributed to protocol-specified sodium and potassium supplementation);
Subject #558: Chest pressure and slight nausea;
Subject #573: Headache;
Subject #574: Pyuria (at screening and during study); nausea

A total of 33 adverse experiences (AEs) were reported for 19 subjects.

06.3.2 **Deaths:** There were no deaths during this study.

06.3.3 **Withdrawals:** Three subjects were withdrawn because of cardiac rhythm disturbances noted following administration of placebo as follows:
Subject #546: 2 minutes of a junctional cardiac rhythm possibly due to angiotensin-II;
Subject #550: ECG monitoring revealed a 8-beat run of ventricular tachycardia;
Subject #551: Junctional rhythm (may be a variant of normal in a subject with high vagal tone)

06.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

06.3.5 **Adverse Events:**
All AEs were mild to moderate in nature and resolved spontaneously without sequale. There was no dose-related increase in the occurrence of AEs. The most frequent were nausea and headache.
Placebo (9 AEs in 8 subjects): Subject #546 and #551 experienced an arrhythmia, #549 reported a viral syndrome, #550 had ventricular tachycardia, #558 reported chest pain and palpitations, #559 and #581 reported nausea, and #560 reported abdominal pain;
Eprosartan (24 AEs in 14 subjects): Subject #549, #571, #573 and #581 reported headache, #549 and #554 reported upper respiratory infection, #549 and #574 reported erythematous rash, #555 and #573 reported abdominal pain, #555, #568 and # 574 reported a viral infection, #556 reported dizziness, #556, #561 and #564 reported nausea, #561 reported vomiting, #571 reported syncope, #571 reported phlebitis, #573 reported backpain, #568 reported diarrhea and #580 reported two episodes of diarrhea.

06.3.6 **Laboratory findings, ECGs, Vital signs**
There were no symptomatic changes in pulse rate or blood pressure associated with the administration of eprosartan. Blood pressure fluctuated widely during the period of observation, and increases in blood pressure were found in response to the vasopressive effects of angiotensin-II.

Increased mean systolic and diastolic blood pressure from baseline following angiotensin-II with PAH (by 16 to 28 mm Hg and 17 to 30 mm Hg respectively) were completely inhibited one hour after dosing with a single 350 mg oral dose of eprosartan, which continued for 12 to 15 hours after dosing, but at 24 hours after dosing, there was no effect of eprosartan. A similar effect was observed with 100 mg and 200 mg doses, but was not obvious with the 10 mg dose.

Apart from one subject (#540) who had bradycardia with atrioventricular junctional rhythm, there were no baseline ECG findings (in PR, QRS and QTc intervals) that were of potential concern. During the course of the study, 3 subjects had ECG changes, namely: Subject #546 had 2 minutes of a junctional cardiac rhythm possibly due to angiotensin-II, #550 had ECG monitoring revealed a 8-beat run of ventricular tachycardia and #551 had junctional rhythm.

Subject #549 and #558 had elevated AST and ALT at several evaluations which returned to normal within the reference ranges at subsequent tests. Also, subject #549 and #562 had elevated CPK which returned to normal subsequently at follow up. Other isolated laboratory values of potential clinical concern include 5 occurrences of elevated urine pH (of 8) in 5 subjects (#549, #552, %558, #561 and #573), an elevated serum potassium (5.9 mEq/l in a hemolysed specimen on subject #541), elevated WBC counts at screening and follow up (#577).

06.4 PHARMACODYNAMIC AND PHARMACOKINETIC RESULTS

06.4.1 Pharmacodynamic Results

4.1.1 Effective Renal Plasma Flow

Part 1: Agonist activity: CL_{PAH} increased compared to placebo in the absence of exogenous angiotensin-II at 1 and 4 hours following a single 350 mg eprosartan dose (Fig Epro-006-1 and 2). The point estimates of the mean difference between active drug and placebo ranged from 165.45 to 86.66 ml/min, representing increases in CL_{PAH} of 27.5% to 13.6%, respectively, relative to placebo. The 90% confidence intervals were NOT contained within the equivalence range defined for this study (-22.7% of placebo, +22.7% of placebo), but were in a direction opposite to that for agonist activity. Similarly, at 24 to 28 hours after dosing, the point estimates of the mean difference between eprosartan and placebo ranged from -18.13 to 25.46 ml/min, with all 90% confidence intervals contained within the equivalence range, suggesting lack of agonist activity.

Figure Epro-06-1 Mean CL_{PAH} after eprosartan/placebo with/without angiotensin II (same day dosing)

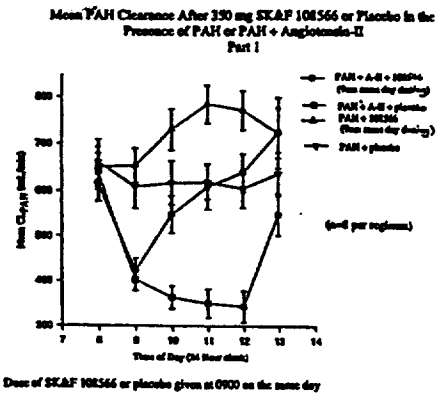
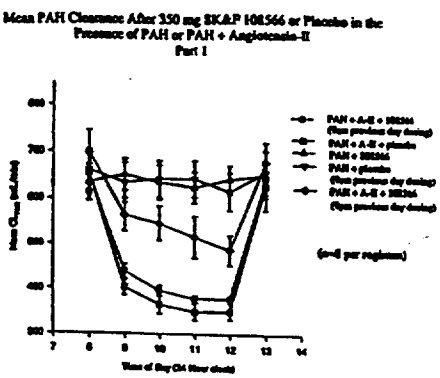


Figure Epro-06-2 Mean CL_{PAH} after eprosartan/placebo with/without angiotensin II (previous day dosing)



Angiotensin-II Inhibitory activity: Following administration of placebo, angiotensin-II caused CL_{PAH} to decline by -206.36 to -270.34 ml/min (33.9% to 43.6%) during the 4-hour observation period compared to placebo without angiotensin-II (Fig Epro-006-1). The associated 95% confidence intervals were -294.48 to -118.24 ml/min, and -380.39 to -160.29 ml/min, respectively. Following a single 350 mg oral dose of eprosartan, complete blockage of the effect of angiotensin II on ERPF was found as indicated by inhibition of angiotensin II-induced decreases in CL_{PAH} as follows:

at 1 hour = -68.85 ml/min (95% confidence interval: - 177.26 to 39.55 ml/min) relative to placebo in the absence of angiotensin.
at 2 hour = -9.67 ml/min (95% confidence interval: -119.72 to 100.38 ml/min);
at 3 hour = 32.73 ml/min (95% confidence interval:- -73.20 to 138.65 ml/min)

Duration of Activity: Figure Epro-006-2 showed that the reduction in CL_{PAH} during infusion of angiotensin II at 24-27 hours after placebo (compared to placebo without angiotensin II) was similar to that at 1-2 hours after placebo. After eprosartan with angiotensin-II, there was inhibition of angiotensin-II-induced decrease in CL_{PAH} (compared to placebo in the absence of angiotensin II) at 1-4 hours, which persisted (to a lesser extent) at 12-15 hours and was absent at 24-27 hours. This suggests that the angiotensin II inhibitory effects of eprosartan were present for 12-15 hours following a single 350 mg oral dose.

Figure Epro-06-3 Dose response of Mean CL_{PAH} after eprosartan/placebo with/without angiotensin II (Part 2)

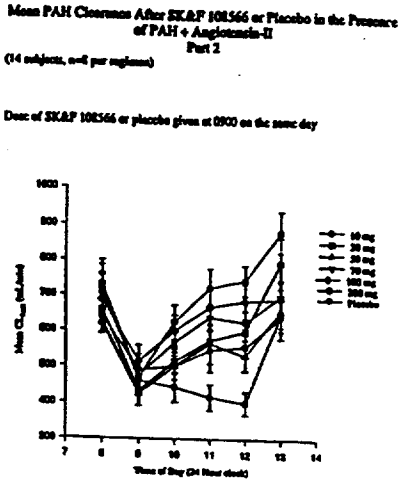
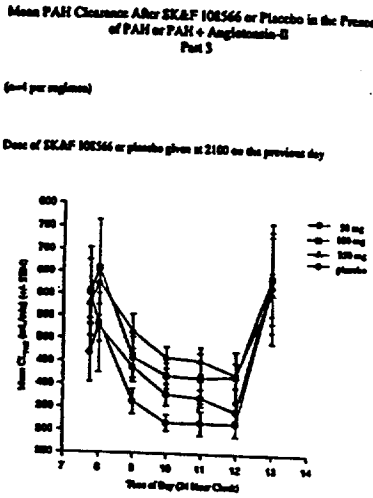


Figure Epro-06-4 Dose response of Mean CL_{PAH} after eprosartan/placebo with/without angiotensin II (Part 3)



Part 2: Figure Epro-006-3 showed that there was a monotonic dose-response in inhibition of the effect of angiotensin II on ERPF (CL_{PAH}) within the dose range of 10-200 mg at various time points (with the exception of 50 mg dose at 3 hour time point)

Part 3: At 12 and 15 hours after dosing, 50, 100 and 350 mg oral single doses of eprosartan produced measurable inhibition of angiotensin II induced decreased in CL_{PAH} (Figure Epro-006-4), being statistically significant at 100 and 350 mg doses.

4.1.2 Serum aldosterone and cortisol and urine electrolyte and creatinine excretion

Aldosterone: A single oral dose of 350 mg of eprosartan blunted the angiotensin-II-induced increase in serum aldosterone in Part 1, but this effect did not persist to 12 or 24 hours after eprosartan (Part 3). A dose related reduction in serum aldosterone concentrations over the range of 10-200 mg eprosartan was observed in Part 2.

Cortisol: Serum cortisol concentrations were not altered by administration of eprosartan or angiotensin II or by study procedures.

Urine sodium, potassium and creatinine excretion: Subjects with low sodium or potassium excretion were given additional oral sodium and potassium supplementation on the evening prior to administration of study medication.

06.4.2 **Pharmacokinetic Results**

Part 2: Peak plasma concentrations of eprosartan were achieved within 1-3 hours in 41 of 48 subjects. Plasma concentrations of eprosartan were measurable up to 4 - 8 hours following administration of 10, 30 and 50 mg doses, and up to 5-15 hours following 70, 100 and 200 mg doses. Median values of Cmax and AUC(0-τ) increased with an increase in dose but were less than dose proportional (Table Epro-006-1), with median Cmax and median AUC(0-τ) increasing approximately 10-fold over the entire 20-fold dose range. There was a wide variability in Cmax and AUC(0-τ) between subjects. Median Tmax ranged from 1 to 2 hours.

Part 3: Peak plasma concentrations of eprosartan occurred within 2 hours in most subjects. At 12 hours post-dose, plasma concentrations of eprosartan ranged from 32.4 to 472 ng/ml for the 350 mg dose, and from not quantifiable to 172 ng for the 100 mg dose and not quantifiable to 18.4 ng/ml for the 50 mg dose. The median Cmax increased with dose without dose proportionality (increasing by 4-fold over a 7-fold dose range), whereas the median AUC(0-τ) increased in an approximately dose proportional manner (Table Epro-006-2). There was a wide range of variation in Cmax and AUC(0-τ) between subjects. The median Tmax ranged from 1.75 to 2.5 hours.

Table Epro-006-1. Pharmacokinetic values for eprosartan administered to healthy volunteers (Part 2)

Parameter	Cmax (ng/ml)	Tmax (h)	AUC(0-t) (ng.h/ml)
10 mg (n=5-8)			
Mean	94.5	1.94	286
Median	77.4	1.50	344
S.D.	38.8	1.29	125
30 mg (n=8)			
Mean	221.5	1.88	590
Median	209.9	1.25	611
S.D.	96.6	1.33	335
50 mg (n=8)			
Mean	273.4	1.38	873
Median	243.0	1.00	734
S.D.	142.8	1.06	723
70 mg (n=8)			
Mean	462.2	1.31	1165
Median	376.8	1.00	719
S.D.	324.5	0.59	1000
100 mg (n=8)			
Mean	461.6	1.56	1182
Median	480.5	1.00	1047
S.D.	135.5	1.05	435
200 mg (n=8)			
Mean	818.9	1.88	2658
Median	714.8	2.00	2620
S.D.	471.1	0.99	1718

Table Epro-006-2. Pharmacokinetic values for eprosartan administered to healthy volunteers (Part 3)

Parameter	Cmax (ng/ml)	Tmax (h)	AUC(0-t) (ng.h/ml)
50 mg (n=4)			
Mean	365.6	1.88	1305
Median	355.6	1.75	1122
S.D.	182.2	0.85	964
100 mg (n=4)			
Mean	566.2	2.88	3242
Median	580.2	2.00	2802
S.D.	319.0	2.10	2564
350 mg (n=4)			
Mean	1195.2	3.25	7983
Median	1264.6	2.50	7523
S.D.	334.0	1.89	4266

06.4.3 **Pharmacokinetic/Pharmacodynamic Analysis**

Part 2 (1 to 3 hours following administration of eprosartan):

Concentration-effect data did not cover the entire range because of limited number of subjects, short duration of angiotensin II infusion and small number of plasma concentration sampling points. For values of ΔCL_{PAH} and

plasma eprosartan concentrations at 1 to 3 hours after dosing, parameter estimates ± asymptotic standard error were approximately 101%±10% and 46 ng/ml ± 20 ng/ml, for E_{max} and IC_{50}, respectively (Figure Epro-006-5). Approximately 80% of maximal inhibition of angiotensin-II induced decreases in ERPF was achieved at plasma eprosartan concentrations of approximately 200 ng/ml. Residual plots indicated a possible departure from the parametric model postulated and may not describe the relationship of ΔCL_{PAH} to eprosartan concentrations adequately. Thus estimates of E_{max} and IC_{50} should be interpreted with caution.

Figure Epro-006-5. ΔCL_{PAH} versus plasma eprosartan concentration 1-3 hours postdose

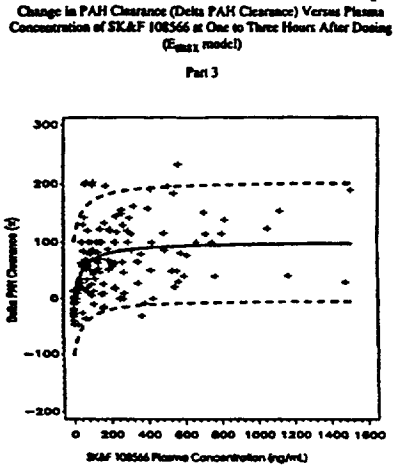
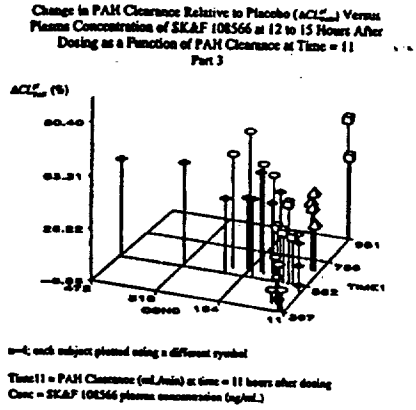


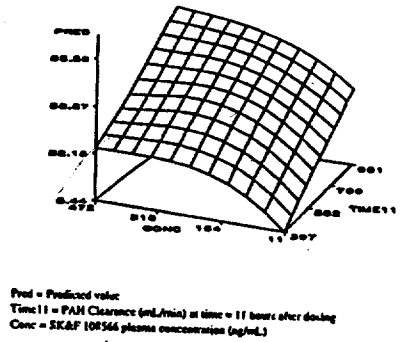
Figure Epro-006-6. ΔCL^{PI}_{PAH} versus plasma eprosartan conc. 12-15 h postdose as function of CL_{PAH} at 11 h



Part 3 (12 to 15 hours following administration of eprosartan):

Concentration-effect data did not cover the entire range because of limited number of subjects, short duration of angiotensin II infusion and small number of plasma concentration sampling points. There is a positive linear increase in ΔCL^{PI}_{PAH} as a function of eprosartan concentration and CL_{PAH} at 11 hours post-dose (Figure Epro-006-6), and the prediction surface for this relationship is shown in Figure Epro-006-7. The change in CL_{PAH} relative to placebo appeared to increase as plasma eprosartan concentrations increased in a quadratic manner ($R^2 = 0.72$).

Figure Epro-006-7. Prediction surface for ΔCL^{PI}_{PAH} versus plasma eprosartan conc 12-15 h postdose as function of CL_{PAH} at 11 h



Pred = Predicted value
Time11 = PAH Clearance (mL/min) at time = 11 hours after dosing
Conc = SK&F 108566 plasma concentration (ng/mL)

06.5 CONCLUSION

06.5.1 Pharmacodynamic Results

Part 1: Agonist activity: This session of the protocol provided evidence suggesting lack of agonist activity of eprosartan

Angiotensin-II Inhibitory activity: Following a single 350 mg oral dose of eprosartan, complete blockage of the effect of angiotensin II on ERPF was found.

Duration of Activity: The angiotensin II inhibitory effects of eprosartan were present for 12-15 hours following a single 350 mg oral dose.

Part 2: This study session showed a monotonic dose-response in inhibition of the effect of angiotensin II on ERPF (CL_{PAH}) within the dose range of 10-200 mg at various time points (with the exception of 50 mg dose at 3 hour time point)

Part 3: At 12 and 15 hours after dosing, 50, 100 and 350 mg oral single doses of eprosartan produced measurable inhibition of angiotensin II induced decreased in CL_{PAH}, being statistically significant at 100 and 350 mg doses.

Aldosterone: A single oral dose of 350 mg of eprosartan blunted the angiotensin-II-induced increase in serum aldosterone in Part 1, but this effect did not persist to 12 or 24 hours after eprosartan (Part 3). A dose related reduction in serum aldosterone concentrations over the range of 10-200 mg eprosartan was observed in Part 2.

Cortisol: Serum cortisol concentrations were not altered by administration of eprosartan or angiotensin II or by study procedures.

06.5.2 Pharmacokinetic Results

Part 2: Peak plasma concentrations of eprosartan were achieved within 1-3 hours. Plasma concentrations of eprosartan were measurable up to 4 - 8 hours following administration of 10, 30 and 50 mg doses, and up to 5-15 hours following 70, 100 and 200 mg doses. Median values of Cmax and AUC(0-τ) increased with an increase in dose but were less than dose proportional with median Cmax and median AUC(0-τ) increasing approximately 10-fold over the entire 20-fold dose range. Median Tmax ranged from 1 to 2 hours.

Part 3: Peak plasma concentrations of eprosartan occurred within 2 hours. The median Cmax increased with dose without dose proportionality (increasing by 4-fold over a 7-fold dose range), whereas the median AUC(0-τ) increased in an approximately dose proportional manner. The median Tmax ranged from 1.75 to 2.5 hours.

06.5.3 Pharmacokinetic/Pharmacodynamic Analysis

Part 2 (1 to 3 hours following administration of eprosartan):

For values of ΔCL_{PAH} and plasma eprosartan concentrations at 1 to 3 hours after dosing, parameter estimates ± asymptotic standard error were approximately 101%±10% and 46 ng/ml ± 20 ng/ml, for E_{max} and IC_{50}, respectively. Approximately 80% of maximal inhibition of angiotensin-II induced decreases in ERPF was achieved at plasma eprosartan concentrations of approximately 200 ng/ml. Residual plots indicated a possible departure from the parametric model postulated and may not describe the relationship of ΔCL_{PAH} to eprosartan concentrations adequately. Thus estimates of E_{max} and IC_{50} should be interpreted with caution.

Part 3 (12 to 15 hours following administration of eprosartan):

Concentration-effect data did not cover the entire range because of limited number of subjects, short duration of angiotensin II infusion and small number of plasma concentration sampling points. There is a positive linear increase in ΔCL^{PI}_{PAH} as a function of eprosartan concentration and CL_{PAH} at 11 hours post-dose. The change in CL_{PAH} relative to placebo increased as plasma eprosartan concentrations increased in a quadratic manner ($R^2 = 0.72$).

Protocol 007 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.105)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *24-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *25-Jun-1997*

07.1 STUDY PROTOCOL

07.1.1 Title

Investigation of the effect of food on the pharmacokinetics of SK&F-108566 in healthy male volunteers

07.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the effect of food on eprosartan pharmacokinetics following a 350 mg dose. Because eprosartan pharmacokinetics are not dose proportional at doses > 200 mg, the effect of food on this dose was investigated.

07.1.3 Objectives

1. To estimate the difference between the pharmacokinetics and tolerability of single oral doses of SK&F 108566 following a standard high fat meal and under fasting conditions in healthy male volunteers, and
2. To describe the effect of SK&F 108566 on urine uric acid excretion.

07.1.4 Study design

The study was a randomized, open-label, single-dose, two-period, period balanced crossover study of two groups (A, and B). Subjects were allocated at random to one of two sequences: AB or BA. Each subject participated in two study periods separated by at least 1 week, in which each received the study medication as a single oral dose of:

1. Regimen A: eprosartan 350 mg, (Lot# U95110, 50 mg tablet x 7) administered to fasted subjects, or
2. Regimen B: eprosartan 350 mg, (Lot# U95110, 50 mg tablet x 7) administered following a standard high fat meal.

07.1.5 Protocol Amendments

There were no amendments to the protocol.

07.1.6 Population enrolled/analyzed

12 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were screened.

Compliance: All study medication was administered with 200 ml tepid water by study personnel.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, and physical examination and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 1 weeks prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period.

07.1.7 Study procedures

Day 1: After a ten-hour fast, patients reported to the clinical pharmacology unit at 7:00 am. Blood and urine specimens were obtained for the pre-dose clinical safety laboratory studies. Subjects voided and then drank 200 ml of water. After 2 hours, the subjects drank an additional 200 ml of water. Urine was collected and pooled for the interval 0-4 hours since subjects drank first volume of water, and analyzed for uric acid, creatinine and sodium. A blood sample was drawn at 4 hours for determination of serum uric acid. Subjects were then discharged, with instructions to collect all urine for the time period 4 to 24 hours.

Day 2: After a ten-hour fast, patients reported to the clinical pharmacology unit at 7:00 am. Assessment of baseline symptoms and vital signs were made. The fed group was given a standard breakfast (2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 2 pats of butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk) equivalent to 1020 calories (58 g carbohydrate, 33 g protein, 58-75 g fat). The meal was given at 7:30 am, and completely consumed within 20 minutes. Subjects allocated to the fed or fasted groups were physically separated during the consumption of the breakfast. At 8:00 am (within 10 minutes of fed subjects finishing the meal), all subjects were administered the study medication with 200 ml of tepid water. No food or drink was permitted for 4 hours after dosing. Subjects drank 240 ml water at 4 hours after dosing. Water, soft drinks with caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing, and lunch and dinner were

given at 5 and 9-10 hours post dose, respectively. Subjects remained in the clinical pharmacology unit for 24 hours after dosing. They remained seated for the first hour after dosing, but thereafter were allowed to ambulate within the clinical pharmacology unit. No vigorous exercise was permitted during their stay in the clinical pharmacology unit. Prior to dosing and at 15, 30, 45, 60, 120, 180, 240, 360 and 1440 minutes post-dosing, sitting blood pressure and pulse rate were obtained. Blood sample (5 ml) collections for pharmacokinetics were done prior to dose administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18 and 24 hours following dosing. Blood samples (5 ml) were also obtained prior to dosing and at 4 hours for serum uric acid. Urine was collected and pooled for the intervals 0-4, 4-8, and 8-24 hours after dosing, the volumes being recorded. Subjects were permitted to leave the center after the 24 hour pharmacokinetics sample was drawn. They returned 1 week following the last study session, at which time safety laboratory tests were done.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

07.1.8 **Pharmacokinetic procedures:**
Following collection in heparinized chilled on ice, blood samples were centrifuged at 4°C and 2300 rpm for 10 minutes, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 7 months. Plasma concentrations of eprosartan were determined by a reversed-phase HPLC method with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml based on a 0.5 ml aliquot. Urine samples were used for exploratory biotransformation work.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ) and AUC(0-τ). The apparent terminal elimination half-life ($T_{1/2}$) was calculated as $\log_e 2/\lambda$. AUC(0-∞) was calculated as the sum of AUC(0-τ) and C(t)/ λ where C(t) was the predicted eprosartan concentration from the log-linear regression analysis at the least measurable time point.

07.1.9 **Endpoints:**
AUC(0-τ) and Cmax were primary endpoints, and Tmax was the secondary endpoint, and that clinical monitoring and laboratory safety data were also secondary endpoints.

07.1.10 **Sample size:**
The planned sample size (12 per group) was based on feasibility. No statistical power calculations were performed.

07.1.11 **Investigator , Center and Study Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center, 51 North 39th Street, Philadelphia, PA. Dates: 16-Dec-1992 to 01-Feb-1993.

07.2. **STUDY POPULATION**

2.1 **Subject disposition:**
12 healthy male subjects 21-35 (mean = 28) years of age, weighing 62.7 to 86.0 (mean = 74.2) kg, and 169-184 (mean = 176) cm tall, were screened and randomized. 9 (75%) were Caucasian, 2 (16.7%) were Black and 1 (8.3%) was Hispanic. All 12 subjects completed the study.

07.2.2 **Withdrawals:** No subject withdrew prior to study completion.

07.2.3 **Protocol violations:**
No protocol violations were reported. Two subjects had pre-existing conditions: Subject #008 had a syncope (vasovagal episode) lasting 1 minute, and Subject #009 reported dizziness (lightheadedness) that lasted 1 minute

07.3. **SAFETY RESULTS**

07.3.1 **General considerations:** 8 adverse experiences were reported for 4 subjects.

07.3.2 **Deaths:** There were no deaths during this study.

07.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

07.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

07.3.5 **Adverse Events:** All AEs were mild in nature, and resolved spontaneously without requiring treatment.

Regimen A (fasted): Subject #006 reported headache, #007 reported dizziness and erythema at IV site, and #019 reported occipital headache

Regimen B (fed): Subject # 006 reported dizziness and eye pain, #008 reported dizziness, and #019 reported headache

07.3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates or blood pressure changes of potential clinical concern. Screening ECGs results were not presented. No post-dose ECGs were done.

Subject #002 had pyuria (urine WBCs = 25/hpf) prior to dosing at Session 1, and intermittently during the study. Subject #007 had an elevated ALT (59 IU/l) at 24 hours after dosing on Day 2 of Session 2; a repeat ALT 6 days later was 35 IU/l. There were no other laboratory changes during the study which were of potential clinical concern.

07.3.7 **Urine Uric Acid, Sodium and Creatinine Excretion**

There were no clinically relevant changes in urine uric acid, sodium or creatinine excretion between the pre-dose and post-dose assessments (Table Epro-007-1). Also, the mean serum uric acid and serum creatinine were essentially identical at all time points post-dose. This suggests that single 350 mg doses of eprosartan did not change uric acid excretion (while losartan has been known to do so) or uric acid levels within 4 or 24 hours of administration.

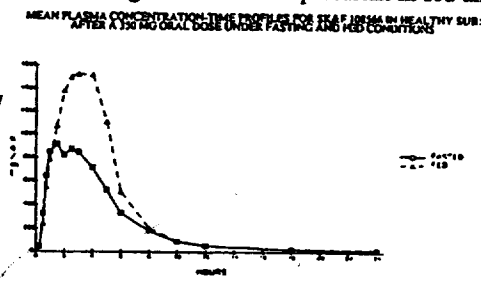
Table Epro-007-1. Mean (SE) urine uric acid, sodium and creatinine excretion in fasted subjects given a single oral dose (350 mg) of eprosartan

	Day 1		Day 2	
	0-4 hours	*0-24 hours*	*0-4 hours*	*0-24 hours*
Creatinine Clearance (ml/min)		101.2 (8.5)		118.0 (9.1)
Urine Creatinine (mg/sample)	336.0 (12.2)	1644.5 (123.9)	369.1 (27.0)	1919.5 (124.3)
Urine Sodium (mEq/sample)	36.8 (5.02)	161.8 (22.8)	54.6 (6.7)	166.7 (15.6)
Urine Uric Acid (mg/sample)	138.4 (9.8)	603.2 (55.2)	170.1 (9.6)	679.1 (35.4)
UUA/UCr	0.4120 (0.0276)	0.3698 (0.0228)	0.4830 (0.0407)	0.3629 (0.0216)
Fractional Excretion of Uric Acid	0.0906 (0.0081)	0.0806 (0.0056)	0.0994 (0.0082)	0.0745 (0.0046)

07.4. **PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS**

Following single oral doses of 350 mg of eprosartan (Figure Epro-007-1), peak plasma concentrations were reached within 1 to 4 hours in the fasted state and within 1 to 5 hours in the fed state. About 70% of subjects had higher plasma concentrations when eprosartan was administered in the fed state compared to the fasted state.

Figure Epro-007-1. Time course of plasma concentrations following a single oral dose of eprosartan in fed and fasted states



In Table Epro-007-2, the AUC(0-τ) was 56% larger, and the Cmax was 80% higher when 350 mg (7 x 50 mg) eprosartan was given after a high fat meal compared to the fasted condition. The 95% confidence intervals (Table Epro-007-3) for AUC(0-τ) and Cmax do not include the value 1.00 indicating a food effect on AUC(0-τ) and Cmax. The high fat meal caused a slight delay in Tmax as the median difference between eprosartan in the fed state to eprosartan in the in the fasted state was 0.63 hours. The 95% confidence interval for Tmax includes the value zero suggesting that the rate of absorption is not different in the fed and fasted states. Overall, the results demonstrate that administration of eprosartan with a high fat meal slightly delayed the rate of absorption, but the extent of absorption was increased - on the average - by 56%.

Although $T_{1/2}$ appeared to be similar (Table Epro-007-2) in the fasted and fed states, it was determined over a time period that was less than two terminal elimination half-lives in a large number of patients, and therefore no statistical analyses could be performed for AUC(0-∞) or $T_{1/2}$. Also, AUC(0-∞) and $T_{1/2}$ were not calculated for subject #007 in the fed state because of variability in the plasma concentrations of eprosartan in the terminal phase.

Table Epro-007-2. Pharmacokinetic values for eprosartan following single oral doses of eprosartan in fed and fasted states

End Point	Eprosartan 350 mg fasted	Eprosartan 350 mg fed
AUC(0-τ) (ng.h/ml)		
Geometric Mean	4810	7509
Mean	5041	7836
Median	4881	7099
S.D.	1600	2459
AUC(0-∞) (ng.h/ml)		
Geometric Mean	5006	7658
Mean	5207	8004
Median	5057	7277
S.D.	1549	2574
Cmax (ng/ml)		
Geometric Mean	1188	2134
Mean	1247	2259
Median	1179	1953
S.D.	411	792
Tmax (hr)		
Mean	2.04	2.88
Median	2.00	2.75
S.D.	0.99	1.33
$T_{1/2}$ (hr)		
Mean	6.60	6.42
Median	5.57	6.03
S.D.	4.39	3.22

Table Epro-007-3. Point Estimates and 90% confidence intervals of comparisons of eprosartan in fed and fasted states

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ)†	B:A	1.56	(1.26, 1.93)
Cmax†	B:A	1.80	(1.48, 2.17)
Tmax§	B-A	0.63	(-0.75 h, 2.25 h)

† Data presented as the ratio of the geometric means for eprosartan in regimen B (fed) : regimen A (fasted)
§ Data presented as the median difference of eprosartan in regimen B (fed) - regimen A (fasted) and 95% C.I.

(Note: The between-subject coefficients of variation for ln-transformed AUC(0-τ) were 32.2% and 32.4% for fasting and fed groups respectively, and for ln-transformed Cmax were 31.3% (fasting and 38.5% (fed). The within-subject coefficients of variation for AUC(0-τ) and Cmax were 24% and 21%, respectively.)

07.5 CONCLUSION

Single oral dose administration of 350 mg eprosartan in fed and fasted states was not associated with adverse events or laboratory values of potential safety concern. Single 350 mg doses of eprosartan did not change uric acid levels or uric acid excretion within 4 or 24 hours of administration, and had no discernible uricosuric effect.

Following single oral doses of 350 mg of eprosartan, peak plasma concentrations were reached within 1 to 4 hours in the fasted state and within 1 to 5 hours in the fed state. About 70% of subjects had higher plasma concentrations when eprosartan was administered in the fed state compared to the fasted state. The AUC(0-τ) was 56% larger, and the Cmax was 80% higher when 350 mg (7 x 50 mg) eprosartan was given after a high fat meal compared to the fasted condition. The high fat meal caused a slight delay in Tmax as the median difference between eprosartan in the fed state to eprosartan in the in the fasted state was 0.63 hours. The results suggest that administration of 350 mg eprosartan with a high fat meal slightly delayed the rate of absorption, but the extent of absorption was increased - on the average - by 56%.

Protocol 008 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** **(Vol 1.105)**

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *25-Jun-1997*
DATE COMPLETED *26-Jun-1997*

08.1. STUDY PROTOCOL

08.1.1 Title

A dose proportionality study of the final commercial formulation of eprosartan in healthy male volunteers

08.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the dose proportionality of the final commercial formulation of eprosartan, an A-II AT_1 receptor antagonist, in single oral doses.

08.1.3 Objectives

1. To assess the dose proportionality and tolerability of the final commercial formulation of eprosartan in single oral doses of 100, 200, 400 and 800 mg, and
2. To assess the safety and tolerability of single oral doses of the final commercial formulation of eprosartan.

08.1.4 Study design

The study was a randomized, open-label, four-period, period balanced, single-dose crossover study of four groups (A, B, C and D). During each study period, subjects received, with 240 ml tepid water, a single dose of:

1. Regimen A: eprosartan 100 mg tablets, (Lot# U94191) or
2. Regimen B: eprosartan 200 mg tablets, (Lot# U94190) or
3. Regimen C: eprosartan 400 mg (2 x 200 mg tablets, Lot# U94190) or
4. Regimen D: eprosartan 800 mg (4 x 200 mg tablets, Lot# U94190)

There was a minimum 3 day interval from the last blood draw to the next study session. Subjects were randomized to sequence ADBC, BACD, CBDA, and DCAB.

08.1.5 Protocol Amendments

There was no protocol amendment to this study.

08.1.6 Population enrolled/analyzed

35 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were screened.

Compliance: Subjects took study medication in the clinical pharmacology unit under nursing supervision.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (13 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 1 week prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each pharmacokinetic study session.

08.1.7 Study procedures

Subjects report to the clinical pharmacology unit between 7-8 a.m. after an overnight fast since 10 p.m. the previous night. Baseline symptoms and signs were recorded at the first session and blood and urine samples obtained for clinical laboratory studies. A light breakfast (cereal, milk, juice and muffin) was served, and completely consumed within 20 minutes. Within 30 minutes of start of breakfast, all subjects were administered the study medication with 240 ml of tepid water. Prior to dosing, sitting blood pressure and pulse were measured. Subjects drank 240 ml water at 2 and 4 hours after dosing. Water, soft drinks with caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing, and lunch and dinner were given at 5 and 10 hours post dose, respectively. Blood samples for pharmacokinetic analysis were drawn at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours following dosing. Subjects remained in the clinical pharmacology unit for 24 hours after dosing and were discharged after collection of the last pharmacokinetic sample. They abstained from ingestion

of xanthine containing drinks or alcohol, and from strenuous exercise for 24 hours prior to and for 24 hours after study drug administration. Subjects returned 1 week following the last treatment period for safety laboratory tests.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

08.1.8 **Pharmacokinetic procedures:**
Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C at 2000g for 20 minutes, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 10 weeks. Plasma concentrations of eprosartan were determined by reverse phase HPLC with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml for a 0.5 ml aliquot.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain Cmax, Tmax, the apparent terminal elimination rate constant (λ), AUC(0-τ) and AUC(0-τ') (τ' is the time of the last quantifiable concentration in common for all dose levels for each subject, assuming absorption profiles were similar for all doses and that absorption was complete by the time of τ'). Dose-normalized Cmax and dose-normalized AUC(0-τ') were obtained by dividing individual estimates by the corresponding dose. It was not possible to estimate $T_{1/2}$, and AUC(0-∞).

08.1.9 **Endpoints:**
AUC(0-τ') and Cmax were primary endpoints, and Tmax was the secondary endpoint. Dose-proportionality was assessed through an equivalence-type approach, where the lowest dose at which the pharmacokinetic profile could be appropriately described served as reference (100 mg). An equivalence range of (0.70 to 1.43) for dose-normalized AUC(0-τ') and dose-normalized Cmax, which were ln-transformed prior to analysis, was used. This range represents a 30% acceptance region which is symmetric on the ln scale.

08.1.10 **Sample size:**
Based on an average within-subject coefficients of variation (CVresid) for AUC and Cmax to be 29.4% and 34.6%, respectively, it was estimated that a sample size of 20 would provide at least 90% power to demonstrate equivalence for AUC(0-τ') and Cmax. Equivalence is demonstrated when the 90% confidence intervals for the ratios of each dose relative to the reference dose for ln-transformed dose-normalized AUC(0-τ) and ln-transformed dose-normalized Cmax are contained within the range (0.70, 1.43). This range represents a symmetric 30% range on the ln scale. No adjustments were made for multiple comparisons.

08.1.11 **Investigator , Center and Study Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center, Philadelphia, PA. Dates: 19-Jan-1995 to 28-Mar-1995.

08.2 **STUDY POPULATION**

08.2.1 **Subject disposition:**
35 healthy male volunteers were screened; 12 failed to meet entrance criteria. 23 subjects, 20-43 (mean = 28) years of age, weighing 57.2 to 93.5 (mean = 78.3) kg, and 168-191 (mean = 179) cm tall, were randomized. 57% were Caucasian, 26% were African-American, 9% were Asian, 4% were Indian and 4% were Hispanic. All received at least one dose of the study medication.

08.2.2 **Withdrawals:** There were no withdrawals from this study.

08.2.3 **Protocol violations:**
Subject #007 (on 200 mg eprosartan) received IV fluids for syncopal episode.
Subject #013 (on 100 mg eprosartan) received Mylanta® for abdominal pain, nausea and flatulence, and Levsin-SL® for nausea/vomiting, and abdominal pain
Subject #023 (on 800 mg eprosartan) received Tylenol® for a cold, and also received Tylenol® and Biaxin® for otitis media with earache while on eprosartan 100 mg.

08.3. **SAFETY RESULTS**

08.3.1 **General considerations:** There were no symptoms and signs prior to the initial dose of study medication. A total of 23 adverse experiences (AEs) were reported for 11 subjects, viz., 7 AEs in 4 subjects on 100 mg, 8 AEs in 8 subjects on 200 mg, 1 AE following 400 mg, and 7 AEs in 7 subjects on 800 mg of eprosartan.

08.3.2 **Deaths:** There were no deaths during this study.

08.3.3 **Withdrawals:** There were no withdrawals due to adverse experiences during this study.

08.3.4 **Serious, Non-fatal Adverse Events:** There was no non-fatal adverse experience during this study.

08.3.5 **Adverse Events:** All AEs were mild to moderate in nature. Headache was the most frequent AE reported.
Regimen A - 100 mg (7 AEs): Subject #006, and #008 reported headache, #008 reported upper respiratory infection, #009 reported pain in left medial thigh, and #013 reported nausea, vomiting and diarrhea;
Regimen B - 200 mg (8 AEs): Subject #004, #006, #008, and #018 reported headache, #007 reported syncope, #010 reported dizziness, #013 reported abdominal pain, and #023 reported upper respiratory infection;
Regimen C - 400 mg(1 AE): Subject #006 reported headache
Regimen D - 800 mg (7 AEs): Subject #006, #008, #010 and #012 reported headache, #005 reported dizziness, #007 reported upper respiratory infection, and #023 reported earache.

08.3.6 **Laboratory findings, ECGs, Vital signs**
No patient in this study exhibited abnormal heart rates. Changes in blood pressure of potential clinical concern were observed as follows:
Regimen A - 100 mg: Subject #015 and #019 had decreased systolic blood pressure, and #020 had decreased diastolic blood pressure;
Regimen B - 200 mg: Subject #012 and #023 had decreased systolic blood pressure, #024 had increased systolic blood pressure, and #015, #019 and #023 had decreased diastolic blood pressure;
Regimen C - 400 mg: Subject #015 had decreased systolic blood pressure on two occasions (1 and 2 h post-dose);
Regimen D - 800 mg: Subject #001 and #012 had decreased diastolic blood pressure.
The above changes in blood pressure occurred sporadically, were not sustained, were asymptomatic and did not appear to be dose-related.

Screening ECGs were normal. Post-treatment ECGs were not done.

Subject #001 (on 200 mg eprosartan) had elevated AST (96 IU/l) at follow-up; at repeat follow up, he had elevated serum ALT 81 IU/l, AST 93 IU/l, CK 2110 IU/l, which subsided one week later to 29 IU/l, 22 IU/l and 125 IU/l, respectively. Subject #002 (on 400 mg eprosartan) had elevated fasting blood glucose at follow up (164 mg/dl) compared to a baseline of 100 mg/dl; fasting blood glucose 2 days later was 104 mg/dl. Subject #007 (on 200 mg eprosartan) had elevated fasting blood glucose at second study session (145 mg/dl) compared to a baseline of 90 mg/dl; fasting blood glucose at follow up was 93 mg/dl. Subject #018 had elevated serum ALT at follow-up visit (100 IU/l compared to a baseline value of 15 IU/l); one week later, it was 30 IU/l.

08.4. PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

The sponsor submitted that the following data were modified for pharmacokinetic analysis:

1. Subjects #009 and #012 (200 mg), and #001 (400 mg) had quantifiable concentrations at pre-dose (0 hr) samples, and these values were changed to NQ (not quantifiable) for AUC calculations.
2. Subjects #009 (100 mg), #004 (200 mg) and #016 (400mg) had quantifiable concentrations in the elimination phase which was preceded by one or two NQ values; these NQ values were changed to 1/2 LLQ (5 ng/ml) for determination of AUC
3. Subject #014 (800 mg) had a large increase in plasma concentration at 24 h post-dose (173.5 ng/ml), and this data-point was excluded from the pharmacokinetic analysis.
4. Subject #007 (200 mg) had plasma concentration at 1.5 hours lower than those at 1.0 and 2.0 hours, which could be due to interchanged samples, and the order of the reported concentrations for 1.0 and 1.5 hours was reversed prior to pharmacokinetic analysis.

Following single oral doses of eprosartan, the mean plasma concentration-time profiles were in general similar with peak plasma concentrations of eprosartan observed at a median time of 3 hours (Table Epro-008-1). Following 100 mg or 200 mg single oral dose, plasma concentrations declined from the peak in a mono- and bi-exponential manner respectively, with plasma concentrations rarely quantifiable after 12 or 16 hours. For 400 mg and 800 mg single oral doses, plasma concentrations generally declined in a bi-exponential manner, and were sometimes quantifiable at 24 hours (the values at 24 hours being usually < 5%, and more commonly <1% of peak concentrations).

The sponsor submitted that no significant sequence or first-order carryover effects were observed for AUC(0-τ), Cmax or AUC(0-τ'). AUC(0-τ), dose-normalized AUC(0-τ), AUC(0-τ'), dose-normalized AUC(0-τ'), Cmax, dose-normalized Cmax, and Tmax are shown in Table Epro-008-1.

Table Epro-008-1. Pharmacokinetic values for eprosartan following single oral doses

End Point	100 mg	200 mg	400 mg	800 mg
AUC(0-τ') (ng.h/ml)				
Mean	1396	2553	4661	7443
Median	1175	2374	4389	6422
S.D.	627	1015	2471	2762
Cmax (ng/ml)				
Mean	439	702	1273	1857
Median	395	654	1244	1732
S.D.	234	255	577	736
Tmax (h)†				
Mean	2.85	2.92	3.15	2.88
Median	2.58	3.02	3.02	3.00
Range	(1.50 - 4.07)	(1.50 - 4.07)	(1.50 - 4.03)	(1.12 - 4.03)
Dose-normalized AUC(0-τ') (ng.h/ml)				
Geometric Mean	12.75	11.90	10.46	8.76
Mean	13.96	12.77	11.65	9.30
Median	11.75	11.87	10.97	8.03
S.D.	6.27	5.07	6.18	3.45
Dose-normalized Cmax (ng/ml)				
Geometric Mean	3.90	3.29	2.94	2.15
Mean	4.39	3.51	3.18	2.32
Median	3.95	3.27	3.11	2.17
S.D.	2.34	1.27	1.44	0.92
AUC(0-τ) (ng.h/ml)				
Mean	1400	2620	4887	7855
Median	1175	2374	4476	6977
S.D.	637	1046	2525	2782
Dose-normalized AUC(0-τ) (ng.h/ml)				
Mean	14.00	13.10	12.22	9.82
Median	11.75	11.87	11.19	8.72
S.D.	6.37	5.23	6.31	3.48

† Tmax presented as median (range).

The mean AUC(0-τ') and the mean Cmax increased with increasing dose over the 100-800 mg single oral dose range, whereas the mean dose-normalized AUC(0-τ') and the mean dose-normalized Cmax showed a decreasing trend with increasing dose (Table Epro-008-1), suggesting saturation of absorption of eprosartan over the 100 mg to 800 mg oral dose range.

The 90% confidence interval for the comparison of dose-normalized AUC(0-τ') for the 200 mg and 400 mg doses relative to the 100 mg reference dose were completely contained within the acceptance range 0.70 to 1.43 (Table Epro-008-2), whereas the 90% confidence interval for the dose-normalized AUC(0-τ') for the 800 mg dose to the 100 mg reference dose was not contained within the acceptance range (Table Epro-008-2).

For the comparison of dose-normalized Cmax, the 90% confidence interval for the ratio of the geometric mean for the 200 mg dose relative to the 100 mg reference dose was contained within the acceptance range 0.70 to 1.43 (Table Epro-008-2); however, the 90% confidence interval for the dose-normalized Cmax for the 400 mg and 800 mg doses to the 100 mg reference dose were not contained within the acceptance range (Table Epro-008-2).

Since both dose-normalized AUC(0-τ') and dose-normalized Cmax for the 200 mg dose were contained within the protocol-specified 30% acceptance range for equivalence (0.70, 1.43), dose-proportionality was concluded for the 200 mg dose relative to the 100 mg reference dose. In this case, 90% interval for the dose-normalized AUC(0-τ') was also contained within the stricter 20% acceptance range for equivalence (0.80, 1.25), typically used in bioequivalence studies.

At doses of 400 mg and 800 mg, the lower limit of the 90% confidence interval for AUC(0-τ') and Cmax fell below the acceptance range, and in the case of 800 mg dose, both the lower and the upper limits of the 90% confidence

interval fell below the acceptance range. Based on point estimates for AUC(0-τ') ratios, the 400 mg dose approximated 330 mg, and the 800 mg dose approximated 550 mg.

For the secondary parameter, Tmax was similar for the 200, 400 and 800 mg doses relative to the 100 mg reference dose (Table Epro-008-1). The median differences between the 200 mg, 400 mg and 800 mg doses and 100 mg reference dose for Tmax were approximately similar (Table Epro-008-2) and the 95% confidence intervals for all three comparisons included the value zero, suggesting that the rates of absorption of the different doses of eprosartan in this study were similar.

Table Epro-008-2. Point Estimates and 90% confidence intervals of comparisons of eprosartan doses

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ')†	200mg : 100mg	0.93	(0.83, 1.06)
AUC(0-τ')†	400mg : 100mg	0.83	(0.73, 0.93)
AUC(0-τ')†	800mg : 100mg	0.69	(0.61, 0.78)
Cmax†	200mg : 100mg	0.85	(0.74, 0.97)
Cmax†	400mg : 100mg	0.76	(0.66, 0.87)
Cmax†	800mg : 100mg	0.55	(0.48, 0.64)
Tmax§	200mg - 100mg	0.02 h	(-0.45 h, 0.48 h)
Tmax§	400mg - 100mg	0.26 h	(-0.02 h, 0.73 h)
Tmax§	800mg - 100mg	-0.01 h	(-0.27 h, 0.49 h)

† Data presented as the ratio of the geometric means of each dose relative to the 100 mg reference dose
§ Data presented as the median difference of each dose and the 100 mg reference dose

(Note: The between-subject coefficients of variation for dose-normalized AUC(0-τ') and dose-normalized Cmax ranged from 36 to 52%. The residual coefficients of variation for dose-normalized AUC(0-τ') and dose-normalized Cmax were 25.3% and 28.7%, respectively. These observed values were lower than that used for the original sample size estimation indicating no adequacies in terms of sample size and power in the assessment of bioequivalence.)

08.5. CONCLUSION

Single oral doses of 100 mg, 200 mg, 400 mg or 800 mg eprosartan to healthy volunteers were not associated with serious adverse experiences in this study. No dose related increase in adverse experience was observed.

Following single oral doses of eprosartan, the mean plasma concentration-time profiles were in general similar with peak plasma concentrations of eprosartan observed at a median time of 3 hours. The mean AUC(0-τ') and the mean Cmax increased with increasing dose over the 100-800 mg single oral dose range, whereas the mean dose-normalized AUC(0-τ') and the mean dose-normalized Cmax showed a decreasing trend with increasing dose, suggesting saturation of absorption of eprosartan over the 100 mg to 800 mg oral dose range.

The dose-normalized AUC(0-τ') and dose-normalized Cmax for the 200 mg dose were contained within the protocol-specified 30% acceptance range for equivalence (0.70, 1.43). Thus, dose-proportionality was concluded for the 200 mg dose relative to the 100 mg reference dose. The 90% interval for the dose-normalized AUC(0-τ') was also contained within the stricter 20% acceptance range for equivalence (0.80, 1.25) used in bioequivalence studies.

At doses of 400 mg and 800 mg, the lower limit of the 90% confidence interval for AUC(0-τ') and Cmax fell below the acceptance range, and in the case of 800 mg dose, both the lower and the upper limits of the 90% confidence interval fell below the acceptance range.

Tmax was similar for the 200, 400 and 800 mg doses relative to the 100 mg reference dose . The median differences between the 200 mg, 400 mg and 800 mg doses and 100 mg reference dose for Tmax were approximately similar, and the 95% confidence intervals included the value zero, suggesting that the rates of absorption were similar.

Protocol 009 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.082 & 1.083)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *04-Jun-1997*
DATE COMPLETED *06-Jun-1997*

09.1. STUDY PROTOCOL

09.1.1 Title

A study of the safety, pharmacokinetics and preliminary efficacy of repeated oral doses of SK&F 108566 in patients with mild to moderate essential hypertension

09.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the safety and pharmacokinetics of eprosartan in patients with mild to moderate essential hypertension.

09.1.3 Objectives

1. The primary objective was to evaluate the safety and tolerability of SK&F 108566 administered orally in repeated single daily doses for one week in patients with mild to moderate essential hypertension, and
2. to obtain pharmacokinetic data on single and repeated dose administration of SK&F 108566 in patients with mild to moderate essential hypertension.
3. The secondary objective was to evaluate the short-term (one week) effect of SK&F 108566 on blood pressure and pulse in patients with mild to moderate essential hypertension.

09.1.4 Study design

The study was a randomized, double-blind, placebo controlled, repeated dose, dose-rising, two-period, period balanced crossover study within each of three dose groups (A, B and C) corresponding to three dose levels of SK&F 108566. Each patient participated in two study periods separated by at least 6 days, in which study medication was administered once daily for 7 days. The dose groups A, B, and C were as follows:

1. Group A: eprosartan (SK&F 108566 oral tablets 50 mg, Lot# U92055 x 1 tablet) 50 mg once daily
2. Group B: eprosartan (SK&F 108566 oral tablets 50 mg, Lot# U92055 x 2 tablets as a single dose) 100 mg once daily
3. Group C: eprosartan (SK&F 108566 oral tablets 50 mg, Lot# U92055 x 7 tablets as a single dose) 350 mg once daily
4. Patients also received matching placebo (Lot# U92053) once daily in a randomized manner.

09.1.5 Protocol Amendments

A protocol amendment was made on 01-Dec-1992 which added a fourth treatment regimen (SK&F 108566 150 mg q 12 h) evaluated in 8 additional patients.

09.1.6 Population enrolled/analyzed

32 non-smoking, adult Caucasian men 18-55 years of age, with mild to moderate essential hypertension (average sitting diastolic blood pressure 95 to 115 mmHg without treatment), weight ≥50 kg and within 25% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All study medication was administered with 120 ml tepid water by study personnel.

Pre-study screening: The screening visit (60 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Patients with acceptable screening examination were instructed to discontinue all anti-hypertensive medications at least 2 weeks prior to administration of study medication. During this washout phase, patients returned at intervals of 1 week (±1 day) for measurement of blood pressure and pulse rate. Those patients whose average sitting diastolic blood pressure at the week -2 and -1 evaluations was between 95 and 119 mmHg were allowed to participate in the study.

09.1.7 Study procedures

Patients remained at the research facility from the evening prior to first dose of study medication to the morning of day 2 till after the second dose of study medication was administered. A 24-hour urine specimen was also obtained prior to dosing on day 1. Measurements of sitting blood pressure and heart rate, and a 12-lead ECG recording were made. A blood specimen was obtained to measure plasma renin activity after the patient had been supine for at least 1 hour. A limited physical examination was made, vital signs were obtained, and the study medication administered with 120 ml tepid water. Blood sample (5 ml) collections for pharmacokinetics were done prior to dose administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours following dosing, the 24 hour

sample being drawn immediately prior to dosing on day 2. Vital signs were recorded immediately before each collection of blood specimen. After obtaining vital signs up to 2 hours after dosing, the patient was allowed to eat breakfast and discharged from the research facility.

Patients returned each morning for the morning dose of the study medication on days 3 through 6. At the morning visit on day 4 or 5, an Accutracker II ambulatory blood pressure monitoring unit was placed for 24 hours to record blood pressure and pulse rate at 15 minute intervals while the patient was awake, and at 30 minute intervals while he was sleeping. 5 ml blood samples were taken on the morning visits on days 4 and 6 prior to dosing.

Urine was collected and pooled during the 24 hour period prior to dosing on day 7. In the morning of day 7, a blood specimen was obtained to measure plasma renin activity after the patient had been supine for at least 1 hour. Blood samples for pharmacokinetics were drawn as on Day 1, except that the 18 and 24 hours specimens were not collected for the regimen of 150 mg q 12 h. Subjects returned 1 week following the last (second) study session, at which time physical examination, recording of vital signs, 12-lead ECG and safety laboratory tests were performed.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

09.1.8 **Pharmacokinetic procedures:**

Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 6 - 8 months. Plasma concentrations of eprosartan were determined by reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) in plasma was 10.0 ng/ml. (LLQ was adjusted to 20 ng/ml in 3 samples during the initial analysis, with lack of sample for reanalysis.)

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain Cmax, Tmax, the apparent terminal elimination rate constant (λ), $T_{1/2}$ (except for 150 mg q 12 h regimen for which an adequate description of the terminal elimination phase could not be obtained), AUC(0-τ), AUC(0-∞). The percent extrapolated was <20% in all but one patient (48.2%, Patient 5, Day 7 of 50 mg/day regimen).

09.1.9 **Endpoints:**

The primary parameters were clinical and laboratory safety data, and plasma concentration data for pharmacokinetics. The secondary parameters were the average sitting diastolic blood pressure, systolic blood pressure, pulse rate, and calculated mean arterial blood pressure {MAP = (SBP-DBP)/3 + DBP}.

09.1.10 **Sample size:**

The planned sample size (8 patients per group) was based on feasibility.

09.1.11 **Investigator , Center and Study Dates:**

Jerry Herron, MD, Arakansas Research Medical Testing Center, Inc., Little Rock, Arkansas, USA.
Study Dates: 19-Oct-1992 to 08-Mar-1993.

09.2 **STUDY POPULATION**

09.2.1 **Subject disposition:**

Of 33 patients screened, 1 withdrew after 5 days of treatment (on 50 mg once daily). 32 Caucasian adult male patients, 21-55 (mean = 46) years of age, weighing 68.2 to 107.3 (mean = 87.4) kg, and 165-192.9 (mean = 180.4) cm tall, were randomized.

09.2.2 **Withdrawals:**

One patient (#006) was withdrawn at his own request after 5 days of treatment with SK&F 108566 50 mg once daily, and was replaced by an additional patient (#033).

09.2.3 **Protocol violations:**

The 18 and 24 hours blood specimens were not collected for the regimen of 150 mg q 12 h.

In 3 blood samples (from Patient #10 at 1.5 and 3 hours, and Patient #15 at pre-dose on Day 1), the initial HPLC assays for eprosartan levels was performed with LLQ adjusted to 20 ng/ml. There was no more sample left for reanalysis with LLQ adjusted to 10 ng/ml as specified by protocol.

SK&F 108566 was known to be stable in human plasma stored at -20°C for 7 months. While samples for 100 mg qd, 350 mg qd and 150 mg q12h were analyzed within 6 months of plasma collection, samples for the 50 mg qd regimen were analyzed within 8 months of collection.

Examination of the plasma concentration-time profiles also showed that some of the patients did not have complete blood sample collections or plasma concentration data. Table Epro-009-1 below shows the missing results.

Table Epro-009-1. List of missing plasma concentration data

Patient #	Day 1: plasma level missing since	Day 7: plasma level missing since
001		8 hours post-dose
002		18 hours post-dose
003	18 hours post-dose	12 hours post-dose
005	8 hours post-dose	8 hours post-dose
008	8 hours post-dose	12 hours post-dose
033		8 hours post-dose
010	12 hours post dose	18 hours post-dose
025		12 hours post-dose
026		12 hours post-dose
027		12 hours post-dose
028		12 hours post-dose
029		12 hours post-dose
030		12 hours post-dose
031		12 hours post-dose
032		12 hours post-dose

09.3 SAFETY RESULTS

09.3.1 **General considerations:** A total of four adverse experiences were reported

09.3.2 **Deaths:** There were no deaths during this study.

09.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

09.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

09.3.5 **Adverse Events:** Four adverse events (all mild to moderate in nature) were reported for 3 patients as follows:

Patient #019 Report nausea on two occasions, both following Placebo
Patient #032 Reported headache following Placebo
Patient #033 Reported headache following SK&F 108566 50 mg once/day.

09.3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates. There were no symptomatic changes in blood pressure. The sponsor submitted that there was no evidence of differences between the 12-lead ECGs obtained at the screening and the follow-up visits, but data were not presented.

There were no apparent changes in any safety laboratory value associated with SK&F 108566, and no values of potential clinical concern were identified. Values of urinary excretion of sodium, potassium and creatinine (U_{Na}, U_K, U_{Cr}) and plasma renin activity were similar following administration of SK&F 108566 or placebo with no apparent dose response. There was no evidence of an effect of SK&F on urine uric acid excretion at the doses studied.

09.4 PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

09.4.1 Primary Efficacy Endpoint: Following single and repeat oral doses of eprosartan (Table Epro-009-2) peak plasma concentrations were reached within 1-3 hours: plasma levels were <10% of peak values after 12 hours. In Table Epro-009-3, Tmax was reached within 1.22 to 1.97 hours, with no differences between single and repeated dosing. $T_{1/2}$ ranged from 4.09 to 9.6 hours. A dose-related increase in mean Cmax, AUC(0-τ) and AUC(0-∞) were found. There was no accumulation with repeated doses. These suggest that eprosartan requires bid dosing.

Table Epro-009-2. Time course of plasma concentrations following single and repeat oral doses of eprosartan

Time	After first single oral dose of:				After 7 days oral administration of:			
(hour)	*50 mg*	*100 mg*	*150 mg*	*350 mg*	*50 mg*	*100 mg*	*150mg bid*	*350 mg*
0	NQ	NQ	NQ	NQ	NQ	22.3	148.3	44.4
0.25	71.8	76.2	115.4	52.5	63.7	186.9	223.5	335.3
0.50	339.0	449.3	677.1	424.5	132.1	664.6	828.1	809.6
0.75	524.2	730.3	1258.5	1068.8	219.4	1073.4	1283.6	1264.8
1.0	507.8	1049.6	1503.9	1439.2	328.3	1224.2	1435.6	1524.0
1.5	673.0	1236.4	1503.6	1542.2	425.4	1393.7	1329.4	1620.2
2.0	699.3	1034.7	1268.4	1651.4	552.7	1309.6	1373.8	1416.0
3.0	668.5	1004.5	984.5	1767.2	513.8	844.4	991.0	1147.8
4.0	509.2	621.8	769.6	1358.1	380.0	603.3	900.3	842.9
6.0	181.0	300.8	268.0	685.8	195.5	267.1	333.2	453.0
8.0	83.3	132.0	139.2	313.3	90.1	154.6	172.3	270.0
12.0	43.6	59.8	58.0	179.2	48.3	53.2	74.5	109.9
18.0	18.3	37.8	34.6	59.6	24.5	35.2	--	57.7
24.0	NQ	18.9	15.3	39.2	16.5	25.9	--	53.5

NQ = not quantifiable

Table Epro-009-3. Pharmacokinetic values for eprosartan following single and repeat oral doses

End-	After first single oral dose of:				After 7 days oral administration of:			
point	*50 mg*	*100 mg*	*150 mg*	*350 mg*	*50 mg*	*100 mg*	*150mg bid*	*350 mg*
Cmax (ng/ml)								
Mean	967.6	1405.9	1647.4	2276.4	672.6	1480.2	1634.9	1818.0
Median	1101.0	1285.1	1790.9	2154.5	395.4	1296.9	1712.1	1627.9
S.D.	583.9	526.3	666.3	752.3	674.9	866.6	710.2	763.4
Tmax (hr)								
Mean	1.75	1.69	1.22	1.91	1.84	1.38	1.81	1.97
Median	1.75	1.50	1.00	1.75	1.75	1.50	1.50	1.75
S.D.	0.92	0.65	0.41	0.98	0.83	0.42	1.19	1.07
AUC(0-τ) (ng.h/ml)								
Mean	3359	5287	6249	10133	2770	5768	6340	8067
Median	2913	4822	6248	7398	1776	5298	6600	8173
S.D.	2421	2643	3192	5253	2783	2792	2818	2936
AUC(0-∞) (ng.h/ml)								
Mean	3442	5477	6422	10486	2923	6284	--	8184
Median	3033	4933	6484	7506	1873	5617	--	6651
S.D.	2425	2657	3171	5418	2766	3015	--	3169
$T_{1/2}$ (h)								
Mean	4.09	7.54	7.92	6.77	5.74	9.60	--	7.76
Median	3.05	6.03	7.83	6.24	5.37	7.73	--	7.81
S.D.	2.78	5.04	3.09	3.22	3.51	7.09	--	1.40
Accumulation Ratio								
Geometric Mean	--	--	--	--	0.78	1.04	1.02	0.80
Minimum	--	--	--	--	0.28	0.50	0.63	0.31
Maximum	--	--	--	--	2.46	2.44	1.63	1.51

Accumulation Ratio = {$AUC_{(0-\tau)}$ on Day 7} ÷{$AUC_{(0-\infty)}$ on Day 1}

09.4.2 Secondary Efficacy Endpoint

There were no symptomatic changes in blood pressure. If a fall in diastolic cuff blood pressure by ≥ 3 mmHg is taken as an acceptable response to treatment, then this response is observed (albeit inconsistently) at 3 hr or 12 hours after dosing, with no apparent treatment response at 24 hours (Table Epro-009-4). This finding also suggests that eprosartan requires bid dosing.

The only dose-related response was found in the diastolic cuff blood pressure 3-hours post-dose. No consistent dose-dependent lowering of systolic or diastolic blood pressure was found in ambulatory blood pressure monitoring.

The 3-hour averaged mean arterial pressure (Figures Epro-009-1) showed a consistent moderate lowering of mean arterial pressure throughout the dosing interval versus placebo, with no discernible dose response.

Table Epro-009-4. Change (placebo subtracted) in cuff and ambulatory systolic and diastolic blood pressure following single and repeat oral doses of eprosartan

Day &	After first single oral dose of:				After 7 days oral administration of:			
Time	*50 mg*	*100 mg*	*150 mg*	*350 mg*	*50 mg*	*100 mg*	*150mg bid*	*350 mg*
Systolic Cuff Blood Pressure (compared to placebo)								
0h	-2.33	-5.25	2.08	4.08	-3.75	0.08	-3.17	-5.08
3h	-3.00	-4.25	-10.50	-5.25	-3.25	-4.75	-8.00	-3.50
12h	1.50	-1.50	-0.50	-1.25	0.25	-3.50	-7.50	-6.25
24h	-1.58	-5.00	-3.25	-2.83	2.00	-2.83	-0.25	-4.67
Diastolic Cuff Blood Pressure (compared to placebo)								
0h	-1.7	0.17	-1.67	-0.58	-3.08	0.75	-2.67	-2.33
3h	-1.75	-4.25	-4.50	-10.00	2.25	-2.75	-8.25	-6.00
12h	-4.25	-1.25	-5.25	-6.00	-1.75	0.75	-3.50	-3.75
24h	-0.17	-0.75	-2.33	-1.25	-0.42	0.17	0.75	-2.25
Ambulatory Blood Pressure Monitoring (Systolic) (compared to placebo)								
0-12h					-18.22	-18.25	-8.47	-14.31
12-24h					-7.41	-2.68	-5.02	-18.21
0-24h					-15.70	-11.99	-7.14	-16.05
0-15h					-17.75	-17.67	-9.00	-16.34
15-24h					-11.76	1.62	-2.41	-15.03
21-24h					-12.33	7.18	-2.15	-10.06
Ambulatory Blood Pressure Monitoring (Diastolic) (compared to placebo)								
0-12h					-7.70	-9.07	-4.57	-5.67
12-24h					-0.42	-2.15	-5.61	-7.78
0-24h					-5.92	-6.38	-5.13	-6.36
0-15h					-7.33	-8.07	-5.22	-6.45
15-24h					-1.92	-1.69	-4.97	-6.44
21-24h					-7.98	-5.68	-7.00	-5.96

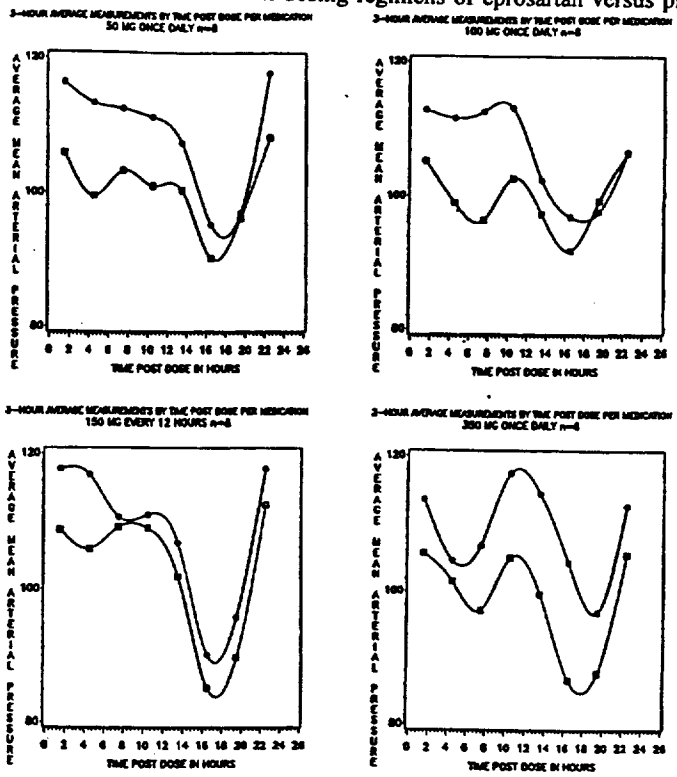
09.5 CONCLUSION

Single and repeat dose administration of varying doses (50, 100 and 350 mg once a day and 150 mg bid) of eprosartan to patients with mild to moderate essential hypertension did not show any significant differences in adverse experiences compared to placebo. There were no abnormal laboratory values of potential safety concern.

The plasma concentrations reached peak values within 1-3 hours, with $T_{1/2}$ between 4.09 and 9.6 hours. A dose-related increase in mean Cmax, AUC(0-t) and AUC(0-∞) were found. There was no accumulation with repeated doses. The pharmacokinetic data suggest that eprosartan requires bid dosing.

Diastolic cuff blood pressure was reduced at 3 to 12 hours after dosing, with no apparent treatment response at 24 hours. Ambulatory blood pressure monitoring and averaged mean arterial pressure did not show dose-dependent lowering of blood pressure.

Fig. Epro-009-1. Averaged mean arterial pressure in relation to time across all dosing regimens of eprosartan versus placebo



Study Medication ●●● PLACEBO ■■■ SKF108566

** *Hours Post Dose Based on Dosing Time of 8:00 AM*

Protocol 018 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.106)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *9-Jun-1997*
DATE COMPLETED *10-Jun-1997*

18.1 STUDY PROTOCOL

18.1.1 Title

Comparison of the bioavailability of the original tablet formulation and a new intermediate release tablet formulation of SK&F 108566 in healthy male volunteers

18.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I and potentially offer therapeutic advantages (absence of side effects e.g., non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the bioavailability of the tablet formulation of eprosartan, an A-II AT_1 receptor antagonist, which was used during early Phase I and IIa studies in comparison to a new immediate release formulation intended for use in later clinical trials.

18.1.3 Objectives

To compare the systemic bioavailability of the original tablet formulation of SK&F 108566 and a newly developed immediate release tablet intended for use in clinical trials.

18.1.4 Study design

The study was a randomized, open-label, three-period, period balanced crossover study of three groups (A, B and C). Each patient participated in three study periods separated by at least one week, in which each received the study medication as a single oral dose of 100 mg The dose groups A, B, and C were as follows:

1. Group A: SK&F 108566 50 mg tablets, (Lot# U93180, new formulation) 100 mg once daily
2. Group B: SK&F 108566 100 mg tablets, (Lot# U93174, new formulation) 100 mg once daily
3. Group C: SK&F 108566 50 mg, tablets (Lot# U93008, original formulation) 100 mg once daily

18.1.5 Protocol Amendments

There were no amendments to the protocol.

18.1.6 Population enrolled/analyzed

24 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All study medication was administered with 120 ml tepid water by study personnel.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 2 weeks prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period.

18.1.7 Study procedures

After a 10 hour overnight fast, patients reported at 7:00 am. Assessment of baseline symptoms and vital signs, and a 12-lead ECG recording were made. A light breakfast (cereal, milk, juice and muffin) was given at 7:30 am, and completely consumed within 20 minutes. At 8:00 am (within 10 minutes of finishing breakfast), all subjects were administered a single 100 mg oral dose of SK&F 108566 with 240 ml of tepid water. No food or drink was permitted for 4 hours after dosing. Subjects drank 240 ml water at 2 and 4 hours after dosing. Water, soft drinks with caffeine or fruit juices were permitted *ad lib* 5 hours after dosing, and lunch and dinner were given at 5 and 9-10 hours post dose, respectively. Subjects remained in the clinical pharmacology unit for 24 hours after dosing. No vigorous exercise was permitted. Sitting blood pressure and pulse measurements were obtained prior to dosing and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Blood sample (5 ml) collections for pharmacokinetics were done prior to dose administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours following dosing. A 12-lead ECG was obtained at 3 and 24 hours after dosing.

Subjects returned 1 week following the last (third) study session, at which time safety laboratory tests were done.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

18.1.8 **Pharmacokinetic procedures**:
Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C and 2300 rpm for 10 minutes, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 3 months. Plasma concentrations of eprosartan were determined by reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) in plasma was 10.0 ng/ml.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), $T_{1/2}$, AUC(0-τ), AUC(0-∞). The percent extrapolated was <12% in all profiles for AUC(0-∞) that could be determined.

18.1.9 **Endpoints:**
AUC(0-τ) and Cmax were primary endpoints, and Tmax and $T_{1/2}$ were secondary endpoints for each dosing regimen. Clinical monitoring and laboratory safety data were also secondary endpoints.

18.1.10 **Sample size:**
The planned sample size (8 per group) was based on feasibility. No statistical power calculations were performed.

18.1.11 **Investigator , Center and Study Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center University of Pennsylvania Health System, Philadelphia, PA. Study Dates: 19-Oct-1993 to 17-Dec-1993.

18.2. **STUDY POPULATION**

18.2.1 **Subject disposition:**
24 male subjects, 19-40 (mean = 25) years of age, weighing 64.0 to 97.9 (mean = 75.7) kg, and 163-192 (mean = 178) cm tall, were screened and randomized.

18.2.2 **Withdrawals:**
No subject withdrew prior to study completion.

18.2.3 **Protocol violations:**
Five subjects (#575, #581, #583, #585 and #601) inadvertently received a single 50 mg oral dose (1 x 50 mg, new formulation) at their first study session I error of the randomization schedule. All five subjects waited one week and then initiated the correct randomization schedule. Adverse events and vital signs and laboratory data from this incorrect dose were reported; blood samples for plasma concentrations of SK&F 108566 were not analyzed.

18.3 **SAFETY RESULTS**

3.1 **General considerations:** A total of nine adverse experiences were reported in six subjects, all of which resolved spontaneously

18.3.2 **Deaths:** There were no deaths during this study.

18.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

18.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

18.3.5 **Adverse Events:** Six adverse events (all mild to moderate in nature, none requiring treatment, and all resolving spontaneously) were reported for 6 subjects as follows:

1. Group A: SK&F 108566 50 mg tablets, new formulation: Subject # 583, # 589 and # 604 reported headache
2. Group B: SK&F 108566 100 mg tablets, new formulation: Subject # 588 reported an upper respiratory infection, Subject # 589 and # 604 reported headache
3. Group C: SK&F 108566 50 mg tablets, original formulation: Subject # 589 reported headache; Subject # 592 reported a viral infection (flu syndrome)
4. Extra group: SK&F 108566 50 mg tablets, new formulation (50 mg dose): Subject # 585 reported headache

18.3.6 **Laboratory findings, ECGs, Vital signs**
No patient in this study exhibited abnormal heart rates. There were no symptomatic changes in blood pressure.

All ECGs were reported as normal. There were no clinically significant changes in the 12-lead ECGs and the ECG intervals (including PR, QRS, QT and QTc) noted in any treatment group.

Two subjects (#581 and # 590) had pyuria, two subjects (#575 and #582) had elevated serum potassium attributable to hemolysis of the blood sample, and 1 subject (#610) had elevated serum ALT of 74.7 IU/L 24 hours post-dose, which decreased to 51.0 IU at one week after the last dosing session.

18.4 PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

Following single oral doses of the original and new formulations of eprosartan (Table Epro-018-1) the mean plasma concentration-time profiles were similar. Peak plasma concentrations were reached within 3-4 hours: plasma levels were <10% of peak values after 12 hours.

Table Epro-018-1. Time course of plasma concentrations following a single oral dose of eprosartan

Time (h)	50 mg x 2 (new formulation)	100 mg x 1 (new formulation)	50 mg x 2 (original formulation)
0	NQ	NQ	NQ
0.50	NQ	NQ	NQ
1.0	69.5 ± 83.1	58.6 ± 61.6	52.4 ± 36.5
1.5	155.8 ± 144.8	198.6 ± 197.3	118.8 ± 86.1
2.0	239.2 ± 177.6	236.1 ± 191.9	190.7 ± 117.1
3.0	316.4 ± 201.7	293.9 ± 120.6	387.5 ± 238.3
4.0	320.4 ± 144.7	307.6 ± 130.8	301.5 ± 156.8
6.0	129.2 ± 64.1	135.1 ± 77.9	116.4 ± 57.3
8.0	53.3 ± 28.1	57.4 ± 38.3	47.9 ± 21.3
10.0	33.9 ± 36.8	29.8 ± 24.7	24.2 ± 11.8
12.0	NQ	13.0 ± 7.7	13.0 ± 7.5
18.0	NQ	NQ	NQ
24.0	NQ	NQ	NQ

NQ = not quantifiable (Mean values not calculated if more than 1/2 of the values were NQ.)

In Table Epro-018-2, the mean Tmax was 3.17 to 3.27 hours, with no differences between the different formulations. The median differences between both of the test formulations (A or B) and the reference formulation (C) for Tmax were 0.00 hours (95% C.I.:-0.50, 0.50 hours). Mean $t_{1/2}$ for treatment formulations A, B and C were 1.94, 2.14 and 2.29 hours, respectively. The mean and median values of Cmax, AUC (0-τ) and AUC (0-∞) were not significantly different between the different formulations. The within-subject residual coefficient of variation for Cmax and AUC (0-τ) were 44.1% and 32.0%, respectively. The new formulations had rapid rate of dissolution, 86-91% within 30 minutes, and 93-95% within 45 minutes.

Point estimates and 95% confidence intervals for the comparisons of the primary pharmacokinetic parameters for the test (Treatment A - new formulation 2 x 50 mg, and Treatment B - new formulation 1 x 100 mg) relative to the reference (Treatment C - original formulation 2 x 50 mg) are shown in Table Epro-01803.

Table Epro-018-3. Point Estimates and 95% confidence intervals of comparisons of eprosartan formulations

Parameter	Comparison	Point Estimate†	95% Confidence Interval
AUC(0-τ)			
	A:C	1.04	(0.86, 1.27)
	B:C	1.03	(0.84, 1.26)
Cmax			
	A:C	1.04	(0.80, 1.34)
	B:C	0.94	(0.73, 1.22)

† Data represent the ratio of the geometric means for the test to reference

Table Epro-018-2. Pharmacokinetic values for eprosartan following single oral doses

End Point	50 mg x 2 (new formulation)	100 mg x 1 (new formulation)	50 mg x 2 (original formulation)
AUC(0-τ) (ng.h/ml)			
Geometric Mean	1368	1382	1445
Mean	1464	1504	1538
Median	1364	1582	1572
S.D.	609	588	523
AUC(0-∞) (ng.h/ml)			
Geometric Mean	1350	1333	1307
Mean	1454	1451	1417
Median	13836	1507	1438
S.D.	623	566	548
Cmax (ng/ml)			
Geometric Mean	390	354	379
Mean	420	384	436
Median	405	384	476
S.D.	177	151	228
Tmax (hr)			
Mean	3.17	3.20	3.27
Median	3.00	4.00	3.00
S.D.	0.87	0.96	0.63
$T_{1/2}$ (h)			
Mean	1.94	2.14	2.29
Median	1.74	1.98	1.91
S.D.	0.89	0.87	1.29
Percent Dissolution at:			
10 minutes	59	71	na
20 minutes	70	80	na
30 minutes	86	91	na
45 minutes	93	95	na

18.5. CONCLUSION

Single oral dose administration of different formulations of eprosartan (100 mg once a day) to healthy male volunteers did not show any significant differences in adverse experiences. There were no abnormal laboratory values of potential safety concern.

With all 3 formulations of eprosartan, the plasma concentrations reached peak values within 3-4 hours, with mean Tmax between 3.17 to 3.27 hours. The median differences between both of the test formulations (A or B) and the reference formulation (C) for Tmax were 0.00 hours (95% C.I.:-0.50, 0.50 hours) suggesting that the rate of absorption of eprosartan from the new wet granulation formulations was comparable to the original direct compress formulation. The mean $T_{1/2}$ was between 1.94 and 2.29 hours.

The new formulations had rapid dissolution rates , within 30 minutes an within 45 minutes. There were no significant differences in the values of the mean and median Cmax, AUC (0-τ) and AUC (0-∞) for the different formulations of eprosartan. suggesting that the bioavailability of the new tablet formulations were similar to the original tablet formulation.

Protocol 020 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.107)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *02-Jul-1997*
DATE COMPLETED *03-Jul-1997*

20.1 STUDY PROTOCOL

20.1.1 Title

A study to determine the balance/excretion, pharmacokinetics and biotransformation of eprosartan (SK&F 108566) given as a single oral (100 mg) and single intravenous (20 mg) doses on separate occasions to healthy male adult subjects

20.1.2 Rationale

A-II receptor antagonists affect conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects , e.g., non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the disposition and elimination of eprosartan using [^{14}C]labeled drug substance administered by oral and i.v. routes.

20.1.3 Objectives

1. To investigate the disposition and routes of elimination of eprosartan following single intravenous and oral administration to human subjects;
2. To quantify and structurally characterize the major compound-related components in human plasma and excreta (urine and feces);
3. To compare concentrations of total radio label and of eprosartan in human plasma following single intravenous and oral administration, to assess the presence of circulating metabolites.

20.1.4 Study design

The study followed an open, 2 part, randomized, crossover design in 4 subjects. Each subject was randomized to receive a 20 mg intravenous dose of eprosartan or a 100 mg oral dose of eprosartan followed by the alternative formulation separated by a minimum interval of 28 days. Subjects then crossed over to the alternative regimen. The clinical phase of each subject lasted 6 weeks.

20.1.5 Protocol Amendments

Because use of phosphoric acid to stabilize drug in urine invalidated the assay for urinary creatinine, an amendment was made that samples would not be collected for creatinine assay.

A second amendment was made in which the blood sampling regimen for metabolite analysis was modified to 0.5, 1 and 4 hours post dose (instead of 1, 2 and 6 hours post dose iv, and 1, 6 and 12 hours post dose oral) because it was noted after assay of the first dosing arm that little radioactivity remained in the plasma at later sampling times.

20.1.6 Population enrolled/analyzed

4 healthy, adult male volunteers 35-60 years of age, weight 50 - 100 kg and within 25% of ideal weight (based on height), normal ECG, normal clinical laboratory tests, negative hepatitis B surface antigen and a negative urine drug screen were enrolled. Subjects who had participated in a radiolabeled study or who had received a total body radiation of >5.0 mSv (upper limit of WHO category II) within the past 12 months, or attempting to father a child, or history of adverse reactions to ACE inhibitors were not enrolled.

Compliance: This was determined by analysis of residues in the oral dose containers and iv dose infusion apparatus.

Pre-study screening: The screening visit (15 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were asked to collect urine and feces for the 24 hour period prior to the first dosing day for assessment of background radiation levels and to act as controls for the metabolite identification studies. Subjects were not permitted to take any prescription or non-prescription medications (except paracetamol for mild analgesia) 1 week prior to and during the study. Subjects were instructed to avoid strenuous physical activity from 24 hours before to 25 hours after dosing. Subjects were asked to refrain from high fiber or spicy foods (e.g., nuts, root vegetables, sweet corn, chili, etc.) and not make any major change in their normal diet from 3 days before dosing until the end of the last fecal collection.

20.1.7 Study procedures

Baseline phase: Subjects report to the clinical unit at 8 a.m. each study day after having fasted from midnight the previous day. A cannula was inserted into a forearm vein, and for i.v. dosing, an additional cannula was placed in

the opposite arm). Blood and urine samples were obtained for drug assay reference and for clinical laboratory studies. Semi-supine vital signs and 12-lead ECG were obtained.

Study phase: Subjects received [^{14}C]eprosartan either as an iv infusion (50 ml) over 30 minutes or as a solution swallowed in 100 ml of phosphate buffer.

Subjects remained recumbent for 4 hours following dosing. After a standing blood pressure measurement, subjects were allowed to ambulate in the clinical pharmacology unit. Supine blood pressure and pulse rate were recorded hourly for 6 hours and at 8, 10, 12 and 24 hours following dosing. A 12-lead ECG was done at 2 and 24 hours.

The study medications consisted of the following:

Solutions of [^{14}C]eprosartan (Batch# M94041, chemical purity 98.5% pfb, 18.36 μCi/ml, Synthetic Isotope Chemistry Unit, Chemical Development, SmithKline Beecham, Harlow, UK) and non-radiolabeled eprosartan (Batch# M94040, chemical purity 99.8% pfb, Chemical Development, SmithKline Beecham, Tonbridge, UK), each at a concentration of 5 mg/ml were used.

For oral administration, 16.19 ml eprosartan and 3.81 ml [^{14}C]eprosartan solutions were added to 80 ml 125 mM phosphate buffer pH 8.3 (Batch# M94039) and mixed thoroughly (to give a concentration of 1 mg/ml solution). After taking an aliquot (2 g), the entire volume of the solution was drunk by the subject using a straw. The container was washed out twice with 50 ml 125 mM phosphate buffer, and the washings were also drunk by the subject using the straw. The dose container and the straw were retained for analysis of residual radioactivity.

For iv administration, 0.24 ml eprosartan and 4.96 ml [^{14}C]eprosartan solutions were added to 59.8 ml of 0.9% sodium chloride (Batch# 401001) and mixed thoroughly (to give a concentration of 0.4 mg/ml). 60 ml of the solution was transferred to a weighed sterile syringe attached to the infusion tubing, and infusion apparatus was re-weighed with the dose solution, and this solution was infused over 30 minutes via a venflon cannula in the forearm vein of the subject at a rate of 10 ml/hour (approximately 50 ml infused, approximately 20 mg eprosartan pfb). The infusion apparatus (syringe, line, three-way taps and cannula) was retained for analysis of residual radioactivity. The unused dose solution (about 5 ml) was used for the assessment of radiochemical purity (by radio-HPLC) and concentration.

To determine the precise dose administered to each subject, the radioactivity in the dose residue was subtracted from that calculated to be in the weighed dose.

Blood samples (10 ml) for plasma radioactivity and eprosartan levels were drawn at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 32 and 48 hours following oral dosing. Additional 20 ml samples for metabolite profiling were taken at 1, 6 and 12 hours; after the first arm, this was modified to 0.5, 1 and 4 hours because of low radioactivity in later samples. Following iv dosing, blood samples (10 ml) for plasma radioactivity and eprosartan determinations were drawn at 0 (predose), 0.25, 0.5 (as the pump was turned off), 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 32 and 48 hours after dosing. Additional 20 ml samples for metabolite profiling were taken at 1, 6 and 12 hour; after the first arm, this was modified to 0.5, 1 and 4 hours because of low radioactivity in later samples.

(N.B. In total, not more than 500 ml of blood were taken from each subject including both blood samples for safety laboratory tests and for pharmacokinetic analysis.)

Urine was collected over timed 24 hour periods (0-6, 6-12 and 12-24 hours post dose during the first 24 hours) from 24 hour pre-dose for 5 days after each dosing day (rather than 7 days as stated in protocol, because of very low radioactivity at 5 days). Volume and pH were measured, a sample was taken for urinary creatinine , then phosphoric acid added to the urine to stabilize drug products in urine.

Feces were collected on the day of dosing for up to 8 days post-dose on each dosing phase.

Subjects remained in the clinical pharmacology unit overnight and fasted from midnight until the 24 hour blood sample. Water, soft drinks without caffeine or fruit juices (except grapefruit juice) were permitted 2 hours after dosing, and lunch, a snack and dinner were given at 4, 7 and 10 hours post dose, respectively. Subjects left the unit following the 24 hour assessment, returning for 32 and 48 hour blood samples.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

Post-study phase: Subjects returned 10-15 days following the last administration of study medication, at which time a 12-lead ECG, semi-supine heart rate and blood pressure recording and safety laboratory tests were done.

20.1.8 **Pharmacokinetic procedures:**

Blood samples collected in lithium heparin tubes and chilled on ice were centrifuged at 4°C and 1500 g_{av} for 10 minutes, and plasma was transferred (divided into equal volumes) to 2 polypropylene tubes (one for radioassay and one for assay of eprosartan). The large plasma samples for metabolic profiling were acidified with 21.3% (v/v) aqueous orthophosphoric acid (150 µl) to prevent potential hydrolysis of acyl glucuronides that may have been present, and then re-assayed for radioactivity. All plasma samples were stored at -70°C to be assayed within 6 months. Plasma concentrations of eprosartan were determined by solid phase extraction with HPLC and UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml for a 0.5 ml aliquot.

Urine samples over time intervals of 0-6, 6-12, 12-24, 24-48, and 48-72 hours and for each 24 hour period for 2 more days, were collected, and an appropriate volume of 21.3% (V/v) aqueous phosphoric acid added. For each collection, the weight of the urine sample was calculated and recorded, and 20 ml aliquots were transferred to Sterivials (for use in metabolite analysis). All urine samples were stored at -70°C.

Each fecal sample was collected into a separate pre-weighed sealable plastic pot, together with the toilet tissue used. Fecal collections continued up to 8 days. All fecal samples were stored at -20°C.

For radioactivity, 3 replicate aliquots each of plasma (150 or 250 µl), each dose solution (0.16-0.25 g), each diluted dose residue (approx. 1 g), urine samples (0.5 g) were assayed after addition of 10 ml Ultima Gold as the liquid scintillant. Five samples of fecal homogenate (0.5 g) were weighed onto Combusto-Pads contained in Combusto-Cones, and, after drying overnight, were combusted in an automated sample oxidizer (model 307). Carbo-Sorb E (8 ml) was used to trap the combustion products, and Permafluor E+ (10 ml) was used as scintillant. Samples were assayed for radioactivity by liquid scintillation counting (10 minutes/sample) using Canberra-Packard Tri-Carb (model 2500TR) or Beckman (model 5801), with quench correction determined by an external standard ratio procedure using sealed quench standards. Twice the background count rate was considered to be the LLQ.

Radiometabolites of [^{14}C]eprosartan were quantified in urine and feces by a binary gradient reversed phase HPLC with on-line radioactivity detection. The radioactive metabolite components in plasma samples were quantified using HPLC with fraction collection (Foxy, Isco., Lincoln, NB) followed by liquid scintillation counting.

Concentration-time data analysis for eprosartan and drug-related material was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), AUC(0-τ), $T_{1/2}$, and AUC(0-∞). Bioavailability was determined as {dose-normalized AUC(0-∞) oral} ÷ {dose-normalized AUC(0-∞) intravenous}. The average theoretical oral bioavailability (F) was calculated as $F = 1 - \{CL_{h,b}/Q_b\}$ assuming that metabolism was exclusively by the liver and where $CL_{h,b}$ was the hepatic blood clearance (i.e., difference between total blood clearance and renal clearance) and Q_b (liver blood flow in man) was assumed to be 87 L/h.

20.1.9 **Endpoints:** There were no efficacy outcomes measured in this study.

20.1.10 **Sample size:**

The number of subjects for the study was based on feasibility. No statistical power calculations were performed.

20.1.11 **Investigator , Center and Study Dates:**

J. Upward, MB, BS, MRCP, MFPM, SmithKline Beecham Clinical Pharmacology Unit, Harlow, Essex CM19 5AW, United Kingdom. Dates: 12-Apr-1994 to 11-May-1994.

20.2. **STUDY POPULATION**

20.2.1 **Subject disposition:**

4 healthy, Caucasian, male volunteers, 36-50 (mean = 42) years of age, weighing 70.7 to 90.8 (mean = 80.5) kg, and 173-183 (mean = 177) cm tall, were randomized.

20.2.2 **Withdrawals:** Subject #003 was withdrawn because of an adverse experience.

20.2.3 **Protocol violations:**

There were no protocol violations apart from minor modifications in procedures that were documented.

20.3. SAFETY RESULTS

20.3.1 **Deaths:** There were no deaths during this study.

20.3.2 **Withdrawals:** Subject #003 was withdrawn prior to dosing for the second arm of the study due to an elevated liver enzyme level detected during the first arm of the study in the pre-dose blood screen.

20.3.3 **Serious, Non-fatal Adverse Events:** There was no non-fatal adverse experience during this study.

20.3.4 **Adverse Events:** No clinically significant abnormalities were noted at pre-study screen or pre-dose screens prior to each dose apart from subject #003 who had elevated ALT pre-dose (75 IU/l) and 24 hours post dose (72/IU/l).

A moderate headache was reported by subject #003 about 44 minutes after administration of the 100 mg oral dose of eprosartan, which lasted 11.5 hours. The subject took a single 1 g dose of paracetamol about 6.5 hours after headache started. He was subsequently withdrawn from the iv arm of the study because of elevated pre-dose ALT.

20.3.5 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates or orthostatic changes in blood pressure.

All 12-lead ECGs from pre-dose, 2 and 24 hours post-dose and follow up were assessed as normal.

Subject #003 had elevated ALT pre-dose (75 IU/l) and 24 hours post dose (72 IU/l). No clinical symptoms were associated with this laboratory abnormality, and other liver enzymes were within the normal range. The elevated ALT was identified after the subject had received the oral dose of eprosartan; he was withdrawn from the subsequent iv arm of the study. Three weeks later his ALT had dropped to 68 IU/l, and after another week, it was 48 IU/l.

20.4. PHARMACOKINETIC RESULTS

20.4.1 **Excretion**

There was little inter-subject variation in the elimination of radioactive material following oral or iv administration. The major route of excretion was via the feces (61 and 90% of dose being excreted after intravenous and oral administration, respectively). Urinary excretion account for means of 37% and 7% of dose being excreted after intravenous and oral administration, respectively. A minimum absorption of approximately 15% of the oral dose (range: 10.1% - 20.0%) was calculated from the urinary excretion of radioactivity of 3 subjects who completed both study days. Mean total recovery of radioactivity was 98% of the dose after oral as well as iv administration.

20.4.2 **Pharmacokinetics**

Following intravenous administration, peak plasma concentrations (Cmax) of eprosartan and of total radioactivity were seen at the end of infusion (0.5 hour), were similar and declined from peak in a bi-exponential manner. Plasma concentrations of eprosartan and total radioactivity were quantifiable up to 10 and 12 hours post-dose, respectively.

Table Epro-020-1. Pharmacokinetic values for eprosartan administered orally or intravenously to healthy volunteers

Parameter	Cmax (ng/ml)	Tmax (h)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng.h/ml)	$T_{1/2}$ (h)
20 mg iv					
Subject #001	2173	0.50	2342	2396	2.18
Subject #002	1655	0.52	1658	1747	3.33
Subject #003	ND	ND	ND	ND	ND
Subject #004	2238	0.50	2489	2536	2.26
Mean	2022	0.51	2163	2226	2.59
Median	2173	0.50	2342	2396	2.26
S.D.	319	0.01	443	421	0.64
100 mg oral					
Subject #001	543	1.00	1222	1356	3.71
Subject #002	701	1.50	1909	1994	4.54
Subject #003	1034	1.50	3449	3622	4.82
Subject #004	405	1.00	1053	1134	3.13
Mean	671	1.25	1908	2026	4..05
Median	622	1.25	1566	1675	4.13
S.D.	271	0.29	1092	1124	0.77

ND: no dose administered

After oral administration, the maximum plasma concentrations (Cmax) of eprosartan and of total radioactivity were seen at the same time with Tmax of 1.0 to 1.5 hour, and declined from peak in a bi-exponential manner. Plasma concentrations of eprosartan were quantifiable for up to 10 to 18 hours post-dose and that of total radioactivity were quantifiable for up to 2 to 12 hours post-dose.

The pharmacokinetics of eprosartan are characterized in Table Epro-020-1, with < 10% extrapolated AUC in all subjects. Following iv eprosartan 20 mg, the mean volume of distribution at steady-state was 17L (approximating extracellular water), and the mean systemic plasma clearance was 9 L, indicating that the drug had low plasma clearance and was not widely distributed. The average blood clearance of eprosartan (based on blood to plasma ratio of 0.62 in man) was approximately 14.7 L/h. From this clearance value and the assumption that eprosartan was completely absorbed and primarily hepatically cleared, a theoretical absolute bioavailability of approximately 83% was predicted. The average absolute bioavailability of the drug following oral administration was 14.7% (range: . These results suggest that low absorption of eprosartan rather than extensive first pass metabolism was the reason for the low bioavailability of eprosartan. The relatively longer $T_{1/2}$ after oral dose (4.05 h) compared to that after intravenous dose (2.59 h) also supports the assumption of slow absorption of eprosartan and absorption throughout the small and large intestine (rather than fecal elimination due to poor solubility of eprosartan).

Table Epro-020-2. Pharmacokinetic values for total plasma radioactivity following oral and intravenous administration of [^{14}C]eprosartan to healthy volunteers

Parameter	Cmax (ng/ml)	Tmax (h)	AUC(0-t) (ng.h/ml)	AUC(0-∞) (ng equivalents.h/ml)	$T_{1/2}$ (h)
20 mg iv radioactivity					
Subject #001	2297	0.50	2576	2626	2.78
Subject #002	1893	0.52	1985	2016	1.99
Subject #003	ND	ND	ND	ND	ND
Subject #004	2369	0.50	2730	2777	2.83
Mean	2186	0.51	2430	2473	2.53
Median	2297	0.50	2576	2626	2.78
S.D.	257	0.01	393	403	0.47
100 mg oral radioactivity					
Subject #001	625	1.00	1427	1750	4.30
Subject #002	810	1.50	2078	NC	NC
Subject #003	1221	1.50	4095	4942	7.14
Subject #004	480	1.00	1139	1351	2.33
Mean	784	1.25	2185	2681	4.59
Median	718	1.25	1753	1750	4.30
S.D.	321	0.29	1333	1969	2.42

ND: no dose administered; NC: not calculable due to terminal phase not adequately defined

The pharmacokinetics of eprosartan derived from plasma radioactivity following oral and intravenous administration of [^{14}C]eprosartan are given in Table Epro-020-2 (with <2% and <20% extrapolated AUC for intravenous and oral administration, respectively). The LLQs for radiochemical quantification were 50.2-51.0 ng equivalents/ml following intravenous administration, and 10.3 - 10.7 ng equivalents/ml following oral administration. For both routes, the mean Cmax, median Tmax and mean $T_{1/2}$ values by plasma total radioactivity were similar to the values for plasma concentrations of eprosartan. The mean AUC(0-τ) and mean AUC(0-∞) for plasma radioactivity following oral and intravenous administration were <15% higher than those for eprosartan, suggesting that the parent drug accounts for the majority of the plasma radioactivity.

20.4.3 **Metabolite evaluation**

Metabolites were designated by a 2-letter code (representing species and biologic medium) followed by a number representing a distinct chemical structure.

Structural characterization and quantification of human radiometabolites in feces:

Following either single intravenous (20 mg) or oral (100 mg) dose of [^{14}C]eprosartan, radiochromatograms of pooled fecal extracts (0-72 h) showed the presence of one radioactive peak (by both positive ion electrospray mass spectrometry and by HPLC retention time data) which corresponded to the parent eprosartan. For fecal samples, extraction efficiency varied from 93% to 111%, and HPLC column recovery from 96.5% to 109%. Under the conditions of collisional induced dissociation (CID) mass spectrum, the positive ion daughters of m/z 425 were consistent with those of authentic standard eprosartan.

Structural characterization and quantification of human radiometabolites in urine:
Following either single intravenous (20 mg) or oral (100 mg) dose of [^{14}C]eprosartan, radiometabolite profiles of pooled 0-12 h urine showed the presence of one radiometabolite in addition to the parent eprosartan. For profiled urine samples, extraction efficiency varied from 100.3% to 104.2%, and HPLC column recovery from 84.3% to 109.6%. Radiometabolites designated as HU1 and eprosartan corresponded to 17.8%-20.3% and 79.3%-80.4% of the total urinary radioactivity, respectively (constituting 5.8-7.5% and 26.3 to 31.9% of the total administered dose, respectively). The urinary metabolite HU1 and parent eprosartan together corresponded to 98.6% of the total radioactivity excreted in 0-12 h urine, and accounted for 35.6% of the total administered dose.

The molecular weight and the LC retention time of the metabolite HU1 were characterized by LC/MS in neat urine, and the structure was elucidated by subjecting a crude isolate to LC/MS/MS analysis. The metabolite HU1 was characterized as an acyl glucuronide. The metabolite HU1 was further characterized by NMR analysis. Based on the spectroscopic data (MS and NMR) the position of acyl glucuronidation could not be assigned.

Structural characterization and quantification of human radiometabolites in plasma:
Following either single intravenous (20 mg) or oral (100 mg) dose of [^{14}C]eprosartan, eprosartan was the only radiochemical peak observed in the plasma (characterized by both positive ion electrospray mass spectrometry and HPLC retention time data). For plasma samples, extraction efficiency varied from 97.8% to 121%, and HPLC column recovery from 88.8% to 108%. Under the conditions of collisional induced dissociation (CID) mass spectrum, the positive ion daughters of m/z 425 were consistent with those of authentic standard eprosartan.

There was no radiochemical evidence of an acyl glucuronide metabolite in the plasma, and no metabolite was detected in the full scan LC/MS spectrum of the plasma sample. It is possible that the presence of acyl glucuronides as circulating metabolites is not observed due to high concentrations of nonspecific esterases in human plasma.

Thus, acyl glucuronidation was the only metabolic pathway found. The acyl glucuronide was not detectable in the plasma nor feces. This metabolite accounted for approximately 20% of the radioactivity in the urine. The majority of radioactivity (exclusively eprosartan) in the feces after intravenous administration and a small proportion after oral dosing may have been excreted into the intestinal lumen via the bile as eprosartan acyl glucuronide, which was hydrolyzed chemically in the bile or by bacteria in the gastrointestinal tract to the parent compound.

20.5 CONCLUSION

Single oral dose of eprosartan 100 mg and intravenous dose of 20 mg given to healthy volunteers were not associated with serious adverse experiences in this study. One subject experienced a headache of moderate severity.

The major route of excretion was via the feces (61 and 90% of dose being excreted after intravenous and oral administration, respectively). Urinary excretion account for means of 37% and 7% of dose being excreted after iv and oral administration, respectively. A minimum absorption of approximately 15% of the oral dose (range: 10.1% - 20.0%) was calculated from the urinary excretion of radioactivity of 3 subjects who completed both study days.

Following iv and oral administration, peak plasma concentrations (Cmax) of eprosartan and of total radioactivity were seen at 0.5 hour and 1.0-1.5 hour respectively, and declined from peak in a bi-exponential manner. Following intravenous eprosartan 20 mg, the mean volume of distribution at steady-state was 17L (approximating extracellular water), and the mean systemic plasma clearance was 9 L, indicating that the drug had low plasma clearance and was not widely distributed. The average blood clearance of eprosartan as approximately 14.7 L/h. A theoretical absolute bioavailability of approximately 83% was predicted from this clearance data. The average absolute bioavailability of eprosartan following oral administration was 14.7% (range: . The $T_{1/2}$ after oral dose (4.05 h) was relatively longer compared to that after intravenous dose (2.59 h).

For both intravenous and oral routes of administration, the mean Cmax, median Tmax and mean $T_{1/2}$ values by plasma total radioactivity were similar to the values for plasma concentrations of eprosartan. The mean AUC(0-τ) and mean AUC(0-∞) for plasma radioactivity following oral and intravenous administration were <15% higher than those for eprosartan, suggesting that the parent drug accounts for the majority of the plasma radioactivity.

Acyl glucuronidation was the only metabolic pathway found. The acyl glucuronide metabolite was not detectable in the plasma nor in the feces. This metabolite accounted for approximately 20% of the radioactivity in the urine. The majority of radioactivity (exclusively eprosartan) in the feces after iv administration, and a small proportion after oral dosing may have been excreted into the intestinal lumen via the bile as eprosartan acyl glucuronide, which was hydrolyzed chemically in the bile or by bacteria in the gastrointestinal tract to the parent eprosartan compound

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DATE OF CORRESPONDENCE:	*11-Oct-1996*	DATE ASSIGNED:	*12-Jun-1997*
DATE RECEIVED:	*18-Oct-1996*	DATE COMPLETED	*13-Jun-1997*

21.1. STUDY PROTOCOL

21.1.1 Title

A study of the pharmacokinetics of multiple oral doses of SK&F 108566 in subjects with renal insufficiency

21.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages over ACE Inhibitors (absence of side effects such as non-productive cough and angioedema). This study evaluates the pharmacokinetics and plasma protein binding of eprosartan following repeated oral 200 mg dosing every 12 hours to normal subjects and to patients with mild, moderate and severe renal impairment.

21.1.3 Objectives

1. To compare the pharmacokinetics of multiple oral doses of eprosartan in subjects who have normal renal function to subjects who have renal insufficiency;
2. To describe the plasma protein binding of eprosartan in subjects who have normal renal function and in subjects who have renal insufficiency; and
3. To describe the safety profile of single and multiple oral doses of eprosartan in subjects with normal and impaired renal function.

21.1.4 Study design

The study was an open-label, parallel-group, multiple dose study in which subjects took eprosartan (Batch # U94068 and U-93235, 100 mg tablets x2) 200 mg q 12 h with food. Subjects returned on Days 2, 4 and 6 for a pharmacokinetic sample to be drawn prior to the morning dose on that day. On Day 7, plasma samples were obtained for pharmacokinetic analysis prior to and for 24 hours after the dosing. Urine was collected over 0-12 h and 12-24 h on Day 7 for endogenous creatinine clearance. Subjects returned for follow up within 5-7 days for a physical examination and a safety laboratory evaluation.

21.1.5 Protocol Amendments

The original protocol was amended on 17 Oct-1994 to modify the collection time of the protein binding samples.

21.1.6 Population enrolled/analyzed

59 adult male and non-pregnant non-lactating female subjects 18-70 years of age, and weight > 50 kg and within 30% of ideal (based on height and body frame) with negative urine drug screen were enrolled.
Subjects were stratified based on the Cockcroft-Gault calculation of creatinine clearance (CL_{CR}) at baseline as follows:

Group A:	Normal renal function (CL_{CR} > 80 ml/min/1.73m^2)
Group B	Mild renal impairment (CL_{CR} 60 - 80 ml/min/1.73m^2)
Group C:	Moderate renal impairment (CL_{CR} 30 - 59 ml/min/1.73m^2)
Group D:	Severe renal impairment (CL_{CR} 5 - 29 ml/min/1.73m^2) not requiring dialysis

Compliance: The initial and final dose of eprosartan and the morning doses on Days 2, 4, and were administered at the research facility under supervision of study staff. Overall compliance was assessed by counting the eprosartan tablets remaining at each visit.

Pre-study screening: The screening visit (30 days prior to the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood and urine samples were obtained for laboratory tests (hematology, chemistry, liver function, urinalysis and drug screen). Female subjects of child-bearing potential were required to have a negative serum pregnancy test, and were instructed to use an IUD or a barrier method of contraception if engaging in sexual intercourse during the interval between screening and follow-up. Subjects returned the next day with all collected 24-hour urine, and had a blood sample drawn (for calculating creatinine clearance and stratifying them into the study) and a brief physical examination and vital signs recorded.

Subjects abstained from alcohol, tobacco and caffeine within 24 hours prior to and during the study. The following medications were not permitted within 14 days prior to and during the study: systemic or inhaled corticosteroids, cyclosporine, cholestyramine, ursodiol, probenecid, trimethoprim, dehydrocholic acid, warfarin, H_2-receptor antagonists, ß-blockers, or NSAIDs, and vitamins.

21.1.7 **Study procedures**

On Day 1, blood and urine samples were collect for clinical laboratory tests, and blood for protein binding of eprosartan, the first dose of eprosartan was administered. On Days 2, 4 and 6, blood samples were obtained for pharmacokinetic analysis before administering study medication. On Day 7, subjects presented after an 8-hour fast, had a brief physical examination and vital signs performed, blood and urine samples were collected, and subjects given a standard breakfast (cereal, milk, apple juice and muffin), and eprosartan administered with 120 ml tepid water. Urine was collected 0-12 and 12-24 hours.

Subjects remained in the clinical pharmacology unit for 24 hours after dosing. They eat identical meals served in the clinical research unit consisting of the same lunch, the same dinner and the same snack. The evening dose of eprosartan was given 12 hours after the morning dose. No vigorous exercise was permitted. Sitting blood pressure and pulse measurements were obtained prior to dosing and at 1, 2, 4, 8 and 12 hours post-dose and standing blood pressure prior to dosing and at 2 and 4 hours post-dose. Blood samples for pharmacokinetic analysis were prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36 and 48 hours following dosing on Day 7.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

21.1.8 **Pharmacokinetic procedures:**

Blood samples for pharmacokinetics were centrifuged at 4°C and 2300 rpm for 10 minutes, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 3 months. Plasma concentrations of eprosartan were determined by reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) in plasma for eprosartan was 10 ng/ml for a 0.5 ml aliquot.

Urine concentrations of eprosartan were quantitated by LC/MS/MS following addition of acetonitrile to each sample. The LLQ for eprosartan in human urine was 50 ng/ml, based on a 0.1 ml urine aliquot. Plasma protein binding of eprosartan was determined using an ultrafiltration method with labeled [^{3}H]eprosartan analyzed by liquid scintillation counting to assess the percent fraction unbound.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), AUC(0-τ), and the unbound AUC(0-τ) and the unbound Cmax. It was not possible to estimate $T_{1/2}$ and AUC(0-∞). Renal clearance was calculated as amount of eprosartan excreted in urine (Ae) over 0-12 h after dosing on Day 7 divided by AUC(0-12) on Day 7, and the percent of the administered 200 mg dose excreted in urine was calculated as 100 x Ae/200 mg.

21.1.9 **Sample size:**

Based on a within-subject coefficient of variation (CV) for AUC of 32.4% in fed subjects, to detect differences of ≥40% on a 2-tailed test with a type I error rate of 5%, symmetric critical range on the $\log_e$ scale, and 90% power, it was estimated that a sample size of 8 per group would be necessary.

21.1.10 **Evaluation criteria:**

Safety Parameters: Blood pressure, pulse rate, ECG data and clinical laboratory data were reviewed.

The pharmacokinetic parameters were percent fraction unbound (%fu), and AUC(0-12), unbound AUC(0-12), Cmax, unbound Cmax, and renal clearance (CLr) plotted against estimated creatinine clearance (CLCr), and Tmax.

21.1.11 **Investigator , Center and Study Dates:**

Edward A. Kelly, MD, Pharmaceutical Product Development Inc., Clinical Research Unit, Inc., 1400 Perimeter Park Drive, Suite 150, Morrisville, North Carolina. Study Dates: 31-Oct-1994 to 09-Jan-1996.

21.2. **STUDY POPULATION**

21.2.1 **Subject disposition:**

Of 59 subjects screened, 25 did not meet entrance criteria. 34 (13 male and 21 female, 24 white and 10 black) subjects, 22-70 (Mean = 45) years of age, weighing 50 to 101.3 (mean = 75.9) kg, and 157-191 (mean = 172) cm tall, were randomized. All 34 subjects received at least one dose of study medication. 31 subjects completed the study.

21.2.2 **Withdrawals:**
3 subjects were withdrawn due to adverse events (Table Epro-021-1).

Table Epro-021-1. Subjects withdrawn from the study

Subject status	Group A	Group B	Group C	Group D	Total
Completed study	7	8	13	3	31
Withdrawn due to Adverse experience	1 #024	0	2 #022 #023	0	3
Total withdrawn	1	0	2	0	3

21.2.3 **Protocol violations:**
1. Prothrombin time which was required by protocol for exclusion evaluation was not done on any subject at screening
2. Urine aliquots (0-12 h) for determination of eprosartan concentrations were not sent to lab on Subjects #001, #002, #003, #004, #005 and #006.
3. Phosphoric acid added to urine samples (0-12 h) may interfere with the determination of endogenous creatinine clearance.
4. 12-24 hr endogenous creatinine clearance was not determined for most (except 8) subjects.
5. Serum pregnancy tests for female patients were not performed on Subject #002 at screening and on Subject #007 at both screening and follow up; Serum pregnancy test at follow up for Subject #002 was borderline.
6. Concomitant medications were taken by almost every subject (consisting of Beconase inhaler, birth control pills, drugs for control of diabetes, aspirin, NSAIDs, antibiotics, etc.

Laboratory data of 24-hour urine collections at screening suggested incomplete urine collections. An estimated creatinine clearance (CL_{CR}) value was calculated from the Cockcroft-Gault formula (uncorrected for body surface area) using the screening serum creatinine value:- $$\text{Estimated } CL_{CR} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{(72) \times \text{serum creatinine (mg/dl)}}$$ (x 0.85 for women)

This estimated CL_{CR} was used to stratify subjects into the 4 renal groups (normal, mild, moderate and severe).

21.3. **SAFETY RESULTS**

21.3.1 **General considerations:** 96 adverse experiences (AEs) were reported for 29 subjects:

Renal function	Adverse events
Normal	23 AEs occurred in 8 subjects
Mild impairment	20 AEs occurred in 6 subjects,
Moderate impairment	46 AEs occurred in 12 subjects,
Severe impairment	7 AEs occurred in 3 subjects

21.3.2 **Deaths:** There were no deaths during this study.

21.3.3 **Withdrawals due to adverse experiences:**
3 subjects were withdrawn due to adverse events (Table Epro-021-1). Subject #022 with moderate renal impairment developed a urinary tract infection, withdrew and was re-enrolled as Subject #031. Subject #023 with moderate renal impairment discontinued medication due to severe diarrhea and nausea. Subject #024 with normal renal function discontinued medication due to moderate hypesthesia, shortness of breath, upset stomach and tachycardia.

21.3.4 **Serious, Non-fatal Adverse Events:** There were no serious non-fatal adverse experiences.

21.3.5 **Adverse Events:** The adverse events were mild to moderate in nature with only 6 considered severe, including 3 reports of headache, 1 report of left hip and thigh pain, 1 report of diarrhea and 1 report of nausea. AEs in subjects with renal impairment were not more severe compared to AEs in subjects with normal renal function.

21.3.6 **Laboratory findings, ECGs, Vital signs**
There were no changes in pulse rates of potential clinical concern. There were 25 changes in systolic or diastolic blood pressure (22 were decreases and 3 were increases) which were asymptomatic and of no clinical significance.

ECG data at follow up were compared to that at screening. Subject #027 (with severe renal impairment) had at follow up a QTc interval of 505 msec (baseline = 440 msec). There were no other findings in PR, QRS and QTc intervals that were of potential concern.

With regard to laboratory tests, all subjects with normal renal function had values within acceptable limits except the following: Subject #013 had elevated WBC count (14.4 thousand/mcl) on Day 7, Subject #024 had elevated serum glucose (282 mg/dl) on Day 1, Subject #025 had protein and blood present in her urine throughout the study, Subject #016 had elevated ALT/SGPT levels throughout the study (73 , 49 and 63 U/l at screening, predose and Day 7+48 hours) Subject #014 had diabetes mellitus with abnormally high serum and urine glucose with ketones in urine on Days 2, 4 and 7. A number of patients with renal insufficiency had abnormal laboratory values consistent with the coincident renal disease. Some had other laboratory abnormalities that were not clinically significant such as elevated WBC count, hyperglycemia, blood or WBC in urine, elevated serum GGT or AST/SGOT or AST/SGPT, hyponatremia (122 mEq/) or hypernatremia (176 and 161 mEq/l in two patients).

21.4. PHARMACOKINETIC RESULTS

21.4.1 Primary pharmacokinetic endpoints

Preliminary analysis by simple linear regression analysis suggested that the pharmacokinetic parameters for eprosartan were related to estimated creatinine clearance. Thus, data pharmacokinetic were analyzed with patients stratified according to their severity of renal function impairment.

Following administration of eprosartan 200 mg q 12 h, steady-state plasma concentrations of eprosartan appeared to be achieved by Days 6 to 7 in subjects with normal renal function and in those with varying renal impairment except the subjects in the severe renal impairment group (Table Epro-021-2). Plasma concentrations tended to increase with decreasing creatinine clearance. While there were individual variations, the concentrations did not show a trend for increasing or decreasing plasma concentrations with repeated dosing apart from the group with severe renal impairment (n=3) where the plasma concentrations increased markedly on Days 6 and 7. Maximum eprosartan plasma concentrations were observed between 2-6 hours post-dose on Day 7. Concentration-time profiles showed apparent biexponential declines in concentrations following Cmax.

Table Epro-021-2. Plasma concentration-time data for eprosartan in patients with renal impairment

	Day 2	Day 4	Day 6	Day 7	Day 7.5
Normal Renal Function (n=7)					
Mean	72.4	136.2	189.5	201.8	126.4
Median	53.5	112.2	82.5	102.0	52.0
S.D.	57.3	95.0	258.0	241.9	195.4
Mild Renal Impairment (n=8)					
Mean	44.4	55.1	47.4	47.0	43.3
Median	38.8	50.9	49.4	43.4	39.7
S.D.	25.9	25.1	19.0	25.2	20.5
Moderate Renal Impairment (n=11)					
Mean	88.0	127.7	188.8	109.9	73.2
Median	84.0	102.2	70.8	83.6	60.8
S.D.	68.2	88.5	192.1	68.4	38.2
Severe Renal Impairment (n=3)					
Mean	247.8	281.2	345.4	829.1	140.3
Median	178.7	273.8	345.4	829.1	113.0
S.D.	175.7	108.1	306.2	405.2	133.5

The mean (and geometric mean of) AUC(0-12) and Cmax were similar for subjects with normal renal function and those with mild renal impairment but were 25-35% greater for subjects with moderate renal impairment and 51-55% greater in subjects with severe renal impairment (Tables Epro-021-3 and Epro-021-4). The median Tmax values were identical (4.00 hours) for subjects with normal renal function and those with mild and moderate renal impairment (Table Epro-021-3).

Eprosartan was highly bound to plasma protein with mean percent fraction bound ranging from 98.4% in subjects with normal renal function and 98.4% in subjects with mild or moderate renal impairment to 97.3% in subjects with severe renal impairment. Individual %fu were similar for the mild, moderate and normal groups, and was the largest for the severe group (Table Epro-021-3).

The mean unbound Cmax and unbound AUC(0-12) were similar for subjects with normal renal function and those with mild renal impairment, but were 53%-61% greater for subjects with moderate renal impairment, and 185-210%

greater for those with severe renal impairment (Table Epro-021-3), and this finding was also observed with geometric means (Table Epro-021-4) of unbound Cmax and unbound AUC(0-12). The point estimates for the mean difference in %fu between each of the mild, moderate and severe groups and the normal group, and the corresponding 95% intervals (Table Epro-021-5) also showed the same trend in a significant (P=0.0001) manner.

%fu for eprosartan increased with decreasing serum albumin concentrations. While subjects with normal renal function or mild renal impairment had albumin concentrations at the higher end of the range, those with moderate or severe renal impairment tended to have albumin concentrations in the lower end of the range. This may account for the above variations in pharmacokinetic parameters in relation to the severity of renal impairment.

Table Epro-021-3. Mean (SD) pharmacokinetic parameters for eprosartan and unbound eprosartan on Day 7 following repeated oral 200 mg q 12 h dosing to subjects with normal renal function and with mild, moderate and severe renal impairment

Parameter	Normal (n=7)	Mild (n=8)	Moderate (n=12)	Severe (n=3)
Eprosartan				
AUC(0-12) (ng.h/ml)	2961 (1558)	2239 (867)	3711 (1772)	4597 (1423)
Cmax (ng/ml)	590 (318)	536 (217)	795 (388)	888 (202)
Tmax (h)*	4.0 (2.0 - 6.0)	4.0 (3.0 - 4.0)	4.0 (3.0 - 6.0)	3.0 (0.0 - 6.0)
Unbound Eprosartan				
%fu (ex vivo)	1.40 (0.22)	1.60 (0.12)	1.60 (0.19)	2.70 (0.51)
Unbound AUC(0-12) (ng.h/ml)	40.0 (18.5)	35.4 (13.2)	61.2 (35.3)	124 (50)
Unbound Cmax (ng/ml)	8.18 (4.49)	8.41 (3.21)	13.2 (7.7)	23.3 (1.4)

* Tmax data presented as median (range)

Table Epro-021-4. Geometric Mean of Pharmacokinetic Parameters for Eprosartan and Unbound Eprosartan on Day 7 following repeated oral 200 mg q 12 h dosing to subjects with normal renal function and with mild, moderate and severe renal impairment

Parameter	Normal (n=7)	Mild (n=8)	Moderate (n=12)	Severe (n=3)
Eprosartan				
AUC(0-12) (ng.h/ml)	2661	2086	3431	4449
Cmax (ng/ml)	525	494	732	873
Unbound Eprosartan				
Unbound AUC(0-12) (ng.h/ml)	37.0	33.3	54.6	118.5
Unbound Cmax (ng/ml)	7.29	7.88	11.64	23.27
Renal clearance (ml/min)	27.97	45.06	14.20	2.12

Table Epro-021-5. Point Estimates and 95% confidence Intervals for %fu (*ex vivo*)

Comparison	Point Estimate	95% Confidence Interval	P
Mild : Normal	0.19%	(-0.05%, 0.44%)	0.0001
Moderate : Normal	0.20%	(-0.03%, 0.42%)	0.0001
Severe : Normal	1.30%	(0.97%, 1.62%)	0.0001

Data represent the mean difference in %fu between groups

Mean renal clearance (CLr) of eprosartan decreased with decreasing renal function across mild to severe impairment groups (Table Epro-021-6) although the individual CLr values are extremely variable (varying about 25-36 fold in the normal and moderate impairment groups). The mean CLr is 41% lower for subjects with moderate renal impairment and 95% lower for those with severe renal impairment, compared to subjects with normal renal function. On the other hand, the mean eprosartan excretion (Ae) and % dose excreted in urine following dosing on Day 7 was approximately similar in all groups except those with severe renal impairment where the renal excretion of eprosartan was reduced to about 10% of the group with normal renal function (Table Epro-21-6). This reduced renal excretion in subjects with severe renal impairment presumably contributed to the observed increases in total and unbound eprosartan plasma concentrations with declining renal function across groups.

Table Epro-021-6. Mean (SD) CLr, Ae and % dose excreted values for Eprosartan on Day 7 following repeated oral 200 mg q 12 h dosing to subjects with normal renal function and to those with mild, moderate and severe renal impairment

Parameter	Normal (n=7)	Mild (n=8)	Moderate (n=12)	Severe (n=2)
CLr (ml/min)	39.2 (27.1)	45.6 (7.3)	23.1 (17.4)	2.16 (0.57)
Ae (mg)	5.57 (3.12)	6.00 (2.29)	4.37 (2.82)	0.57 (0.10)
% Dose Excreted	2.78 (1.56)	3.00 (1.14)	2.18 (1.41)	0.28 (0.05)

21.5. CONCLUSION

Repeat dose oral administration of eprosartan 200 mg twice daily for 7 days to subjects with normal renal function and those with mild, moderate or severe renal function impairment showed no increase in the frequency or severity of adverse experiences.

Following repeated administration, plasma concentrations of eprosartan appeared to achieve steady state levels by 6 to 7 days except in the case of subjects with severe renal function impairment. Eprosartan was highly bound to plasma protein, with the unbound fraction being very small (1.4-1.6%) in subjects with normal renal function or mild to moderate renal impairment, but was relatively larger (2.7%) in subjects with severe renal impairment. The total and unbound plasma concentrations increased with decreasing renal function, being almost similar in subjects with normal renal function and those with mild renal impairment, but were, respectively, 25-35% and 53-61% greater in subjects with moderate renal impairment, and 51-55% and 185-210%, respectively, greater in subjects with severe renal impairment.

The mean (and geometric mean of) AUC(0-12) and Cmax were similar for subjects with normal renal function and those with mild renal impairment but were 25-35% greater for subjects with moderate renal impairment and 51-55% greater in subjects with severe renal impairment. The median Tmax values were identical (4.00 hours) for subjects with normal renal function and those with mild and moderate renal impairment. Similarly, the mean unbound Cmax and unbound AUC(0-12) were similar for subjects with normal renal function and those with mild renal impairment, but were 53%-61% greater for subjects with moderate renal impairment, and 185-210% greater for those with severe renal impairment, and this finding was also observed with geometric means of unbound Cmax and unbound AUC(0-12). The point estimates for the mean difference in %fu between each of the mild, moderate and severe groups and the normal group, and the corresponding 95% intervals also showed the same trend in a significant (P=0.0001) manner.

The mean renal clearance and excretion of eprosartan in urine decreased as severity of renal function impairment increased, being, respectively 95% and 90% lower in subjects with severe renal impairment.

In two other studies where eprosartan was administered at a dose of 1200 mg/day for a week, subjects had Cmax and AUC(0-τ) that were, respectively, 3 and 4 times greater than that observed in the present study, and tolerated the drug well without any increase in adverse events compared to placebo. It is possible that no dose adjustments may be required when eprosartan is administered to patients with mild, moderate or severe renal impairment. It is desirable, however, to have pharmacokinetic data on a larger number of patients with severe renal impairment than in this study (only 3 subjects), and (as steady state was not evident in patients with severe renal impairment by Day 7) for a longer period of administration.

Protocol 022 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol 1.110)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *13-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *13-Jun-1997*

22.1. STUDY PROTOCOL

22.1.1 Title *A study of the effect of hepatic disease on the pharmacokinetics of a single oral dose of SK&F 108566*

22.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages over ACE Inhibitors (absence of side effects such as non-productive cough and angioedema). This study evaluates the pharmacokinetics and plasma protein binding of eprosartan following a single oral 100 mg dose to normal subjects and to patients with chronic hepatic insufficiency.

22.1.3 Objectives

1. To compare the pharmacokinetics of a single 100 mg oral dose of eprosartan in male subjects who have normal hepatic function and in male subjects who have chronic hepatic insufficiency;
2. To describe the plasma protein binding of eprosartan in male subjects who have normal hepatic function and in male subjects who have chronic hepatic insufficiency; and
3. To describe the safety profile of eprosartan in subjects with normal and impaired hepatic function.

22.1.4 Study design

The study was an open-label, parallel-group, single dose study in which subjects took eprosartan (Batch # U93234) 100 mg with 240 ml tepid water. Plasma samples for pharmacokinetics were obtained prior to and for 24 hours postose. Subjects returned within one week for follow up physical examination and safety laboratory evaluation.

22.1.5 Protocol Amendments

There were no amendments to the protocol.

22.1.6 Population enrolled/analyzed

8 subjects with chronic hepatic insufficiency and 8 (age and weight matched) healthy adult male volunteers 18-65 years of age, and weight > 50 kg and within 20% of ideal (based on height and body frame) with negative urine drug screen were enrolled. The 8 subjects with hepatic insufficiency had documented clinical history of chronic hepatic insufficiency documented by liver biopsy, liver/spleen scan or clinical laboratory tests, with serum albumin 2.6-4.0 g/dl and prothrombin time ≥1.2 times the upper limit of the laboratory reference range.

Compliance: All study drugs were administered by study personnel

Pre-study screening: The screening visit (30 days prior to the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood and urine samples were obtained for laboratory tests (hematology, chemistry, liver function, urinalysis and drug screen).

Subjects abstained from alcohol, tobacco and caffeine within 24 hours prior to and for 96 hours following the dose of study medication. The following medications were not permitted within 14 days prior to and during the study: systemic or inhaled corticosteroids, cyclosporine, cholestyramine, ursodiol, probenecid, trimethoprim, dehydrocholic acid, warfarin, H_2-receptor antagonists, ß-blockers, NSAIDs, aspirin and vitamins.

22.1.7 Study procedures

On the study day, subjects presented after an 8-hour fast, had a brief physical examination and vital signs performed, a 12-lead ECG was obtained, blood and urine samples were collected for clinical laboratory tests, and subjects given a standard breakfast (cereal, milk, apple juice and muffin), and 100 mg eprosartan administered with 240 ml tepid water. Subjects remained in the clinical pharmacology unit for 24 hours after dosing. They eat identical meals served in the clinical research unit consisting of the same lunch, the same dinner and the same snack. No vigorous exercise was permitted. Subjects were given 240 ml water at 2 and 4 hours after dosing, and then allowed water, fruit juices (except grapefruit) or soft drinks without caffeine at will 5 hours after dosing. Sitting blood pressure and pulse measurements were obtained prior to dosing and at 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours post-dose. All urine samples were collected and pooled for 24 hours after dosing. 24 hour total urinary creatinine was determined to measure endogenous creatinine clearance. A brief physical examination and 12-lead ECG were done, and blood

and urine samples taken at 24 hours after which the subject was permitted to leave the research facility. Subjects returned within 5 to 10 days for follow up physical examination, 12-lead ECG and safety laboratory tests.

Blood samples for pharmacokinetic analysis were prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours following dosing.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

22.1.8 **Pharmacokinetic procedures**:
Blood samples for pharmacokinetics were centrifuged at 4°C and 2000 g for 10 minutes, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 27 weeks. Plasma concentrations of eprosartan were determined by reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) in plasma for eprosartan was 10 ng/ml for a 0.5 ml aliquot.

Plasma protein binding of eprosartan was determined using an ultrafiltration method with labeled [^{3}H]eprosartan analyzed by liquid scintillation counting to assess the percent fraction unbound.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ_1), AUC(0-τ), and the unbound AUC(0-τ) and the unbound Cmax. It was not possible to estimate $T_{1/2}$, and AUC(0-∞).

22.1.9 **Sample size:**
Based on a within-subject coefficient of variation (CV) for AUC of 32.4% in fed subjects, to establish equivalence in AUC between the two groups, with a type I error rate of 5% and symmetric 50% range on the $\log_e$ scale, and 90% power on a 2-tailed test , it was estimated that a sample size of 8 per group would be necessary.

22.1.10 **Evaluation criteria:**
Safety Parameters: Blood pressure, pulse rate, ECG data and clinical laboratory data were reviewed.

The pharmacokinetic parameters:
The primary endpoint was AUC. The secondary parameters were Cmax, Tmax and the plasma protein binding.

22.1.11 **Investigator , Center and Study Dates:**
Malcolm Robinson, MD, Okalahoma Foundation for Digestive Research, 711 Stanton L. Young Blvd., Oklahoma City, Okalahoma, USA. Study Dates: 18-Jul-1994 to 09-Jan-1995.

22.2 STUDY POPULATION

22.2.1 **Subject disposition:**
16 Caucasian male subjects (8 normal and 8 with chronic hepatic insufficiency) were enrolled. The 8 normal subjects were 26-61 (Mean = 47) years old, weighed 70.3 to 100.7 (mean = 84.1) kg, and 169-193 (mean = 182) cm tall, and had estimated creatinine clearance of 74-109 (mean = 87) ml/min/1.73M^2. The 8 subjects with chronic hepatic insufficiency were 37-63 (Mean = 49) years old, weighed 73.9 to 119.8 (mean = 93.8) kg, and 173-193 (mean = 181) cm tall and had estimated creatinine clearance of 72-196 (mean = 111) ml/min/1.73M^2; one subject had advanced, 5 had moderate and 2 had minimal hepatic insufficiency by Child's Classification.

22.2.2 **Withdrawals:**
There were no subject discontinuations due to adverse experiences.

22.2.3 **Protocol violations:**
During the study, concomitant medications were used by all subjects with hepatic insufficiency, including 2 subjects who received prohibited medications (Subject #004 received indomethacin, and Subject #006 received atenolol and prednisone). The medications in both subjects were withheld from midnight on the night preceding the study drug administration until 5 hours after dosing.

Laboratory data of 24-hour urine collections at screening suggested incomplete urine collections. An estimated creatinine clearance (CL_{CR}) value was calculated from the Cockcroft-Gault formula (uncorrected for body surface area) using the screening serum creatinine value:- Estimated CL_{CR} = $\frac{(140 - age) \times weight\ (kg)}{(72) \times serum\ creatinine\ (mg/dl)}$ (x 0.85 for women)

This estimated CL_{CR} was used to compare the two groups of patients (section 2.1 above).

22.3 SAFETY RESULTS

22.3.1 **General considerations:** 6 of 8 subjects in the hepatic insufficiency group reported 15 AEs, and 3 of 8 normal subjects reported 4 AEs.

22.3.2 **Deaths:** There were no deaths during this study.

22.3.3 **Withdrawals due to adverse experiences:**
There were no subject discontinuations due to adverse experiences.

22.3.4 **Serious, Non-fatal Adverse Events:** There were no serious non-fatal adverse experiences.

22.3.5 **Adverse Events:** The adverse events were mild to moderate in nature, except in one subject (#005) in the hepatic group who reported nausea 22 hours prior to dosing reported as severe, but this subject tolerated the study medication without incident. The most frequent AE was headache reported by 3 subjects with hepatic insufficiency and 3 normal subjects. Other AEs reported included dizziness (1), pain in right shoulder, pain in left side and heels, weakness, fatigue, loss of appetite, abdominal pain, and dry mouth and eyes.

22.3.6 **Laboratory findings, ECGs, Vital signs**
There were no changes in pulse rates of potential clinical concern. Three subjects in hepatic insufficiency group had decreased blood pressure (1 systolic, 2 diastolic). Among normal subjects, 2 had decreased diastolic blood pressure and 1 had increased diastolic blood pressure. All events were asymptomatic and of no clinical significance.

There were no ECG changes from baseline which were of potential clinical concern.

With regard to laboratory tests, all healthy subjects with normal hepatic function had values within acceptable limits. A number of patients with hepatic insufficiency had abnormal laboratory values consistent with the coincident hepatic disease.

22.4 PHARMACOKINETIC RESULTS

22.4.1 **Primary pharmacokinetic endpoints**
Maximum plasma concentrations of eprosartan after single oral 100 mg dose were observed at median times of 4 and 6 hours, respectively, following dosing for the healthy and hepatic insufficiency groups (Figure Epro-022-1). Following Cmax, plasma eprosartan concentrations generally declined in a monoexponential manner and were no longer quantifiable after approximately 12 hours in both healthy subjects and 4 subjects with hepatic insufficiency. (However, 4 subjects with hepatic insufficiency had quantifiable eprosartan levels at 24 hours.)

The mean percent bound eprosartan in plasma was 98.07% for the hepatic group (pre-dose albumin range: 3.2-3.7 g/dl) and 98.23% for the healthy group (pre-dose albumin range: 3.9-4.2 g/dl). The %fu (percent fraction unbound) in 0 hour samples by the *in vitro* method was similar for both groups (1.46% and 1.63% for hepatic insufficiency and healthy groups, respectively). The *ex vivo* method also showed that the average %fu in the hepatic insufficiency group was similar to that in the healthy group (Table Epro-022-1). There was no relationship between serum albumin concentrations and mean %fu (which is different from that reported in Protocol 021 with renal insufficiency subjects).

The mean (and geometric mean of) AUC(0-τ) for total and unbound eprosartan were higher for the hepatic insufficiency group compared to healthy subjects (Tables Epro-0.22-2 and Epro-022-3). However, there was no difference between the mean (and geometric mean of) Cmax for total and unbound eprosartan for the hepatic insufficiency group compared to healthy subjects (Tables Epro-0.22-2 and Epro-022-3) with point estimate approaching 1 (Table Epro-022-4). It was possible that the high AUC(0-τ) in subjects with hepatic insufficiency

was contributed mainly by Subject #004 who had AUC(0-τ) that was about 3-fold greater than the mean AUC(0-τ) for this group without him. If data from Subject #004 was excluded, the point estimate for AUC(0-τ) became 1.23 (Confidence intervals = 0.86, 1.75).

Figure Epro-022-1. Plasma concentrations of eprosartan following single oral 100 mg dose administration to subjects with hepatic impairment and healthy subjects

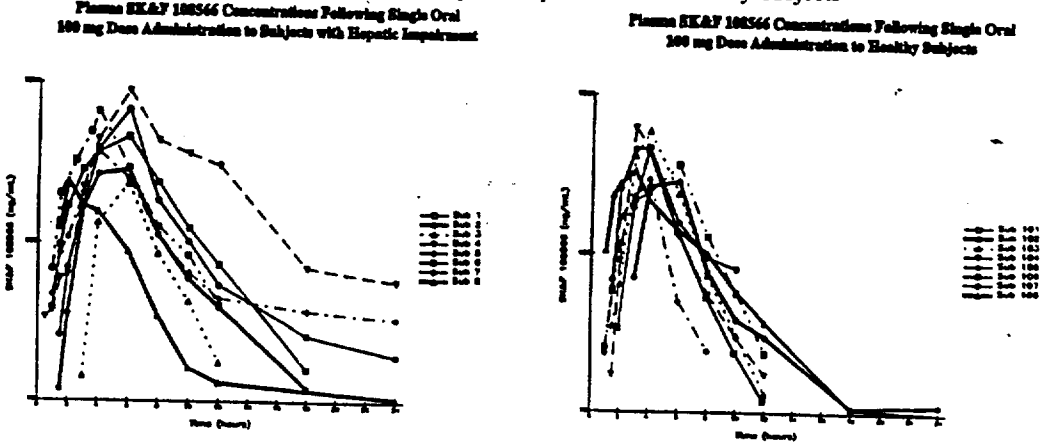

Table Epro-022-1. Percent fraction unbound (%fu) for eprosartan at 0 (pre-dose), 1, 6 and 12 hours following single oral 100 mg dose to subjects with hepatic insufficiency and healthy subjects. Values are mean (SD)

Time (hr)	Hepatic (n=8)	Healthy (n=8)
0 *	1.46 (0.23)	1.63 (0.37)
1	1.86 (0.34)	1.84 (0.37)
6	1.87 (0.46)	1.70 (0.19)
12	2.05 (0.40)	1.78 (0.33)
Mean ex vivo data	1.93 (0.33)	1.77 (0.21)

* %fu determined at 0 hours using in vitro data

Table Epro-022-2. Mean (SD) pharmacokinetic parameters for eprosartan and unbound eprosartan following single oral 100 mg dosing to subjects with normal hepatic function and with hepatic insufficiency

Parameter	Hepatic (n=8)	Healthy (n=8)
Eprosartan		
AUC(0-τ) (ng.h/ml)	2610 (1624)	1616 (379)
Cmax (ng/ml)	486 (243)	428 (128)
Tmax (h)*	6.00 (2.00 - 6.00)	4.00 (3.00 - 6.00)
$T_{1/2},\lambda_1$ (h)	2.45 (0.66)	2.08 (0.92)
Unbound Eprosartan		
Unbound AUC(0-τ) (ng.h/ml)	52.6 (43.2)	28.5 (7.2)
Unbound Cmax (ng/ml)	9.51 (5.93)	7.62 (4.51)

* Tmax data presented as median (range)

Table Epro-022-3. Geometric Mean of Pharmacokinetic Parameters for Eprosartan and Unbound Eprosartan following single oral 100 mg dose to subjects with normal hepatic function and with hepatic insufficiency

Parameter	Hepatic (n=8)	Healthy (n=8)
Eprosartan		
AUC(0-τ) (ng.h/ml)	2225	1570
Cmax (ng/ml)	436	413
Unbound Eprosartan		
Unbound AUC(0-τ) (ng.h/ml)	42.3	27.7
Unbound Cmax (ng/ml)	8.28	7.26

Although the Tmax were slightly prolonged in subjects with hepatic insufficiency (Table Epro-022-2), the point estimate for the median difference in Tmax between the hepatic insufficiency group and healthy group was 1.00 hour (90% confidence interval = 0.00 h, 2.00 h) which was not likely to be important pharmacokinetically. The estimated $T_{1/2},\lambda_1$ were similar for both the hepatic insufficiency and healthy groups (Table Epro-022-2).

Table Epro-022-4. Point Estimates and 95% confidence Intervals for hepatic:healthy subjects

Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ) (ng.h/ml)	1.42	(0.94, 2.14)
Cmax (ng/ml)	1.06	(0.73, 1.52)
Unbound AUC(0-τ) (ng.h/ml)	1.53	(0.98, 2.39)
Unbound Cmax (ng/ml)	1.14	(0.77, 1.69)

Data represent the ratio of geometric means for the hepatic group relative to the healthy group

5. CONCLUSION

Single oral dose of eprosartan 100 mg to subjects with hepatic insufficiency and healthy subjects showed no increase in the frequency or severity of adverse experiences.

Eprosartan was highly bound to plasma protein, with the unbound fraction being very small (1.93%) in subjects with hepatic insufficiency and 1.77% in healthy subjects. The percent fraction unbound of eprosartan were similar over the interval of 12 hours post-dose. The means of AUC(0-τ) for total and unbound eprosartan were higher for the hepatic insufficiency group than healthy subjects whereas the mean Cmax for total and unbound eprosartan were not different between subjects with hepatic insufficiency and healthy subjects. This apparent lack of change in Cmax despite an increase in AUC in subjects with hepatic insufficiency suggests a decreased rate of absorption, increased volume of distribution and/or decreased clearance rather than altered bioavailability. The $T_{1/2},\lambda_1$ and Tmax were comparable between the two groups suggesting no marked change in clearance with hepatic insufficiency.

In two other studies where eprosartan was administered at a dose of 1200 mg/day for a week, subjects had Cmax and AUC(0-τ) that were, respectively, 3 and 4 times greater than that observed in the present study, and tolerated the drug well without any increase in adverse events compared to placebo. It is possible that no dose adjustments may be required when eprosartan is administered to patients with hepatic insufficiency.

APPEARS THIS WAY
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Protocol 023 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.111)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *17-Jun-1997*
DATE COMPLETED *18-Jun-1997*

23.1 STUDY PROTOCOL

23.1.1 Title

Investigation of the effect of repeated oral doses of SK&F 108566 on the single dose pharmacokinetics of orally administered digoxin in healthy male volunteers

23.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. Since hypertension and cardiac disease often occur together in the same patient population, it is likely that eprosartan will be prescribed together with digoxin. A single dose of digoxin added to steady state concentrations of potentially interacting medication has been an acceptable design to screen for a potential interaction. This study determines the pharmacokinetics of a single oral dose of digoxin when administered alone and when administered during repeated oral dosing with eprosartan.

23.1.3 Objectives

1. To compare the pharmacokinetics of single oral doses of digoxin (0.6 mg) given alone or when co-administered with orally administered eprosartan which has been dosed to steady-state conditions, and
2. To evaluate the safety and tolerability of concomitant oral administration of digoxin and eprosartan.

23.1.4 Study design

The study was a randomized, open-label, two-period, period balanced crossover study of two groups (A and B) separated by a washout period of at least 14 days, in which each of the young healthy male volunteers received the study medication given within 20 minutes after finishing a light meal (one bowl of cereal with milk, one muffin and 240 ml apple juice) as follows:

1. Regimen A: A single 0.6 mg oral dose of digoxin (Lanoxicaps® (Lot# X-94064) 0.2 mg capsules x 3)
2. Regimen B: SK&F 108566 200 mg (Lot #-93235, 100 mg tablets x 2) orally q 12 h for 7 days with a single 0.6 mg oral dose of digoxin (Lanoxicaps® (Lot# X-94064) 0.2 mg capsules x 3) given on Day 4.

23.1.5 Protocol Amendments

There were no amendments to the protocol.

23.1.6 Population enrolled/analyzed

12 healthy, non-smoking, adult male volunteers 18-45 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All study medications were administered under the supervision of the investigator or his nominee.

Pre-study screening: The screening visit (15 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, Hepatitis B and C tests, HIV test, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 2 weeks prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period.

23.1.7 Study procedures

After an 8-hour overnight fast, subjects attended FOCUS Clinical Drug Development, GmbH.

Days 1 to 3: Subjects assigned to Regimen A were not required to show up. Subjects assigned to Regimen B had an alcohol blow test performed prior to the morning dose, and baseline symptoms and signs recorded. A 12-lead ECG recording was made. Blood pressure and pulse rate were recorded. Blood and urine samples for clinical safety laboratory tests and urine drug screen were taken. Study drug (eprosartan) was administered q 12 h in the morning and evening within 20 minutes after finishing a light meal. Blood pressure and pulse were measured prior to and 2 hours after each dose. Volunteers had to stay for at least 3 hours after dosing, but are free to leave thereafter until the next scheduled dose.

Day 4: An alcohol blow test was performed, and baseline adverse experiences, blood pressure, pulse rate and 12-lead ECG were recorded, and blood and urine samples taken (for digoxin assay) before dosing. Subjects assigned to Regimen A received 0.6 mg digoxin with 150 ml still mineral water within 20 minutes after finishing a light meal in the morning. Subjects assigned to Regimen B received 0.6 mg digoxin together with 200 mg eprosartan administered with 150 ml still mineral water within 20 minutes after finishing a light meal in the morning. They again received eprosartan (200 mg) with 150 ml still mineral water within 20 minutes after finishing a light meal 12 hours after the morning dose.

Blood pressure and pulse were measured at 0.5, 1, 2, 4 and 8 hours after the digoxin dose. ECG was recorded at 2, 4 and 8 hour after the digoxin dose. Adverse experiences were recorded at 2 and 12 h after the digoxin dose. A lunch was served at 4 hours, a light snack at 8 hours and a light supper about 11.5 hours after digoxin dosing. Volunteers stayed in the unit overnight until the 24 hour digoxin blood sample was taken.

Days 5 to 7: An alcohol blow test was performed, and adverse experiences were recorded. Blood pressure and pulse rate were measured at +24 and +96 hours after digoxin dose for both groups. Subjects assigned to Regimen B had, in addition, eprosartan administered with a 12 hour interval 20 minutes after finishing a light meal. Volunteers had to stay for at least 3 hours after dosing, but are free to leave thereafter until the next scheduled dose.

Post-treatment phase: Subjects returned 7-10 days following the last pharmacokinetic sampling in the second study period, at which time safety laboratory tests, vital signs and an ECG were done.

Blood sample (5 ml) collections for pharmacokinetics were done prior to dose administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 84 and 96 hours after oral administration of digoxin. After dosing, all urine was collected over 0-12, 12-24, 24-36, 36-48, 48-60, 60-72, 72-84, and 84-96 hour intervals.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

23.1.8 **Pharmacokinetic procedures:**

Blood samples collected in heparinized tubesand chilled on ice were centrifuged, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed for digoxin within 2.5 months. Plasma concentrations of digoxin were determined by radioimmunoassay. The lower limit of quantification (LLQ) for this method was 0.1 ng/ml based on 50 µl aliquots. The volumes of 12-hour collections of urine were recorded, and 10 ml aliquots stored at -20°C. Since no interaction was deduced from plasma data, urine samples were not analyzed for digoxin.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), $T_{1/2}$, AUC(0-τ), AUC(0-∞). The percent extrapolated was determined by the ratio of [AUC(0-∞) - AUC(0-τ)] to [AUC(0-∞) x 100].

23.1.9 **Endpoints:**

AUC(0-τ) for digoxin was the primary endpoint. The secondary endpoints were Cmax, Tmax, $T_{1/2}$, and AUC(0-∞).

23.1.10 **Sample size and Statistics:**

Based on a within-subject coefficient of variation of 11.4% for AUC(0-τ), a sample size of 12 per regimen was estimated to provide 90% power to demonstrate equivalence for AUC. Lack of interaction of eprosartan on the pharmacokinetics of digoxin was assessed through an equivalence-type approach. Eprosartan was considered by the sponsor to have no effect on the pharmacokinetics of digoxin if the 90% confidence intervals for the ratio of AUC values was completely contained within the range (0.70, 1.43).

23.1.11 **Investigator , Center and Study Dates:**

A. Port, MD. FOCUS Clinical Drug Development, GmbH. Dates: 15-Jun-1994 to 04-Aug-1994.

23.2. **STUDY POPULATION**

23.2.1 **Subject disposition:**

12 healthy male volunteers 24-39 (mean = 31) years of age, weighing 60 to 102 (mean = 78.8) kg, and 170-197 (mean = 182) cm tall, were enrolled and randomized. All received both treatments.

23.2.2 **Withdrawals:**
There were no withdrawals in this study.

23.2.3 **Protocol violations:**
Subjects 1, and 3-12 were reported to have ECG recorded at follow-up visit, but raw data (ECGs) could not be found, and thus were considered not performed.

23.3 SAFETY RESULTS

23.3.1 **General considerations:** No symptoms and signs were present prior to the initial dose of study medication. A total of 6 adverse events were reported for 4 subjects following treatment with study medication.

23.3.2 **Deaths:** There were no deaths during this study.

23.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

23.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

23.3.5 **Adverse Events:** All AEs were mild to moderate in nature.

1. Regimen A (digoxin alone) (2 AEs in 2 subjects): Subject #002 reported a stiff neck and #012 had hyperbilirubinemia.
2. Regimen B (eprosartan plus digoxin) (4 AEs in 2 subjects): Subject #002 reported headache 3 times, #006 reported fatigue and eye pain (pressure on eyes), and #008 reported pain in the stomach

23.3.6 **Laboratory findings, ECGs, Vital signs**
One subject (#002) on Regimen A (digoxin alone) had fall in systolic blood pressure. During Regimen B (digoxin plus eprosartan), 8 subjects had 11 episodes of changes in blood pressure. Subjects #001, #004, #007, #008, #009 had fall in diastolic blood pressure, subjects #004, #007, #009 and #010 had fall in systolic blood pressure, and subjects # 003 and #005 had rise in systolic blood pressure. These changes were isolated and were not associated with symptoms.

There were no clinically significant findings in ECG intervals or morphology apart from an AV block grade I that occurred 2 hours after digoxin in subject #009. ECGs were not performed at follow-up (except subject #002).

There were no changes in laboratory parameters outside of the range for potential clinical concern with the exception of the following 2 subjects: (i) Subject #012, while on Regimen A, had hyperbilirubinemia (1.73 mg/dl at follow-up vs baseline value of 0/87 mg/dl), and (ii) Subject #002 had hyperglycemia (149.4 mg/dl at pre-dose on Day 5 vs a baseline value of 88.2 mg/dl).

23.4. PHARMACOKINETIC RESULTS

Following a single oral dose of digoxin either alone or with steady state eprosartan (Figure Epro-023-1) the mean plasma concentration-time profiles of digoxin were similar. Peak plasma concentrations of digoxin were reached at 1.5 hours post-dose, and the plasma concentrations of digoxin declined in an apparent bi-exponential manner.

In Table Epro-023-1, AUC(0-τ), Cmax and Tmax were similar for Regimen B (eprosartan and digoxin) and Regimen A (digoxin alone). Since no interaction was deduced from the plasma data, urine samples were not analyzed for digoxin, and no calculations for renal clearance of digoxin were made.

AUC(0-∞) values generally had extrapolated areas of >20%, but all extrapolated areas were <40% (except subject #007 which was 40.9%). The time period over which $T_{1/2}$ was calculated was < 3 half-lives. Thus, both AUC(0-∞) and $T_{1/2}$ may not be accurate, and AUC(0-∞) was used only as a secondary endpoint.

Using an equivalence-type approach, eprosartan would be considered to have no effect on the pharmacokinetics of digoxin if the 90% confidence interval for the ratio of AUC was completely contained within the range [0.70, 1.43]. In Table Epro-023-2, the 90% confidence intervals for the ratios of the geometric means for digoxin with eprosartan relative to digoxin alone for AUC(0-τ), AUC(0-∞), and Cmax were completely contained with the above range, and AUC(0-τ) and Cmax also met the more stringent 90% confidence interval criterion of [0.80, 1.25], suggesting that eprosartan can be considered to have had no effect on the pharmacokinetics of digoxin.

Figure Epro-023-1. Mean plasma concentration-time profiles of digoxin

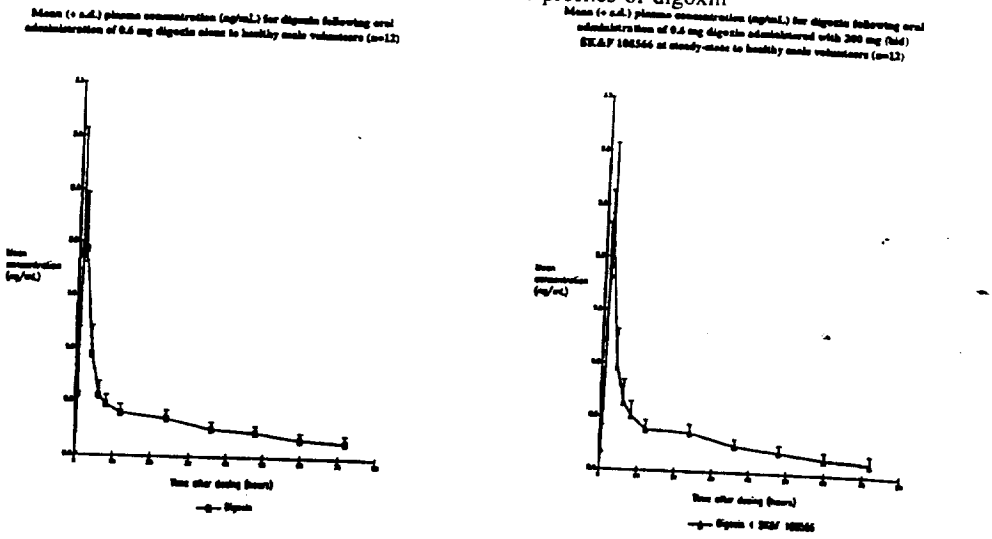

Table Epro-023-1. Pharmacokinetic values for digoxin following single oral dose without and with steady-state eprosartan

End Point	Digoxin	Eprosartan+Digoxin
AUC(0-τ) (ng.h/ml)		
Geometric Mean	23.7	23.5
Mean	24.3	24.2
Median	25.4	25.5
S.D.	5.9	5.9
AUC(0-∞) (ng.h/ml)		
Geometric Mean	31.6	32.3
Mean	32.6	33.0
Median	33.0	33.7
S.D.	9.0	7.5
Cmax (ng/ml)		
Geometric Mean	2.44	2.45
Mean	2.53	2.57
Median	2.39	2.65
S.D.	0.76	0.81
Tmax (h)		
Mean	1.5	1.7
Median	1.5	1.5
S.D.	0.5	0.8
T1/2 (h)		
Mean	39.8	46.9
Median	40.8	44.6
S.D.	7.2	15.7

Table Epro-023-2. Point Estimates and 95% confidence intervals of comparisons of digoxin and digoxin plus steady-state eprosartan

Parameter	Comparison	Point Estimate	95% Confidence Interval
AUC(0-τ)†	B:A	0.99	[0.90, 1.09]
Cmax†	B:A	1.00	[0.86, 1.17]
AUC(0-∞) †	B:A	1.01	[0.81, 1.26]
Tmax (h)§	B-A	0.25	[-0.25, 0.50]
T1/2 (h)*	B-A	5.95	[-4.38, 16.28]

† Data presented as the ratio of the geometric means for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)
§ Data presented as the estimated median difference in Tmax for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)
* Data presented as the mean difference in $T_{1/2}$ for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)

Tmax was similar for both regimens (Table Epro-023-1) with a median difference of only 0.25 h (Table Epro-023-2). $T_{1/2}$ was on the average 5.95 hours longer for digoxin with steady-state eprosartan than for digoxin alone (Table Epro-023-2), but as mentioned above, these $T_{1/2}$ values were determined over a time period of < 3 half-lives and were, therefore, not well defined.

23.5 CONCLUSION

Single oral dose administration of digoxin 0.6 mg to healthy male volunteers with or without steady state eprosartan did not show any significant differences in adverse experiences. All adverse experiences were mild to moderate in nature and all resolved during the study. There were no abnormal laboratory values of potential safety concern.

The mean plasma concentration-time profiles of digoxin were similar, and peak plasma concentrations of digoxin were reached at 1.5 hours following a single oral dose of digoxin alone or with steady state eprosartan. AUC(0-τ), Cmax and Tmax were similar for eprosartan and digoxin compared to digoxin alone.

Using an equivalence-type approach, the 90% confidence intervals for the ratios of the geometric means for digoxin with eprosartan relative to digoxin alone for AUC(0-τ), AUC(0-∞), and Cmax were completely contained within the range [0.70, 1.43], and AUC(0-τ) and Cmax also met the more stringent 90% confidence interval criterion of [0.80, 1.25], suggesting that eprosartan can be considered to have had no effect on the pharmacokinetics of digoxin. $T_{1/2}$ was on the average 5.95 hours longer for digoxin with steady-state eprosartan than for digoxin alone, but these $T_{1/2}$ values were determined over a time period of < 3 half-lives and were, therefore, not well-defined.