CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20850

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 17 1998

NDA 20-850 (BB)
MICARDIS™ (Telmisartan)
Tablets (40 and 80 mg)

SUBMISSION DATES: SEPT. 11, 1998

BOEHRINGER INGELHEIM

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA Amendment

BACKGROUND:

Telmisartan is an angiotensin II receptor antagonist currently under review for the treatment of hypertension. The sponsor provided an acceptable *in vitro* dissolution method but based on the dissolution data submitted to the NDA, it was recommended that the dissolution specification should be changed from Q[ ]% in[ ]minutes to Q[ ]% in[ ]minutes. The sponsor has provided additional dissolution data and requested that the specification should be Q[ ]% in[ ]minutes.

COMMENTS

The sponsor has provided additional dissolution data for 15 full-scale production batches which indicate that 2 of the batches failed at). Additionally, dissolution data on the another batch (different shape but same quantitative composition) with low dissolution values (Lot No. 40824) used in pivotal clinical trials (74.6% dissolved in[ ]minutes) indicate that the bioavailability is similar to that from batches with high dissolution values (mean posthoc population Cmax for 160 mg dose is 1840 ng/ml compared to 2052 ng/ml obtained from Study 502.114). The data from the new 15 full-scale production batches indicate that all the tablet batches should pass a specification of Q[ ]% in[ ]minutes.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I has reviewed the sponsor's NDA amendment and recommends the dissolution specification for telmisartan tablets should be Q[ ]% in[ ] minutes. Please, forward this recommendation to the sponsor.

/S/ 9/17/98

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. El-Tahtawy, Ph.D. 9/17/98

cc: NDA 20-850, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy).

AUG - 7 1998

NDA 20-850
Priority: 1 S
MICARDIS™ (Telmisartan)
Tablets (40 and 80 mg)

IND

BOEHRINGER INGELHEIM

SUBMISSION DATES: SEPT. 26, 1997
OCT. 21, 1997
OCT. 30, 1997
JUNE 4, 1998
JUNE 8, 1998
IND- JULY 14, 1997

REVIEWER: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: Original NME

SYNOPSIS:

The sponsor has studied the pharmacokinetics (single and multiple dose), metabolism and excretion of telmisartan, a new angiotensin II receptor antagonist, and has investigated the dose proportionality of telmisartan to include the dosing range covered in the proposed package insert. Absolute bioavailability is about 42% at 40 mg dose and 57% at 160 mg dose and telmisartan plasma concentrations increase with dose in a more than proportional manner. Telmisartan does not undergo oxidative metabolism by P450 enzymes and glucuronidation is the only metabolic pathway. Telmisartan is highly protein bound (>99.5%) and the plasma protein binding remains unchanged over the therapeutic plasma concentration range. Telmisartan exhibits gender effects (females tend to have higher plasma levels and lower oral clearance than males). Telmisartan plasma levels are increased in patients with hepatic impairment and decreased in patents with renal impairment. The concentration-effect relationship showed that three dose levels (40, 80 and 120 mg) were near the plateau region of the dose-response curve. Drug interaction between telmisartan and digoxin, paracetamol (acetaminophen), hydrochlorothiazide, ibuprophen, amlodipine, glibenclamide and warfarin were studied. Co-administration of telmisartan with high fat meal results in dose-dependent decrease in plasma concentrations. The clinical trial formulation is bioequivalent to the to-be-marketed formulation. An *in vitro* dissolution method has been provided but the recommended dissolution specification has been changed from Q % at minutes to Q % at

RECOMMENDATION:

The Division of Pharmaceutical Evaluation I has reviewed the sponsor's NDA 20-850 recommends approval provided that the comments below (page xxv) are satisfactorily addressed by the sponsor. Please forward the appropriate comments on page xxv to the sponsor.

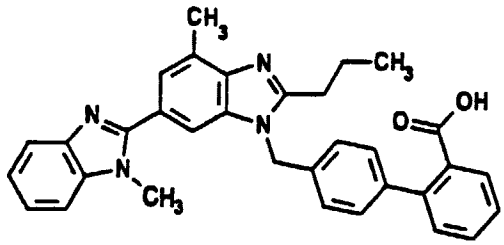
TABLE OF CONTENTS:

BACKGROUND: Telmisartan is a synthetic compound with structure shown in Figure 1. Telmisartan blocks all physiologically relevant actions of angiotensin II by binding to the AT_1 receptor. Telmisartan is a low-solubility, high-permeability drug (Case 2 of the Biopharmaceutics Classification System). It is proposed to be used for the treatment of hypertension, and headache, pain, fatigue, dizziness and peripheral edema are some of adverse effects that have been reported. The sponsor has submitted 26 pharmacokinetics / pharmacodynamics studies and 2 *in vitro* studies in support of the NDA and all the studies were reviewed. The proposed dosing is 80 mg once daily.

FIGURE 1a. Physical and Chemical Characteristics of Telmisartan

Physical appearance: White to off-white/yellowish, odorless crystalline powder

Structural formula:



4'-(2-Propyl-4-methyl-6-(methylbenzimidazolyl-2-yl)benzimidazol-1-ylmethyl)biphenyl-2-carboxylic acid

Empirical formula: $C_{33}H_{30}N_4O_2$

Molecular weight: 514.63

Solubility1
Organic solvents: Soluble in chloroform, slightly soluble in methanol, very slightly soluble in 96% ethanol

Aqueous solvents: Strongly pH dependent, practically insoluble in water, sparingly soluble in strong acid (except insoluble in HCl), practically insoluble at pH 3 to 9, soluble in strong base

1 According to USP definition

Polymorphism: Exhibits two different polymorphic modifications, Form A (thermodynamically more stable) and Form B, and a third pseudopolymorphic form containing formic acid and water

Melting point: 269 ± 1°C (polymorphic Form A), 183 ± 1°C (polymorphic Form B)

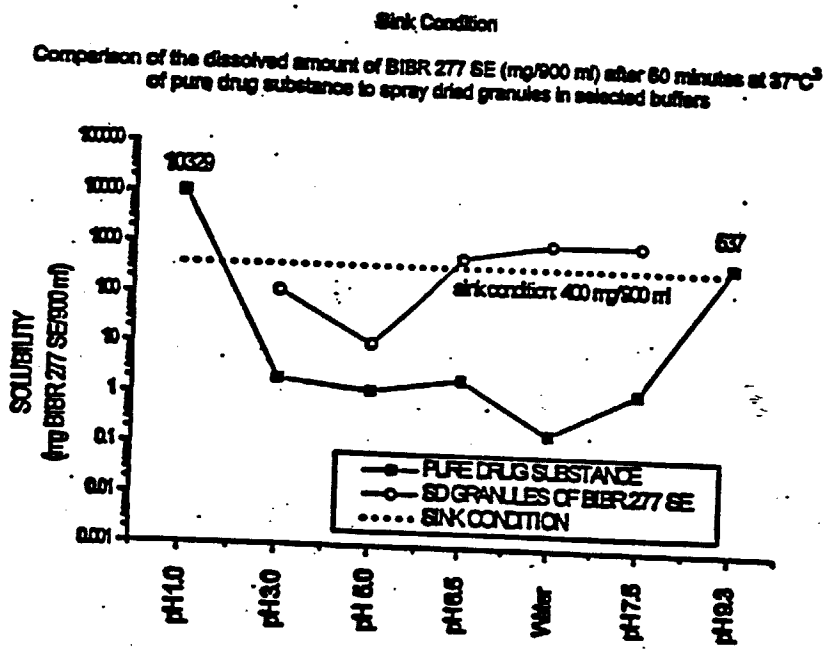
Dissociation constant: $pK_{a1} = 3.5 \pm 0.1$, $pK_{a2} = 4.1 \pm 0.1$, $pK_{a3} = 6.0 \pm 0.1$

Apparent partition coefficient: $\log P_{app} = 3.2$

Hygroscopicity: Not hygroscopic

Isomerism: Contains no chiral centers and does not exist in other isomeric forms.

Figure 1b. SOLUBILITY OF TELMISARTAN



SUMMARY OF BIOAVAILABILITY / PHARMACOKINETICS / PHARMACODYNAMICS

1. BIOAVAILABILITY/BIOEQUIVALENCE:

A. Absolute Bioavailability: With reference to a 40 mg IV dose (infusion), the absolute bioavailabilty of telmisartan given as 40 mg non-market (clinically tested) tablet averaged 42.4% (95% CI - 31.6-59.9) while that of the solution (40 mg) is 47.3% (95% CI - 35.5-63.4; Study 502.106). With reference to a 160 mg IV dose (infusion), the absolute bioavailabilty of telmisartan given as 160 mg non-market (clinically tested) tablet averaged 57.4% (95% CI - 50.6-65.0) while that of the solution (160 mg) is 57.5% (95% CI - 50.7-65.2; Study 502.112). The absolute bioavailability of approximately 57 % for the 160 mg solution and tablets is somewhat higher than the 47 % and 42 % absolute bioavailability of the 40 mg solution and tablet respectively, observed in Study 502.106. This may be explained by the short time saturation processes probably being responsible for the nonproportional increase in plasma concentrations. With high dose of telmisartan, saturation of presystemic elimination processes, i. e. conjugation to glucuronic acid in the gut wall and/or liver, probably results in a greater fraction of drug reaching the blood circulation.

B. Bioequivalence: Bioequivalence was evaluated on log-transformed parameters and 90% confidence intervals were reported. Study 502.127 was a replicate bioequivalence study that compared the 80 mg clinical trials tablet formulation to the 80 mg commercial tablet formulation.The clinical batches and the final formulation from the production site were bioequivalent based on conventional average bioequivalence. Individual bioequivalence was demonstrated with respect AUC_{0-t} and $AUC_{0-\infty}$, but not with respect to C_{max}.. The failure to show individual bioequivalence with respect to C_{max} was solely due to the fact that for C_{max} the observed within-subject variability for the clinical (reference) formulation (CV=31%) was smaller than the observed within-subject variability of the commercial (test) formulation (CV=48%). (*NOTE*: The within-subject CV of the test (production) formulation was in fact consistent with the within-subject variability observed in previous studies with the reference (clinical) formulation (CV=50% and CV=57%, respectively, in studies 502.128 and 502.114), while the within-subject CV of the reference (clinical) formulation in the present study was lower (CV=31%) than in the previous studies).

C. Food effect: The effect of a standard high fat meal (caloric content = 1067 Kcal) on the absorption of telmisartan administered as a single 40 mg and 160 mg dose was evaluated (Study 502.113). With administration of 40 mg telmisartan with a high fat meal, bioequivalence was observed with regard to AUC but not with Cmax (Cmax was reduced by approximately 20% with food). With the 160 mg dose, a prominent food effect was reflected by a lack of bioequivalence with regard to both AUC and Cmax.; AUC was reduced by approximately 20% and C_{max} was reduced by approximately 60 % (Table 1) while t_{max} was delayed and occurred at 1.8 h after concomitant food intake compared to 0.7 h in the fasted state. (*COMMENTS*: With a delayed drug absorption due to a coadministered high caloric meal, metabolic processes

(glucuronidation) occurring in the liver and probably other organs (e. g. gut wall, kidney) are capable of eliminating a larger fraction of the drug than compared to the administration in the fasted state. It follows that food probably increases the presystemic elimination of telmisartan).

Table 1: Statistical assessment of bioequivalence (point estimators and confidence interval limits obtained by parametric (analysis of variance) and non-parametric approaches (Mann-Whitney test for t_{max})

	40 mg fed/ fasted			160 mg fed/ fasted		
parameter	lower limit	point estimator	upper limit	lower limit	point estimator	upper limit
C_{max}	0.582	0.744	0.952	0.344	0.440	0.563
C_{max}/AUC	0.618	0.793	1.018	0.423	0.543	0.697
AUC_{0-48h}	0.791	0.868	0.953	0.695	0.763	0.838
$AUC_{0-\infty}$	0.834	0.939	1.057	0.721	0.811	0.913
t_{max}	1.061	1.581	2.450	1.732	2.450	2.981

II. PHARMACOKINETICS:

Pharmacokinetics of telmisartan were evaluated in several studies in healthy volunteers as well as in the target population of patients with hypertension. Single IV doses covered a range from 10 to 120 mg (30 minutes infusion). Single oral doses and multiple doses covered a range from 10 to 320 mg. Telmisartan is rapidly absorbed after oral administration with T_{max} ranging from 0.5-2.8 hours. After single IV administration, C_{max} and AUC increased (Tables 2 & 3) in a proportional manner over a dose range of 10-120 mg (Study 502.111, Study 502.105). Following IV administration telmisartan concentrations declined bi-exponentially with a terminal half-life ($t_{1/2}$) of 18-23 hours, systemic clearance (CL_s) of 860-940 ml/minute (exceeds maximum liver clearance of about 750 ml/min) and the volume of distribution at steady state (V_{ss}) of 460-483 liters (>10 times the approximate volume of total body water thus indicating extensive protein and/or tissue binding).

After single or multiple oral dose administration, C_{max} and AUC increased (Tables 4 & 5) in a more than dose proportional manner with high intersubject variability in telmisartan plasma concentrations and accumulation ratio ranging from 1.5 to 2.0 (Study 502.201, Study 502.202).

Table 2: Summary of pharmacokinetic parameters (means ± % CV) for telmisartan Following a 30 Minute Infusion to Healthy Volunteers (Study 502.111)

Parameter	80 mg Dose	120 mg Dose
	mean ± CV%	mean ± CV%
C_{max} [ng/ml]	1340 ± 21.9	1790 ± 15.7
$t_{1/2}$ [h]	23.0 ± 28.1	19.6 ± 26.8
$AUC_{0-\infty}$ [ng · h/ml]	1630 ± 32.9	2660 ± 36.8
MRT_{tot} [h]	11.0 ± 55.8	10.9 ± 52.5
Cl_{tot} [ml/min]	880 ± 28.1	867 ± 49.1
V_{ss} [l]	509 ± 37.9	461 ± 22.5

Table 3: Summary of Pharmacokinetic Parameters (means ± % CV) for telmisartan Following a 30 Minute Infusion to Healthy Volunteers (Study 502.105)

	dose	10 mg	20 mg	40 mg
parameter	unit	mean ± CV%	mean ± CV%	mean ± CV%
C_{max}	[ng/ml]	151 ± 5.27	310 ± 7.57	618 ± 10.5
$t_{1/2}$	[h]	n.a.	n.a.	18.6 ± 11.6
$AUC_{0-\infty}$	[ng · h/ml]	n.a.	n.a.	781 ± 34.9
$MRT_{0-\infty}$	[h]	n.a.	n.a.	10.2 ± 51.1
CL_{tot}	[ml/min]	n.a.	n.a.	942 ± 36.3
V_{ss}	[l]	n.a.	n.a.	483 ± 20.6

n.a.: not applicable

Table 4: Summary of Pharmacokinetic Parameters (means ± CV %) for Telmisartan Following Oral Administration (Solution) on Day 1 and at Steady State (Study 502.201)

dose	C_{max}	$C_{max,ss}$	$AUC_{day\ 1}$	AUC_{ss}	$t_{max,ss}$ *	R_A (AUC)
[mg]	[ng/ml]	[ng/ml]	[ng·h/ml]	[ng·h/ml]	[h]	
10	8.94 ± 44	12.89 ± 36	81.77 ± 52	152.9 ± 47	2.0 (0.25 , 2.0)	2.0
20	29.7 ± 47	46.3 ± 59	276.1 ± 42	527.5 ± 56	2.0 (1.50 , 2.0)	1.8
40	70.4 ± 45	88.2 ± 44	485.5 ± 47	729.1 ± 47	1.5 (0.50 , 2.0)	1.5
60	159 ± 33	328 ± 41	1249 ± 38	2556 ± 43	0.51 (0.25 , 1.0)	2.0
80	366 ± 50	601 ± 84	1044 ± 38	2248 ± 81	0.50 (0.50 , 0.50)	2.0
100	767 ± 56	1041 ± 27	2284 ± 37	3403 ± 33	0.50 (0.50 , 0.50)	1.5
120	1131 ± 57	2017 ± 21	2946 ± 26	5743 ± 41	0.50 (0.25 , 1.0)	1.9
160	1520 ± 47	2871 ± 85	3177 ± 57	5357 ± 72	0.50 (0.25 , 0.50)	1.6

* median (min , max)

The accumulation ratio, $R_A = AUC_{ss} / AUC_{day\ 1}$.

Table 5. Pharmacokinetic Parameters (Mean ± SD) Following the three Doses on Day 28 (Study 502.202)

Dose	Kel	$C_{max,ss}$	$t_{max,ss}$	$t_{½}$	$AUC_{0-\tau}$	CL/F
mg	hr^{-1}	ng/mL	hr	hr	hr·ng/mL	L/hr/lb
40	0.034 ±0.0223	159 ± 104	1.6 ± 1.0	25.2 ± 11.3	1655 ± 1169	0.226 ± 0.183
80	0.038 ± 0.016	693 ± 606	1.3± 1.3	21.6 ± 11.1	3728 ± 3356	0.230 ± 0.186
120	0.040 ± 0.021	1635 ± 1406	1.4 ± 1.5	21.8 ± 13.0	5657 ± 4578	0.209 ± 0.143

III. METABOLISM:

Following both intravenous and oral of administration of ^{14}C-telmisartan, the recovery of radioactivity at 144 hours was on average 102% (range 100 to 106%) after oral and 98% (range 93 to 102%) after intravenous administration. Radioactivity was almost exclusively excreted via the feces (<1% in urine) and similar profiles of telmisartan and total activity in plasma were obtained suggesting that extent of metabolism is minor. Only glucuronides were identified in

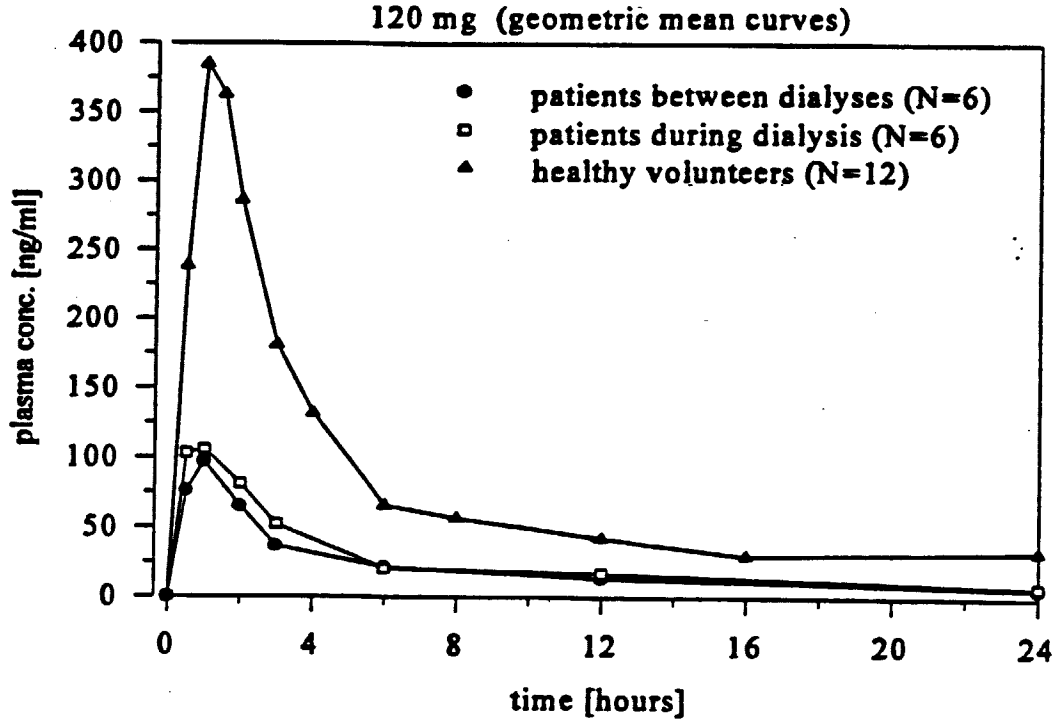
urine and plasma (2.7 to 12.5% by both routes of administration). Measurements of the total radioactivity in plasma revealed that the bioavalability of orally administered telmisartan was incomplete (on average 50%).

The results obtained from the in vitro human microsomal metabolic studies (Protocol B 782) showed that telmisartan did not cause significant inhibition of CYP1A2 catalyzed phenacetin O-dealkylation, CYP2D6 catalyzed bufuralol 1'-hydroxylation, CYP3A4 catalyzed nifedipine oxidation, CYP3A4 catalyzed testosterone 6β-hydroxylation and CYP2B6 catalyzed S-mephenytoin N-dealkylation. An inhibition was observed for CYP2C19 catalyzed S-mephenytoin 4'- hydroxylation that was independent of telmisartan concentration (and therefore may not be related to potential inhibition of the CYP2C19 molecule but rather due to the effect on the membrane integrity of the microsomal membrane-bound CYP2C19). A minor inhibition was observed for CYP2C9 catalyzed tolbutamide hydroxylation at 10 μM telmisartan concentration (more than 7-fold the steady-state concentration after administration of 80 mg telmisartan and therefore not considered therapeutically relevant). Based on the results from the in vitro studies, it could be concluded that clinically relevant drug-drug interactions as a result of metabolic inhibition of other drugs that are substrates of CYP 450 enzymes by therapeutic doses of telmisartan are unlikely.

IV. SPECIAL POPULATIONS:

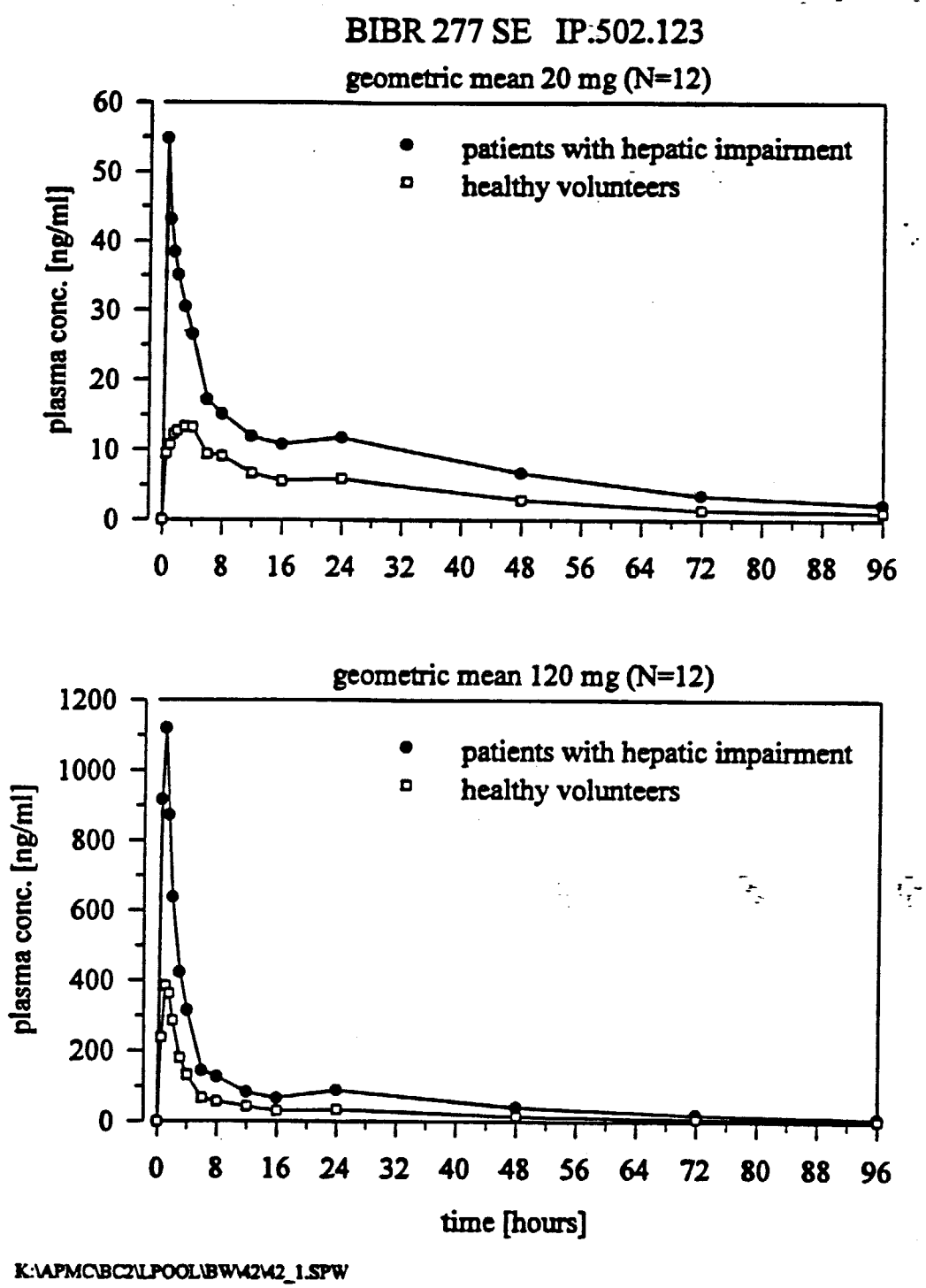
A. Renal Impairment: Severely renal impaired patients were administered single 120 mg oral dose of telmisartan either between or during dialysis (Study 502.118). The plasma concentration-time profile (Figure 2) of telmisartan in subjects with severe renal insufficiency is characterized by a marked reduction in C_{max} and AUC. Compared with values obtained in healthy controls (Study 502.123), there was a 3.3 fold decrease in C_{max}, and a 4.4 fold decrease in $AUC_{0-\infty}$ in patients with severe renal insufficiency. Telmisartan is not removed by hemofiltration. Telmisartan is bound to plasma proteins to an extent of > 99% in the subjects with renal impairment as well as in the healthy controls. It is surprising that although telmisartan is not dialysable and it has similar protein binding in renal pateints and healthy volunteers, the exposure in these patients is markedly lower. A possible explanation (discussion with medical officer) was that acid-base balance is known to change in these patients and this could result in change in pH. Altered bioavailability could be the explanation due to pH dependent solubility of telmisartan.

FIGURE 2: Plasma Concentration-Time Profiles from a Single 120 mg Dose of telmisartan in Subjects with Severe Renal Insufficiency. Data for Healthy Volunteers are taken from Study 502.123



B. Hepatic Impairment: Study 502.123 compared the pharmacokinetics of telmisartan in normal subjects and patients with impaired liver function following single oral dose of 20 and 120 mg telmisartan and 120 mg IV dose to a subset of patients with hepatic impairment. The data obtained from the study (Figure 3) showed that: (i) At the 20 mg dose level there was a 6.5 fold increase in C_{max}, a 2.7 fold increase in $AUC_{0-\infty}$ and about 50% decrease in oral clearance with coresponding 1.5 fold increase in t1/2 in subjects with liver disease compared to the control group., (ii) At the 120 mg dose level, there was approximately 3 fold increase in C_{max} and $AUC_{0-\infty}$ and about 60% decrease in oral clearance in subjects with liver disease compared to the control group. In comparison to the pharmacokinetic profile of telmisartan after intravenous administration to healthy subjects, clearance was reduced in liver insufficient subjects, (iii) The absolute bioavailability of telmisartan in hepatically impaired subjects was close to 100 %, whereas in healthy subjects absolute bioavailability was approximately 50%, (iv) As increase in bioavailability and decrease in hepatic clearance implies a multiplicative effect on the $AUC_{0-\infty}$, a dose reduction of telmisartan should be considered when administered orally to patients with liver disease, (v) Telmisartan is bound to plasma proteins to an extent of > 99% in the subjects with hepatic impairment as well as in the healthy controls.

FIGURE 3: Plasma concentration-time plots of telmisartan after oral administration of 20 and 120 mg



C. Age and Gender: Elderly subjects (6 male, 6 female; age 65-78 years) were administered a

single dose of 20 mg and 120 mg telmisartan tablet (Study 502.124) daily for seven days. Compared with data obtained in young healthy controls (Study 502.109, Study 502.119), there was no evidence of any significant change in C_{max} and AUC variables in healthy elderly subjects. At the 120 mg telmisartan dose level, the $C_{max,ss}$ in elderly male and female subjects in this study (mean 592 ng/ml, range 105 to 2007 ng/ml) was comparable with values obtained in young controls in another study (mean 573.9 ng/ml, range 153.8 - 1918ng/ml). The mean AUC_{ss} in elderly subjects in this study was 2200 ng·h/ml (range 545 to 11500 ng·h/ml) compared with 1462 ng·h/ml (range 437.4 to 4246 ng·h/ml) in young controls (males) in another study (Study 502.119). The higher mean value in the elderly can be ascribed to higher plasma concentrations in the female elderly and a single, high value of 11500 ng·h/ml for AUC_{ss} for subject no. 8 (male). When the AUC_{ss} in the male elderly was recalculated excluding data for this subject, the value obtained (1440 ng·h/ml) was comparable with that reported for healthy young controls (Study 502.119). At the 20 mg dose level, $C_{max,ss}$ and AUC_{ss} in elderly subjects in this study were of the same order of magnitude as in controls. At the 120 mg dose level, C_{max} and $C_{max,ss}$ were significantly higher in female than male subjects; this may be attributable to differences in metabolic capacity between the sexes (Table 6). No decrease in protein binding of telmisartan was present in elderly subjects. Study 502.202 also showed that there are gender differences in the disposition of temilsartan (see pharmacokinetics / pharmacodynamic relationship below).

Table 6: Gender effects in the pharmacokinetics of telmisartan (Study 502.124)

N	dose [mg]	sex []	C_{max} [ng/ml]	$C_{max,ss}$ [ng/ml]	AUC_{0-24h} [ng·h/ml]	AUC_{ss} [ng·h/ml]
6	20	m	16.3	26.7	152	317
5*	20	m	14.5	20.6	119	221
6	20	f	19.6	29.9	167	260
6	120	m	284	329	1140	2040
5*	120	m	260	247	856	1440
6	120	f	1000	1060	1780	2380

*: subject 8 excluded from calculation of means

V. DRUG INTERACTIONS:

A. Digoxin: Study 502.119 examined the effects of steady state telmisartan (120 mg daily for 7 days) on the steady state pharmacokinetics of digoxin. The data obtained from the study showed that upon co-administration of telmisartan with digoxin: (i) There are increases in $AUC_{144-168}$, C_{max} and C_{min} of digoxin (21%, 50% and 14%, respectively). However, the

90% confidence interval for the geometric mean of C_{min} was confined within the pre-defined 80-125% range of no interaction., (ii) The pharmacokinetics of telmisartan are similar to those in healthy subjects without concomitant drug administration (Study 502.124).

B. Warfarin: In Study 502.120, the effect of multiple dose administration of telmisartan on the steady state pharmacodynamics and pharmacokinetics of warfarin was evaluated. The mean INR_{pre} (the international normalized ratio) under steady state conditions remained unchanged during the treatment phases with warfarin alone, as well as during combined treatment indicating that there is no apparent pharmacodynamic interaction between telmisartan and warfarin with regard to anticoagulant effect of warfarin. A small but statistically significant ($p=0.0006$) decrease in warfarin plasma trough concentration was observed but this did not result in decreased anticoagulation (i.e. lower INR values), suggesting that a direct correlation between pharmacodynamics and pharmacokinetics seems to be absent. This may be caused by a stereoselective effect on the metabolism of the less potent (R)-warfarin enatiomer, which in turn can result in a decrease of total warfarin plasma concentrations, without affecting the coagulation The pharmacokinetics of telmisartan are similar to those in healthy subjects without concomitant drug administration (Study 502.124)

C. Paracetamol (Acetaminophen): Paracetamol is mainly eliminated by conjugation to glucuronic acid and sulfate. Because telmisartan is also exclusively metabolised by glucuronidation a potential metabolic interaction might arise from the common elimination pathway for both drugs. In Study 502.121 the effect of concomitant administration of 120 mg telmisartan on the pharmacokinetics of 1 g paracetamol (acetaminophen) was studied. Bioequivalence of the two treatments was demonstrated for paracetamol with respect to AUC but not with Cmax (Cmax increased by increased by approximately 15 % with administration with telmisartan). The pharmacokinetics of telmisartan are similar to those in healthy subjects without concomitant drug administration.

D. Hydrochlorothiazide (HCTZ): Study 502.114 compared the steady state pharmacokinetics of telmisartan with and without the co-administration of hydrochlorothiazide (HCTZ), and the steady state pharmacokinetics of HCTZ with and without the co-administration of telmisartan. Bioequivalence of the two treatments was demonstrated for telmisartan with respect to AUC but not with Cmax. Bioequivalence of the two treatments was demonstrated for HCTZ with respect to AUC, Cmax and amount of HCTZ excreted in urine. A trend towards higher AUC_{0-24} and C_{max} for both drugs (especially for telmisartan) alone and in combination was noted in female subjects. The interaction is not clinically significant.

E. Ibuprofen: Study 502.125 examined the influence of co-administered telmisartan 120 mg daily on the pharmacokinetics of R-(-)-/S-(+)-Ibuprofen 400 mg t.i.d. over an administration period of 7 days. Bioequivalence of the two treatments was demonstrated for the ibuprofen enantiomers after both treatment regimens thus showing that concomitant administration of

telmisartan had no influence on the pharmacokinetics of ibuprofen. The pharmacokinetic profile of telmisartan at steady state was similar to that observed in previous clinical trials. It is therefore concluded that concomitant administration of ibuprofen had no significant effect on the pharmacokinetic profile of telmisartan. There was a trend towards higher C_{max} and lower oral clearance for telmisartan in female subjects. The interaction is not clinically significant.

F. Amlodipine: Study 502.126 examined the safety and pharmacokinetic interactions between amlodipine and telmisartan. Bioequivalence of the two treatments was demonstrated for the amlodipine after both treatment regimens with respect to AUC and Cmax of amlodipine but urinary excretion of amlodipine was increased by approximately 17%. The pharmacokinetic profile of telmisartan at steady state was similar to that observed in previous clinical trials. It is therefore concluded that concomitant administration of amlodipine had no significant effect on the pharmacokinetic profile of telmisartan

G. Glibenclamide: Study 502.122 examined the the safety and pharmacokinetic interactions between glibenclamide and telmisartan. Bioequivalence of the two treatments was demonstrated for the glibenclamide after both treatment regimens with respect to AUC but not with Cmax of glibenclamide (Cmax increased by about 17%). The pharmacokinetic profile of telmisartan at steady state was similar to that observed in previous clinical trials. It is therefore concluded that concomitant administration of glibenclamide had no significant effect on the pharmacokinetic profile of telmisartan.

VI. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP

In Study 502.103 the following objectives were investigated: (1) determination of the pharmacodynamic action of telmisartan at three dose levels after a single dose (with emphasis on attenuation of the blood pressure response to angiotensin II stimulation), (2) assessment of the pharmacokinetics and tolerability of telmisartan. Telmisartan dose-dependently inhibits the pressor and pulse rate response to angiotensin II infusion, with a virtually maximum inhibition of increase in diastolic blood pressure already occurring at the middle dose level (40 mg). The inhibitory effect has a fast onset of action and a long duration of action and once daily treatment seems feasible. A hyperbolic pharmacodynamic-pharmacokinetic relationship is observed which can be described with the Hill equation (Tables 7 & 8, Figure 4).

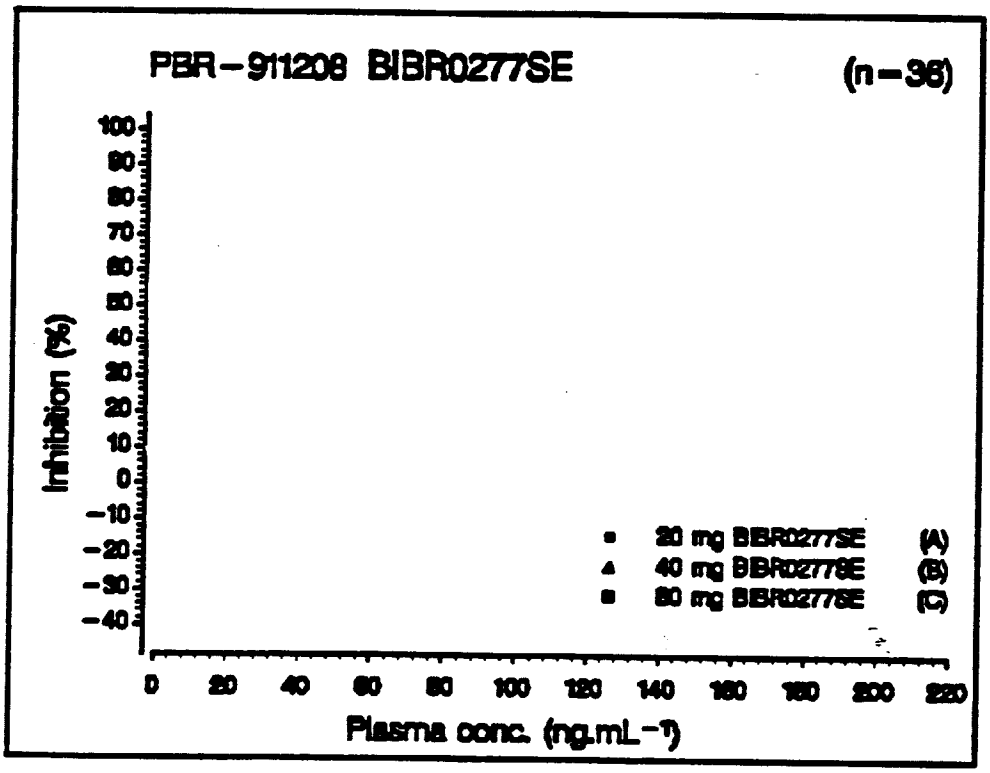
Table 7. Summary of Hill equation Parameters for %Inhibition of Diastolic Pressure versus Telmisartan Plasma Concentration

Parameter	Estimate	95% Confidence Interval (asymptotic)
E_{max}	101	78 - 124
EC_{50}	12.2	1.8 - 22.7
γ	0.61	0.43 - 0.79

Table 8. Summary of Hill equation Parameters for AUEC versus $AUC_{0-\infty}$

Parameter	Estimate	95% Confidence Interval (asymptotic)
E_{max}	2919	844 - 4993
EC_{50}	229	-142 - 601
γ	1.00	-0.23 - 2.23

Figure 4. Plot of inhibition of diastolic blood pressure response to angiotensin II challenge versus telmisartan plasma concentrations as observed after single dose administration of telmisartan or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups - 3 telmisartan doses and placebo)



The objectives of Study 502.203 were to evaluate the efficacy and safety of telmisartan 20, 40, 80, 120 and 160 mg, daily in comparison to placebo and to assess the dose-response relationship in patients with mild-to-moderate hypertension. When considering all patents who received telmisartan, no strong relationship was found between effect (supine DBP reduction) and plasma telmisartan concentration. For responders (defined as having supine DBP ≥ 10 mmHg reduction and/or trough ≤ 90 mmHg) in the 20 mg dose group and in the pooled 20 mg and 40 mg dose groups, a sigmoidal E_{max} model best described the relationship between the supine diastolic blood pressure lowering effect and plasma telmisartan concentration; the respective estimated E_{max} (maximal effect) was 19.8 and 18.7 mmHg, and

the respective EC_{50} (concentration at half maximal effect) was 3.53 and 2.32 ng/mL (Tables 9 & 10, Figure 5). Independent of dose, females tended to have higher plasma concentrations than males (Figure 6).

TABLE 9. Parameter Estimates for the Sigmoidal E_{max} Model for Responders

Dose Group	Parameter	Estimate	Approx. S.E.	Approx. P > |T|
20 mg	E_{max} (mmHg)	19.8	2.84	0.0001
	EC_{50} (ng/mL)	3.53	1.70	0.0016
	Sigmoidicity factor	1.17	0.51	0.0252
20 and 40 mg	E_{max} (mmHg)	18.7	2.30	0.0001
	EC_{50} (ng/mL)	2.32	0.93	0.0133
	Sigmoidicity factor	0.74	0.34	0.0333

TABLE 10. Mean Observed E_{max} on Day 28 for All Patients

Dose Group (mg)	Mean Observed E_{max} (mmHg)	S.D.	N
20	16.9	6.1	39
40	18.8	8.4	44
80	18.9	6.7	39
120	20.6	9.0	43
160	21.0	9.7	42
All	19.3	8.2	207

FIGURE 5. Sigmoidal E_{max} Model for Supine DBP Reduction and Telmisartan Plasma Concentration as Observed in Responder Patients in the Pooled 20-mg and 40-mg Dose Groups (Solid Line: Fitted Line, Dotted Lines: Approximate 95% Confidence Bands, *: Observed Data)

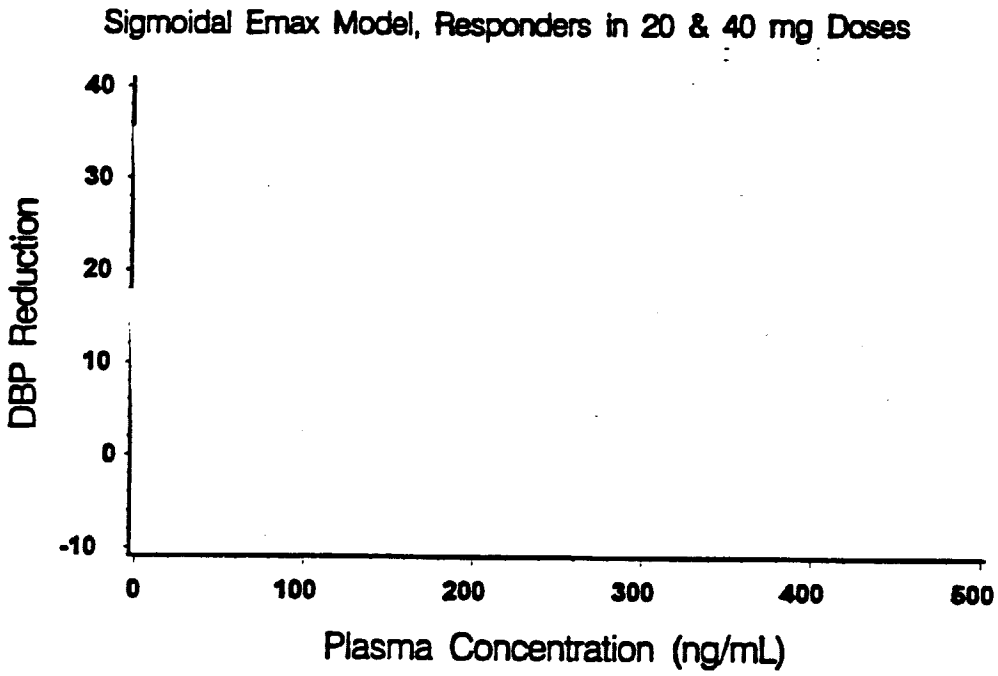


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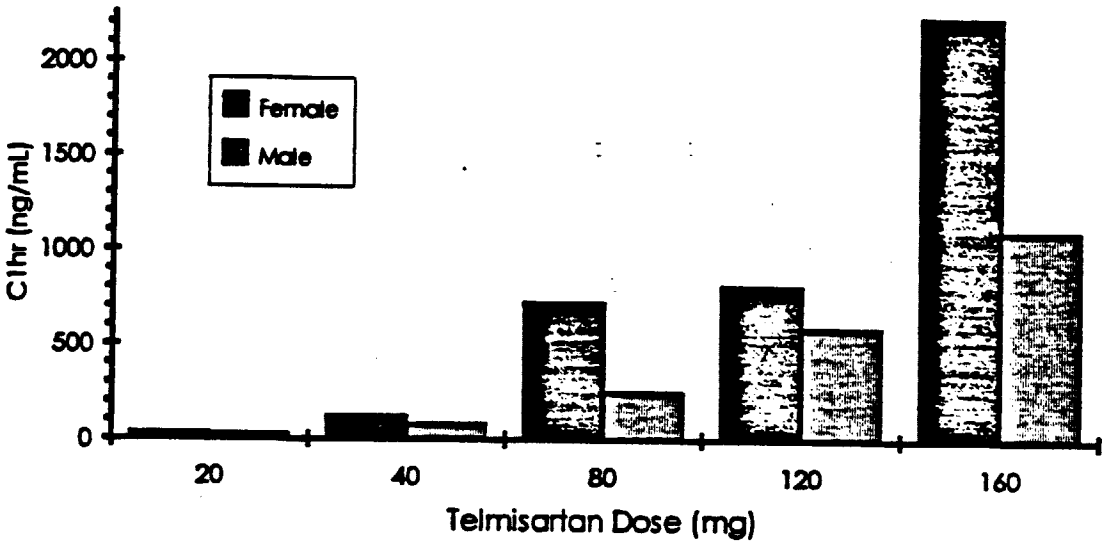
FIGURE 6. Comparison of One-Hour Telmisartan Concentration on Day 28 by Gender



The objectives of Study 502.202 were : (1) to assess the dose response relationship of the antihypertensive effect of telmisartan over the dose range of 40 to 120 mg and to identify doses of telmisartan which, administered once daily, lowered diastolic blood pressure at the end of the dosing interval when compared with placebo after 28 days of dosing, (2) to assess the safety of telmisartan over this dose range relative to placebo and enalapril 20 mg and (3) the evaluation the pharmacokinetics and pharmacodynamics of telmisartan following the 4-week treatment in these hypertensive patients. There are gender and race differences in the disposition of temilsartan. Hispanics and Blacks generally had 2 to 3-fold higher mean Cmax, Cmin, and AUCs compared to Whites (Tables 11 & 12). Females had higher plasma mean concentrations compared to males. Mean peak diastolic or systolic effect did not correspond with the mean peak plasma telmisartan concentration in any of the three dose groups (Figure 7) and there were no corresponding increases in mean peak effect with many fold increase in mean telmisartan plasma concentrations. Weak correlations were observed between plasma levels and effects and the concentration-effect relationship showed that at the three dose levels (40, 80 and 120 mg) were near the plateau region of the dose-response curve. There are appears to be both gender and race differences in the effect of temilsartan on supine blood pressure with females showing greater effect and males and Hipanics showing greater effect than Blacks and Whites.

TABLE 11. Mean ± SD for Pharmacokinetic Parameters by Race

Parameter	White (N=78)	Hispanic (N=24)	Black (N=10)	Other (N=2)
$AUC_{0-\tau}$ /Dose	33.7 ± 24.4	78.6 ± 47.1	54.9 ± 40.8	34.3 ± 11.7
C_{max}/Dose	6.4 ± 6.6	13.6 ± 11.1	15.3 ± 13.0	5.1 ± 2.5
$t_{1/2}$	23.3 ± 13.3	20.8 ± 5.2	21.2 ± 5.4	39.3 ± 24.5

Table 12. Mean ± SD for Pharmacokinetic Parameters for All Males and Females

Parameter	Males (N = 69)	Females (N = 45)	Female/Male Ratio
$AUC_{0-\tau}$ /Dose	37.6 ± 27.8	56.4 ± 44.8	1.50
C_{max}/Dose	6.4 ± 5.9	12.3 ± 11.6	1.92
$t_{1/2}$	21.7 ± 11.4	24.6 ± 12.4	1.13

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Figure 7. Mean Plasma Telmisartan Concentration Profiles and Change in DBP in Patients on Day 28

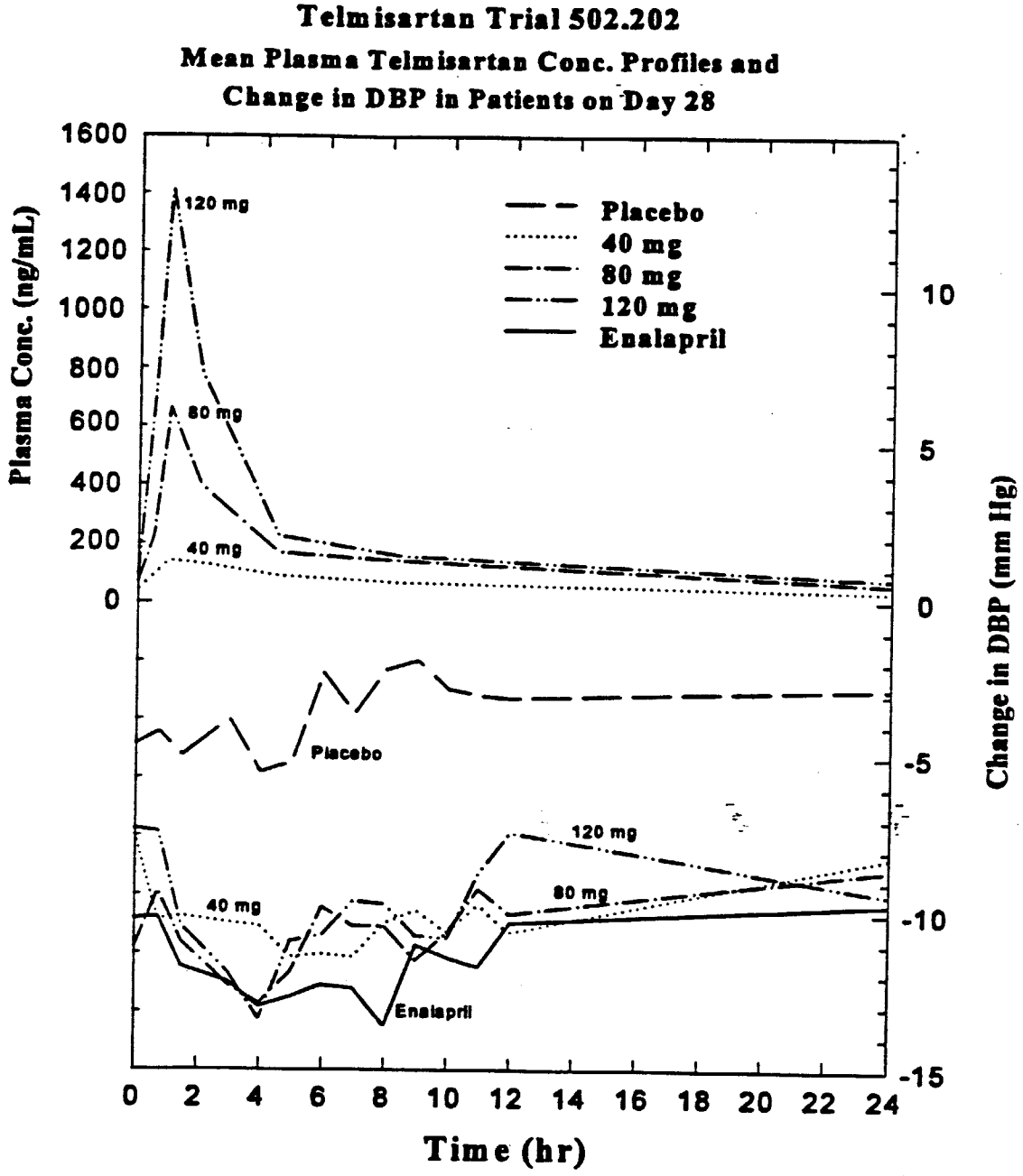
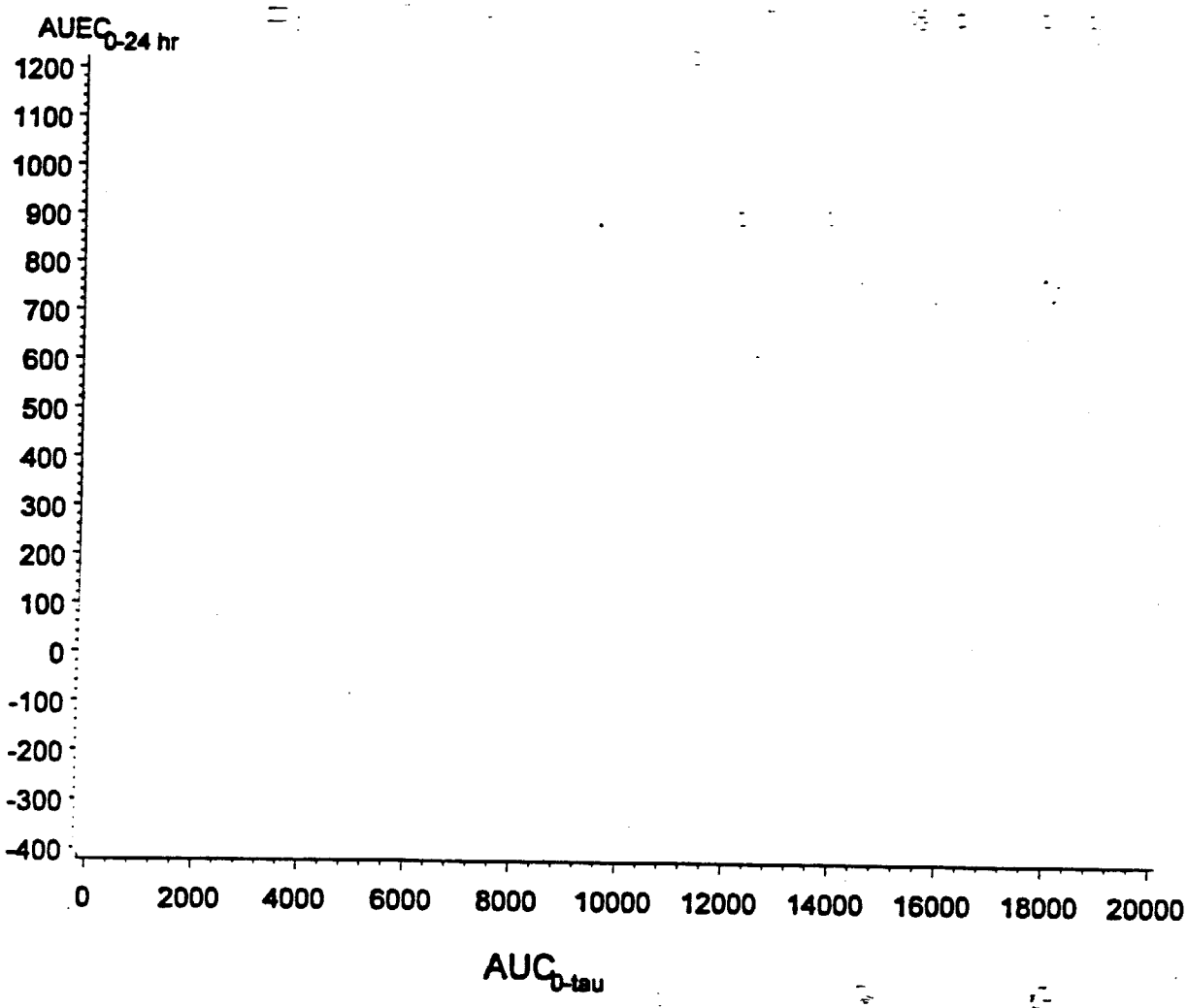


FIGURE 8. Plot of $AUEC_{0\text{-}24\ hr}$ for DBP vs $AUC_{0\text{-}\tau}$ on Day 28 (Study 502.202)



The statistician's review shows that the dose response curves seem to have reached a plateau at some dose level between 20 and 80 mg telmisartan (See attached Figures from biostatistician review).

VII. POPULATION PHARMACOKINETICS

The objective of the population pharmacokinetic analysis was to determine the effects of a variety of covariates on the pharmacokinetic parameters of telmisartan using pooled clinical study data (Studies 502.202, 502.203, 502.206, 502.210, 502.211, 502.214, 502.218 and 502.114). A total of 5921 plasma telmisartan concentrations collected from 1194 individuals during steady state dosing were included in the analysis. A majority (5249 samples, 89% of total) of these concentrations were from plasma samples collected during the 6 hours or

24 ± 5 hours (trough) after dose at the visits. Population analysis demonstrated that telmisartan clearance appeared to be related to gender, race, telmisartan dose, alcohol consumption, cigarette smoking and HCTZ co-administration. A significant effect of gender on V_2 and dose on Ka was also found. No or little effects of age, weight, body surface area, creatinine clearance or the existence of congestive heart failure were shown on the clearance of telmisartan. Females showed a 62% lower V_2 and approximately a 30% lower CL than males depending on the effects of other covariates. Comparing the race effect on CL, the ratios for Hispanic : white : black : other were 0.72 : 1 : 1.42 : 1.38. Telmisartan dose caused a significant nonlinear increase in Ka, indicative of a nonlinear increase of C_{max} with dose. Although to a smaller degree, dose also reduced the CL in a nonlinear fashion. The ratios for non-smoker : ex-smoker : smoker were: 1 : 1.33 : 1.07. While alcohol consumption caused a 15-25% increase in CL, HCTZ coadministration caused a 10-20% decrease in CL.

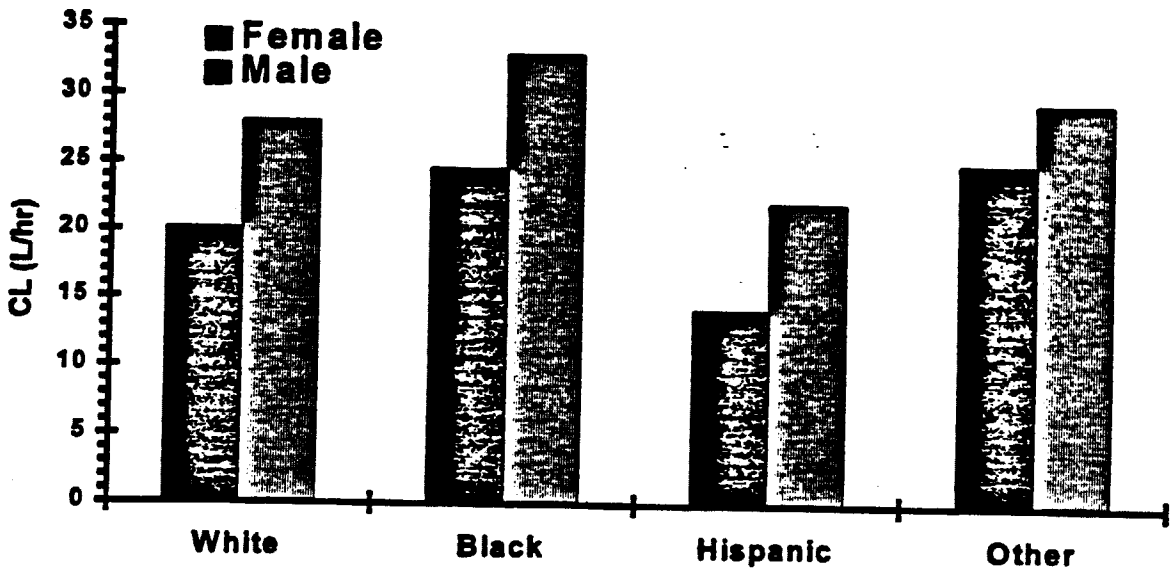
High interindividual variability was found for CL, Q, V_3 and Ka with %CV of 66, 95, 108 and 92, respectively. Intraindividual or residual variability can best be described by a model with a combination of exponential and additive errors with a magnitude of 72% CV of expected concentration plus a constant of 21 ng/mL.

The population analysis showed that telmisartan pharmacokinetics can be affected by various sources of factors, which could explain the reasons that the plasma concentrations were highly variable. Although many covariates are identified, no dosage adjustment is recommended because of the wide therapeutic range of the drug.

TABLE 13: Summary of Posthoc Individual Telmisartan CL by Race and Gender

Race	White		Black		Hispanic		Other	
Gender	Female	Male	Female	Male	Female	Male	Female	Male
N	295	635	67	87	39	57	5	9
Mean	20.37	28.48	25.1	33.17	14.25	23.23	26.37	28.52
CV	42.61	37.18	34.1	34.05	43.13	35.37	40.15	54.45
Median	20.12	27.94	24.59	32.97	14.21	22.12	25	29.46

FIGURES 9: Comparison of Posterior Estimate of Individual CL by Gender and Race



VIII. FORMULATION: The two tablet formulations to be marketed (40 and 80 mg) are prepared from a common blend and, thus, contain proportional quantities of all ingredients (Table 14).

TABLE 14 Quantitative Composition of Telmisartan Tablets

	mg per Tablet	
Ingredient	40 mg	80 mg
Telmisartan		
Sodium hydroxide		
Povidone		
Meglumine		
Purified water*		
Sorbitol		
Magnesium stearate		
Total weight		

*Does not appear in final product

IX. DISSOLUTION: The proposed dissolution method of USP Apparatus II at 75 rpm, phosphate buffer, pH 7.5 is appropriate but the specification should be changed from Q % in minutes to Q % in minutes.

X. ASSAY:

XI. PLASMA PROTEIN BINDING: Telmisartan is highly bound to plasma protein (>99.5%) and the plasma protein binding remains unchanged over 100-5000 ng/ml concentration range (equivalent to a 320 mg dose). Telmisartan is bound to serum (>99.6) and the main serum protein involved is HSA (>99.8). Telmisartan displays saturable binding to AAG and non-saturable binding to GG and significant binding to lipoproteins. The erythrocyte uptake of telmisartan is significant but very low in the presence of serum indicating a very high binding capacity of serum (albumin).

XII. PEDIATRIC POPULATION: The pharmacokinetics of telmisartan has not been described in the pediatric population.

XIII. INFLUENCE OF RACE: The population pharmacokinetic analysis showed race affects telmisartan clearance, the ratios for Hispanic : white : black : other were 0.72 : 1 : 1.42 : 1.38 (see population pharmacokinetics above). Study 502.202 also showed that there are race differences in the disposition of temilsartan. Hispanics and Blacks generally had 2 to 3-fold higher mean Cmax, Cmin, and AUCs compared to Whites (see pharmacokinetics / pharmacodynamic relationship above).

XIV. LABELING: The clinical pharmacology section of the labeling is deficient and the firm has been advised to modify it accordingly (see comments below).

COMMENTS TO BE SENT TO THE FIRM:

/S/ 8/3/98

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. /S/ 8/7/98

Biopharm Day - 07/29/98: Lesko, Mehta, Hunt, Parekh, U,

cc: NDA 20-850, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy),
HFD-340 (Vish).

FROM BIOSTAT. REVIEW (NDA 20-850)

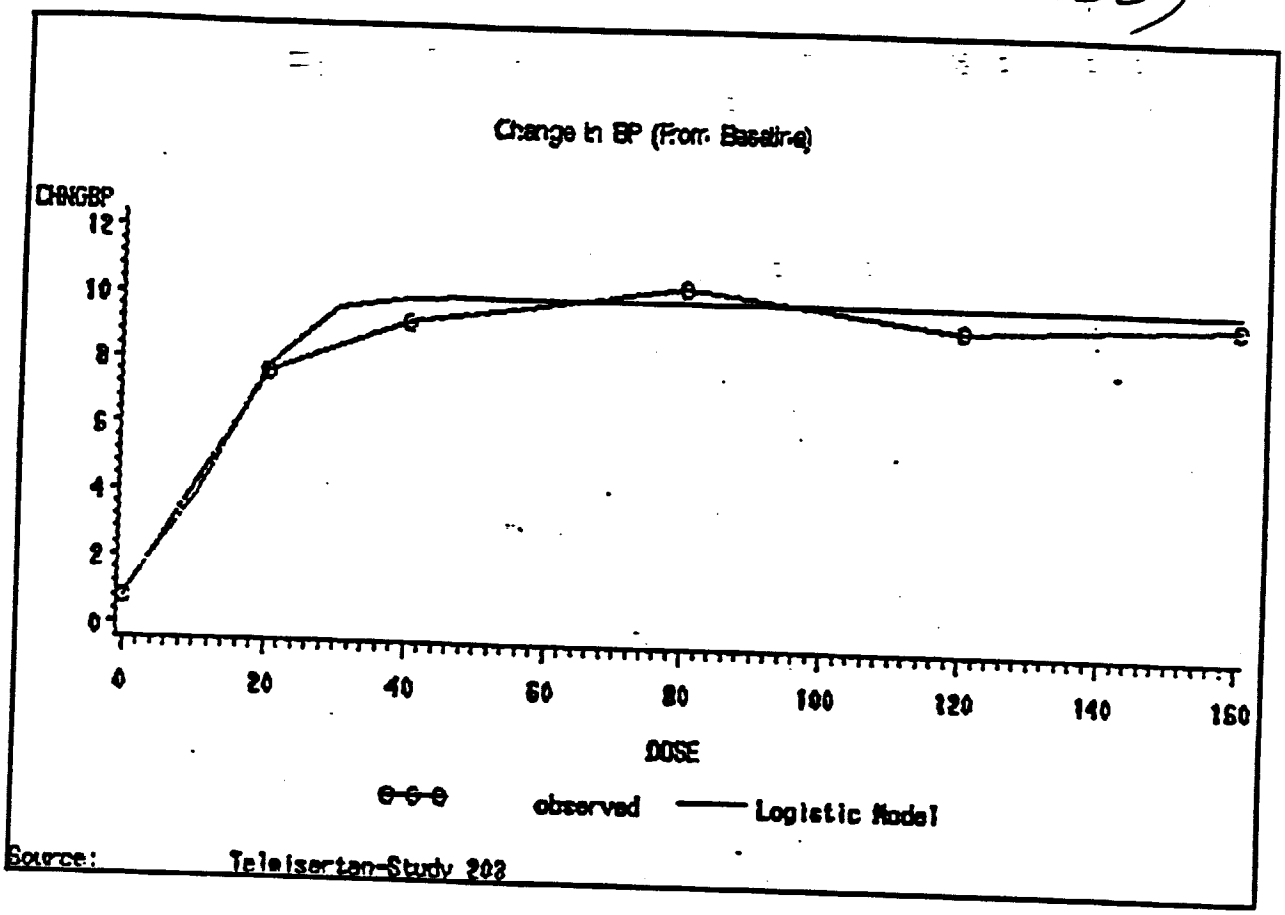


Figure 1. The observed changes from baseline in SuDBP and the estimated logistic model for dose response. (Study 502.203).

Model : Change= 10/[1 + 4.7.Exp(-(0.106)dose)].

RMSE=7.776.

The dose levels studied were 0, 20, 40, 80, 120, and 160 mg.

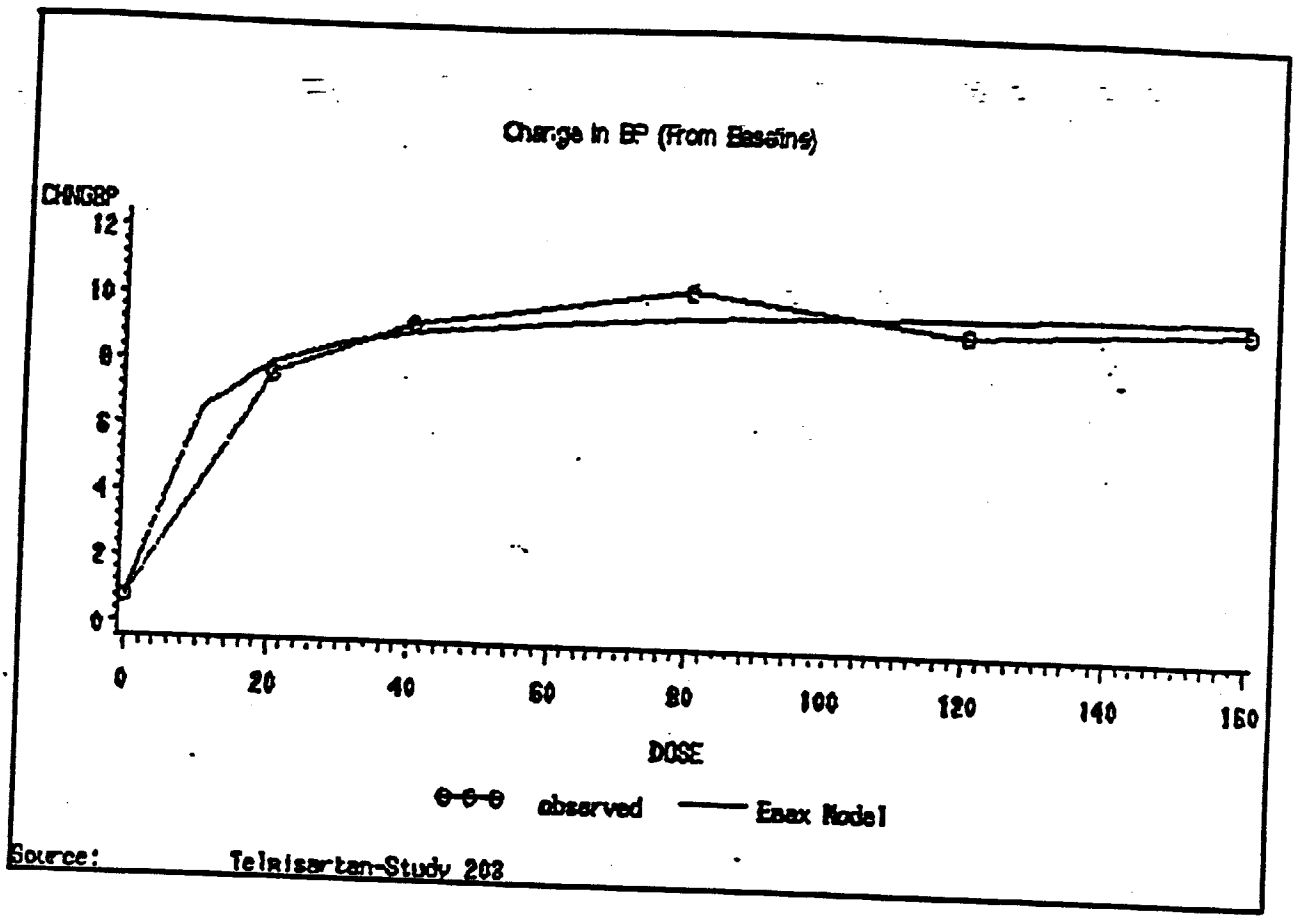


Figure 2. The observed changes from baseline in SuDBP and the estimated E_{MAX} model for dose response. (Study 502.203).

Model: Change= $C + (E_{MAX} + Dose)/(EC_{50} + Dose)$, where

C=Unknown constant representing placebo effect,
E_{MAX}=Maximum expected effect, and
EC_{50}=Dose level producing an effect half of E_{MAX}.

Estimated Model : Change= 0.8 + (9.49).dose/(6.75 +dose).

RMSE=7.775.

The dose levels studied were 0, 20, 40, 80, 120, and 160 mg.

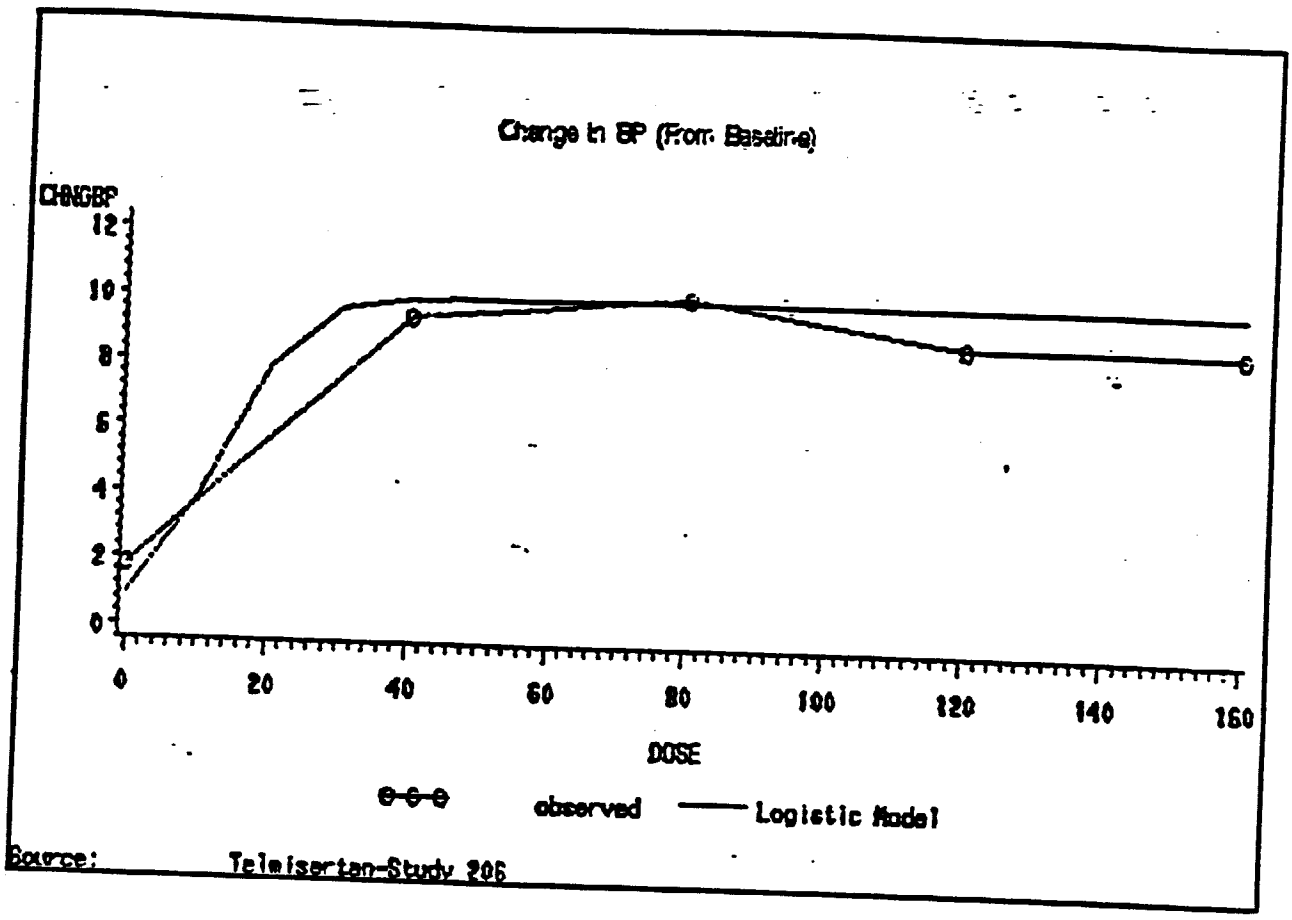


Figure 3. The observed changes from baseline in SuDBP and the estimated logistic model for dose response. (Study 502.206).

Model : Change= 10/[1 + 9.94.Exp(-(0.171)dose)].

RMSE=7.76.

The dose levels studied were 0, 40, 80, 120, and 160 mg.

XX VIII

APPENDIX

METABOLIC PROFILING

STUDY 502.110 **VOLUME: 1.1092 PAGES: 1 - 421**

INVESTIGATOR AND LOCATION:

STUDY DATE: September 7-21, 1993.

OBJECTIVES: (i) To assess the metabolic profile for both oral and intravenous routes of administration, (ii) to compare the pharmacokinetics of the ^{14}C-labelled compound after single dose oral and intravenous administration, (iii) to obtain an indication on the absolute bioavailability, (iv) to determine the ratio of ^{14}C-radioactivity in blood cells and (v) plasma to determine the protein binding of ^{14}C-radioactivity.

FORMULATIONS:
40 mg ^{14}C- telmisartan (oral dose) Batch: Ch.-B.30705; radioactive dose was 54 µCi
40 mg ^{14}C- telmisartan (intravenous dose) Batch: Ch.-B.30706; radioactive dose was 54 µCi

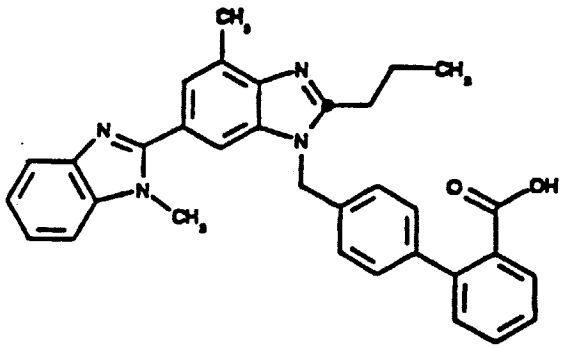


Figure 1. Structural formula of ^{14}C- telmisartan (^{14}C- BIBR 0277 SE)

STUDY DESIGN:
A randomized, open, single dose study in two parallel groups (5 subjects per group) receiving either oral or intravenous ^{14}C-telmisartan. ^{14}C-telmisartan was administered either as a single oral dose (40 mg; 54 µCi) or as a single intravenous infusion over 20 min (40 mg; 54 µCi) under fasting conditions. Blood samples were taken at regular intervals after administration of ^{14}C-telmisartan. All urine produced until 144 h post-dose and faeces produced until discharge was collected. Radioactivity was determined in plasma, urine and faeces by means of

counting and the mass balance of ^{14}C-telmisartan and its radioactive metabolites was determined. At specific time-points (1 and 3 hours after oral dose, 0.5 and 3 hours after the start of infusion) blood samples (25 ml) were taken for identification of metabolites. Blood samples (10 ml) were collected at 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 h after oral administration; and at 0 (predose) 5, 10, 15, 19, 21, 23, 26, 30, 35, 45 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 h after the start of the infusion. Urine samples were collected blank (pre-dose), 0-4, 4-8, 8-12, 12-16, 16-24, 24-48, 48-72, 72-96, 96-120 and 120-144 h after administration of after each dose.

ASSAYS:

DATA ANALYSIS: ($AUC_{0-\infty}$), the amount of radioactivity excreted in urine (A^{urine}_{144}) and faeces (A^{faeces}_{144}) and the total amount of radioactivity excreted (A^{total}_{144}), AUC, Cmax, Tmax, $t_{1/2}$, MRT, K_{el}, %Dose excreted and bioavailability were calculated.

RESULTS: Tables 1- 5 and Figures 2-5 summarize the data obtained from the study.

Table 1. Summary statistics on excretion parameters derived from total radioactivity in urine and faeces as observed after single administration of [^{14}C]BIBR 0277 SE
A = oral administration of 40 mg
B = intravenous infusion of 40 mg over 20 min

parameter		mean	SD	CV (%)	median	range
A^{urine}_{144}	A	0.49	0.20	41	0.42	0.35 - 0.84
(% of actual dose)	B	0.91	0.38	42	0.85	0.52 - 1.49
A^{faeces}_{144}	A	101.99	2.58	2.5	102.48	99.32 - 105.65
(% of actual dose)	B	97.57	3.53	3.6	99.51	92.30 - 100.85

Table 2. Summary statistics on pharmacokinetic parameters derived from total radioactivity in plasma as observed after single dose administration of [^{14}C]BIBR 0277 SE
A = oral administration of 40 mg
B = intravenous infusion of 40 mg over 20 min

parameter		mean	SD	CV (%)	median	range
c_{max}	A	51.3	17.3	34	46.7	33.7 - 70.3
(ng eq.mL^{-1})	B	1203.0	131.9	11	1158.0	1031 - 1357
t_{max}	A				0.50	0.25 - 1.00
(h)	B				0.35	0.35 - 0.35
k_{el}	A	0.0490	0.0046	9	0.0485	0.0447 - 0.0538
(h^{-1})	B	0.0382	0.0100	26	0.0376	0.0270 - 0.0505
$t_{1/2}$	A	14.2	1.3	9	14.3	12.9 - 15.5
(h)	B	19.1	5.1	27	18.6	13.7 - 25.6
AUC_{0-6}	A	196	84	43	182	102 - 322
(ng eq.mL^{-1}.h)	B	821	82	10	817	742 - 952
$AUC_{0-\infty}$	A	672	282	42	523	495 - 997
(ng eq.mL^{-1}.h)	B	1343	87	7	1382	1213 - 1395
MRT	A	18.9	2.4	13	18.9	16.5 - 21.3
	B	13.3	2.0	15	13.3	11.2 - 15.3

Table 3. Summary statistics on pharmacokinetic parameters of BIBR 0277 SE as observed after single dose administration of [^{14}C]BIBR 0277 SE
A = oral administration of 40 mg
B = intravenous infusion of 40 mg over 20 min

parameter		mean	SD	CV (%)	median	range
c_{max}	A	44.7	19.1	43	38.1	27.9 - 71.9
(ng.mL^{-1})	B	1196.0	148.4	12	1120.0	1040 - 1360
t_{max}	A				1.00	0.50 - 1.00
(h)	B				0.35	0.35 - 0.35
k_{el}	A	0.0518	0.0111	21	0.0491	0.0411 - 0.0697
(h^{-1})	B	0.0361	0.0044	12	0.0382	0.0312 - 0.0407
$t_{1/2}$	A	13.8	2.6	19	14.1	9.9 - 16.9
(h)	B	19.5	2.5	13	18.2	17.0 - 22.2
AUC_{0-6}	A	180	91	51	167	82 - 316
(ng.mL^{-1}.h)	B	785	81	10	761	699 - 914
$AUC_{0-\infty}$	A	491	302	62	402	206 - 997
(ng.mL^{-1}.h)	B	1132	184	16	1171	821 - 1306
MRT	A	17.0	2.6	15	18.4	13.2 - 19.6
	B	10.6	3.4	32	11.5	5.5 - 14.3

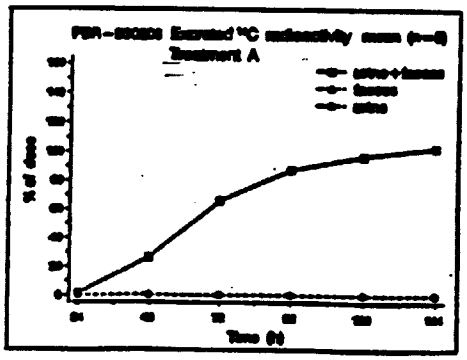
Table 4. Summary the ratios of the $AUC_{0-\infty}$ for oral versus intravenous administration for total radioactivity and BIBR 0277 SE, and for the ratio of the $AUC_{0-\infty}$ for BIBR 0277 SE in plasma versus total radioactivity in plasma after intravenous administration.

		95% confidence interval
ratio of $AUC_{0-\infty}$ for total radioactivity in plasma	0.50	0.18 - 0.82
ratio of $AUC_{0-\infty}$ for BIBR 0277 SE in plasma	0.43	0.11 - 0.76
ratio of $AUC_{0-\infty}$ for BIBR 0277 SE versus total radioactivity in plasma	0.84	0.68 - 1.01

TABLE 5: Relative distribution of metabolites in plasma and urine (pooled samples)

plasma			
time point	parent compound	glucuronide	not retained
i.v.0.5 hour	95.5 %	2.7 %	1.8 %
i.v.3hours	85.6 %	12.5 %	3.5 %
p.o. 1 hour	85.0 %	10.9 %	2.6 %

urine			
time interval 0 - 12 hours	parent compound	glucuronide	not retained
i.v.	4.6 %	84.0 %	0 %
i.v.glucuronidase	82.4 %	11.1 %	1.3 %
p.o.	5.5 %	92.8 %	1.6 %
p.o. glucuronidase	97.5 %	2.7 %	0 %



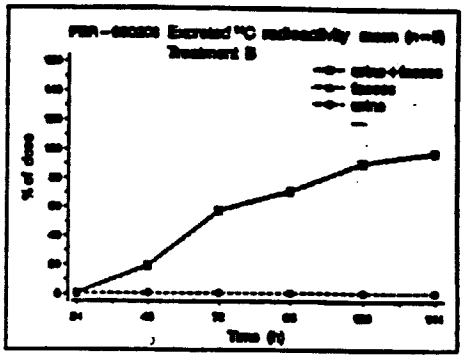


Figure 2

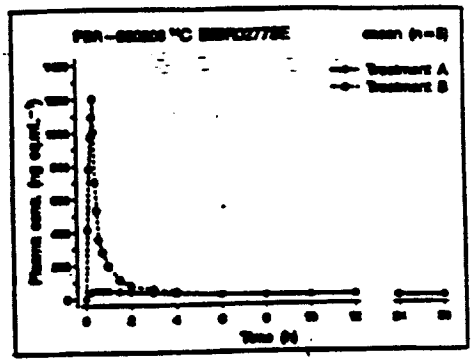


Figure 3.

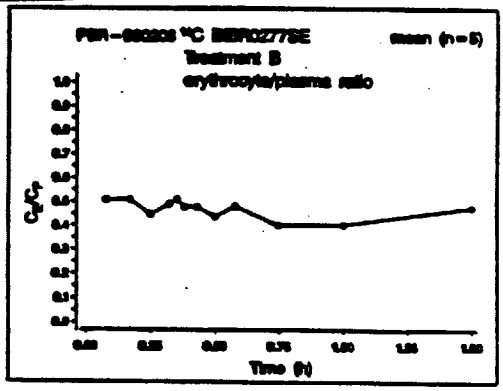
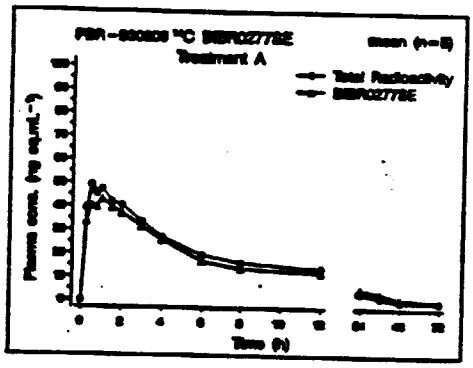


Figure 4.



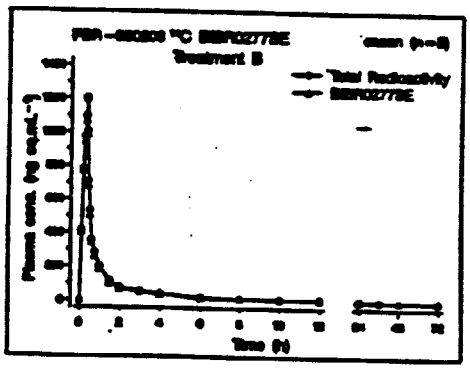


Figure 5

CONCLUSIONS: The results obtained from the study show that:

(i) Measurements of the total radioactivity in plasma revealed that the absorption of orally administered [^{14}C]BIBR 0277 SE was incomplete (on average 50%).

(ii) The recovery of radioactivity at 144 h after administration was on average 102% (range 100 to 106%) after oral and 98% (range 93 to 102%) after intravenous administration.

(iii) Radioactivity was almost exclusively excreted via the feces (<1% in urine) .

(iv) The absolute bioavailability of orally administered BIBR 0277 SE was on average 43% and that on average 84% of the total radioactivity in plasma reflected the parent compound.

(v) Telmisartan binds extensively to plasma proteins (>99%, %unbound radioactivity = 0.46%).

(vi) The accumulation of radioactivity in erythrocytes is subtantial (Figure 4).

(vii) Following oral and intravenous administration, similar profiles of telmisartan and total activity in plasma were obtained suggesting that extent of metabolism is minor. Only glucuronides were identified in urine and plasma (2.7 to 12.5% by both routes, Table 5).

SINGLE DOSE PHARMACOKINETICS

STUDY 502.111 **VOLUME: 1.101** **PAGES: 1 - 351**

INVESTIGATOR AND LOCATION:

STUDY DATE: October 1993.

OBJECTIVES: To investigate the tolerability and pharmacokinetics of telmisartan in healthy male volunteers after 30 min infusion of 80 and 120 mg telmisartan.

FORMULATIONS: Telmisartan injection (40 mg/ampoule), Pharmaceutical code ANT 0301A1A , Charge No 30106
Placebo injection, Pharmaceutical code ANT 0301A0A Charge No 30105

STUDY DESIGN:

A randomized, single blind, placebo controlled, intravenous dose-rising study in 12 healthy volunteers. Two groups of six healthy male volunteers were administered a single dose (80 or 120 mg) of telmisartan or placebo formulated as an aqueous solution containing mannitol, hydrochloric acid (gaseous) and sodium hydroxide as excipients. The placebo formulation contained mannitol only. The doses were administered as an intravenous infusion over a time of 30 min. Blood samples of 5 ml volume were collected from all volunteers at baseline (pre-dose) and at 5, 7.5, 10, 15, 20, 25, 29 min during infusion and 1, 3, 6, 9, 15, 30, 45 min, 1, 1.25, 1.5, 2.5, 3.5, 6.5, 8.5, 12.5, 24.5 and 48.5 h after dosing. Plasma samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

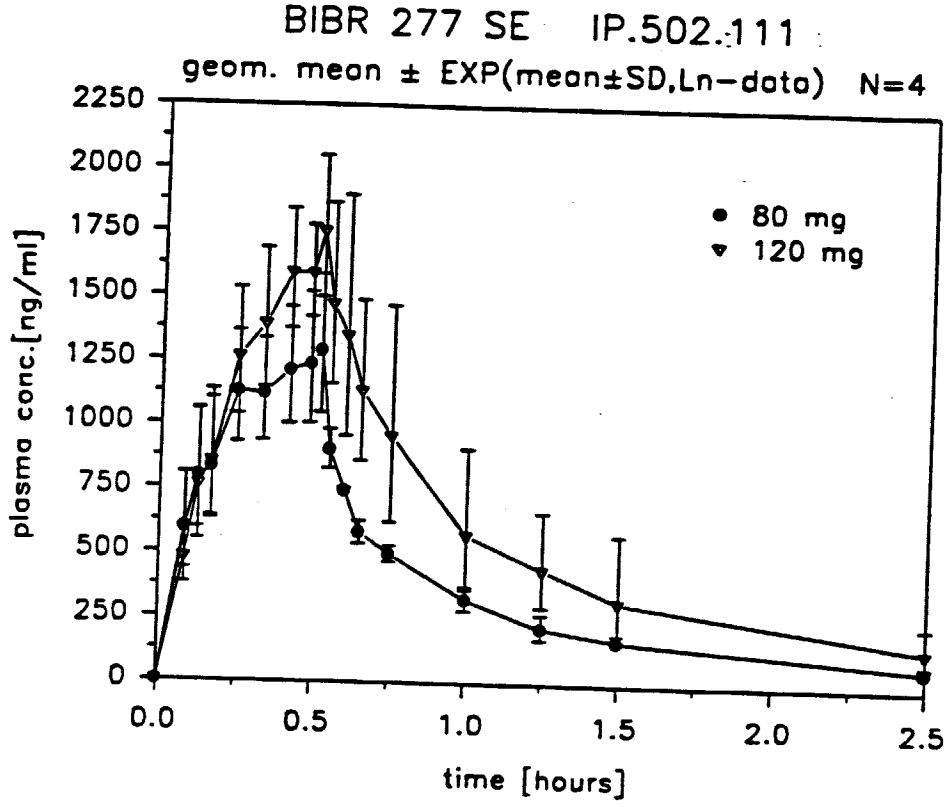
DATA ANALYSIS: AUC, Cmax, Tmax, $t_{1/2}$, Vdss, and CL, were calculated.

RESULTS: Table 1 and Figure 1 summarize the pharmacokinetic data obtained from the study.

Table 1: Summary of pharmacokinetic parameters for Telmisartan Following a 30 Minute Infusion to Healthy Volunteers

Parameter	80 mg Dose	120 mg Dose
	mean ± CV%	mean ± CV%
C_{max} [ng/ml]	1340 ± 21.9	1790 ± 15.7
$t_{1/2}$ [h]	23.0 ± 28.1	19.6 ± 26.8
$AUC_{0-\infty}$ [ng · h/ml]	1630 ± 32.9	2660 ± 36.8
MRT_{tot} [h]	11.0 ± 55.8	10.9 ± 52.5
Cl_{tot} [ml/min]	880 ± 28.1	867 ± 49.1
V_{ss} [l]	509 ± 37.9	461 ± 22.5

Figure 1: Plasma concentration-time profiles of BIBR 277 SE in healthy male volunteers after administration of 80 and 120 mg (n = 4) as an intravenous infusion over 30 minutes



CONCLUSIONS: The results obtained from the study show that following intravenous administration of 80 and 120 mg telmisartan (Table 1):

(i) AUC and C_{max} increased in a dose-proportional manner.

(ii) Terminal $T_{1/2}$ ranged from 19.6 to 23.0 hours.

(iii) Plasma clearance ranged from 867 to 880 ml/min (exceeds maximum liver clearance of about 750 ml/min) while volume of distribution at steady state ranged from 461 to 509 liters (>10 times the approximate volume of total body water) thus indicating extensive protein and /or tissue binding .

SINGLE DOSE PHARMACOKINETICS

STUDY 502.101 **VOLUME: 1.084** **PAGES: 1 - 354**

INVESTIGATOR AND LOCATION:

STUDY DATE: June 29 to July 30, 1992

OBJECTIVES: The primary objective was the investigation of the tolerability and pharmacokinetics of the telmisartan in healthy volunteers.

FORMULATIONS:
Telmisartan Oral Solution , Formulation Codes PL302A1A - PL309A1A.
Placebo Solution, Formulation Codes PL302A0A.

STUDY DESIGN: A randomized, single blind, placebo controlled, oral dose-rising study in 32 healthy volunteers, 4 subjects per dose. At each dose level, one of the four volunteers was randomly assigned to receive placebo in a double-blind fashion. Eight dose levels ranging from 1 to 160 mg telmisartan solution were evaluated. Blood samples (approximately 5 ml) were taken at 0, 0.5, 1, 2, 6, 12 and 24 h for all dose groups but the 40 mg dose. At the 40 mg dose level, blood samples were taken at the following sampling points: 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 32 and 48 h postdose. Total urine was collected in fractions during the following time periods: 0 to 6 h, 6 to 12 h and 12 to 24 hours. Plasma samples and urine were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: AUC, Cmax, tmax, and $t_{1/2}$ were calculated.

RESULTS: Table 1 and Figure 1 summarize the data obtained from the study.

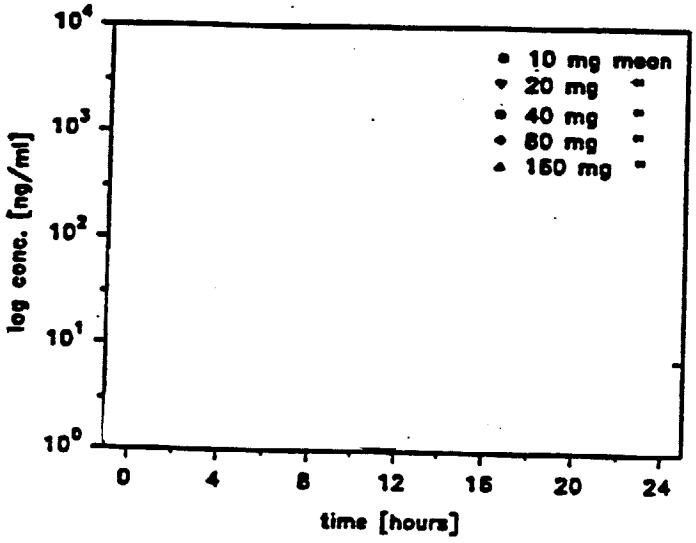
Table 1. Mean (SD) Parameter Values for Telmisartan Following Administration of Oral Solution to Healthy Volunteers

dose [mg]		C_{max} [ng/ml]	t_{max} [h]	$AUC_{0-24\ h}$ [ng·h/ml]	MRT [h]	CL/f [ml/min]	V_z/f [l]	$t_{1/2}$ [h]
2.5	mean	0.68	2.83	n.d.	n.d.	n.d.	n.d.	n.d.
	± SD	0.06	2.84	n.d.	n.d.	n.d.	n.d.	n.d.
5	mean	2.55	3.21	n.d.	n.d.	n.d.	n.d.	n.d.
	± SD	0.85	2.43	n.d.	n.d.	n.d.	n.d.	n.d.
10	mean	3.96	1.00	49.1	11.3	4536	2602	9.69
	± SD	2.75	0.87	37.8	8.16	4109	791	6.76
20	mean	15.5	1.50	91.4	11.4	3140	2403	9.50
	± SD	6.69	0.87	19.5	7.04	846	1308	6.17
40	mean	48.1	2.00	363	20.7	1301	1785	15.7
	± SD	21.3	0.00	96	4.06	352	613	3.37
80	mean	207	2.00	779	8.33	2744	1871	7.12
	± SD	157	2.60	752	1.30	2289	1902	1.54
160	mean	2268	0.50	3577	6.55	711	498	8.06
	± SD	1365	0.00	1179	2.77	205	151	0.15

n.d.: not determined

NB: Amount of free telmisartan excreted into urine after administration of 160 mg telmisartan was less than 0.01% of the dose and after glucuronidase/arylsulfatase treatment was less than 1% of the dose.

Figure 1: Plasma Concentration-Time Profiles of Telmisartan Following Administration of Oral Solution to Healthy Volunteers



CONCLUSIONS: The results obtained from the study show that following administration of 1 to 160 mg oral solution of telmisartan (Table 1):

(i) Telmisartan was rapidly absorbed with t_{max} ranging from 0.5 to 2.8 hours.
(ii) AUC and C_{max} increased in non-proportional manner with dose
(iii) Terminal $t_{1/2}$ ranged from 8.1 to 15.7 hours for the 10 to 160 mg dose range.

DOSE - RESPONSE STUDY

STUDY 502.103 **VOLUMES: 1.085 - 1.1086**

INVESTIGATOR AND LOCATION:

STUDY DATE: October 10 to December 3, 1993.

OBJECTIVES:

Primary: to determine the pharmacodynamic action of telmisartan at three dose levels after a single dose (with emphasis on attenuation of the blood pressure response to angiotensin II stimulation).

Secondary: to assess the pharmacokinetics and tolerability of telmisartan .

FORMULATIONS:

Telmisartan Oral Solution (0.4 mg per mL), batch No. 20815; treatment A
Telmisartan Oral Solution (0.8 mg per mL), batch No. 20816; treatment B
Telmisartan Oral Solution (1.6 mg per mL), batch No. 20817; treatment C
Matching Placebo solution (batch No. 20813); treatment P

STUDY DESIGN: A double-blind, placebo-controlled, randomized, parallel, single dose study in 48 helthy volunteers. 20, 40 or 80 mg telmisartan or placebo (treatments A, B, C and P, respectively) was given as a single dose after a ten-hour fast. On day -1 the test dose of angiotensin II was determined. This test dose of angiotensin II was defined as a dose giving approximately 30 mmHg increase in systolic blood pressure and was established by stepwise increasing the angiotensin II dose. This test dose was used for challenges performed before and at regular intervals for 48 h after medication intake. Blood pressure and pulse rate were measured continuously from 15 min before until 15 min after each challenge. Blood samples (approximately 5 ml) were taken at 0, 15, 30, 60, 90 min and 2, 4, 6, 8, 12, 24, 36 and 48 h after drug administration and for determination of renin activity, angiotensin II, noradrenaline and aldosterone in plasma at 0 (pre-dose), 0.5, 2, 4, 8, 24 and 48 h. Total urine was collected for determination of urinary flow and sodium, potassium and creatinine: -24--21, -21--18, -18--12, -12-0, 0-3, 3-6, 6-12, 12-24, 24-36, 36-48 h. Plasma samples and urine were stored at -20°C until analyzed.

ASSAY:

DATA ANALYSIS: $AUC_{0-\infty}$, C_{max}, t_{max}, E_{min}, t_{min}, E_{max}, E_{24}, t_{25}, AUEC (for diastolic pressure), k_{el} and $t_{1/2}$ were calculated.
To explore the pharmacodynamic-pharmacokinetic relationship hysteresis plots were constructed and individual data (effect versus concentration and AUEC versus $AUC_{0-\infty}$) were modelled according to the Hill sigmoid E_{max} equation.

RESULTS: Tables 1- 4 and Figures 1-12 summarize the data obtained from the study.The increase in disatolic pressure {Δ diastolic (%)} after angiotensin II infusion was considered the main pharmacodynamic assessment because beat to beat fluctuations were larger for mean arterial pressure (MAP), systolic pressure and pulse rate.

Table 1. Summary of Hill equation Parameters for %Inhibition of Diastolic Pressure versus Telmisartan Plasma Concentration (Treatments B & C)

Parameter	Estimate	95% Confidence Interval (asymptotic)
E_{max}	101	78 - 124
EC_{50}	12.2	1.8 - 22.7
γ	0.61	0.43 - 0.79

Table 2. Summary of Hill equation Parameters for AUEC versus $AUC_{0-\infty}$ (Treatments B & C)

Parameter	Estimate	95% Confidence Interval (asymptotic)
E_{max}	2919	844 - 4993
EC_{50}	229	-142 - 601
γ	1.00	-0.23 - 2.23

Table 3. Summary of the pharmacodynamic parameters of the diastolic blood pressure response to angiotensin II challenge as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)

P = placebo A = 20 mg B = 40 mg C = 80 mg

parameter	treatment	n	mean ± SD	median	range
E_{max} (%)	P	12	23.7 ± 10.4	21.0	7.1 - 42.2
	A	12	60.7 ± 14.9	61.6	30.2 - 80.2
	B	12	80.1 ± 9.5	80.3	64.7 - 100.0
	C	12	89.6 ± 15.4	96.3	49.4 - 100.0
t_{max} (h)	P	12	-	8.00	0.25 - 36.00
	A	12	-	5.00	1.00 - 48.00
	B	12	-	1.50	0.50 - 6.00
	C	12	-	1.00	0.50 - 2.00
E_{min} (%)	P	12	-23.9 ± 15.1	-20.2	-55.6 - -4.5
	A	12	-7.8 ± 26.4	-3.1	-57.4 - 24.8
	B	12	8.0 ± 14.7	11.4	-12.5 - 27.9
	C	12	10.6 ± 15.9	7.5	-15.6 - 39.0
AUEC (%.h)	P	12	61 ± 470	16	-819 - 710
	A	12	1220 ± 863	1551	-198 - 2504
	B	12	1801 ± 644	1888	348 - 2707
	C	12	2172 ± 595	2308	889 - 3056
E_{24} (%)	P	12	5.5 ± 13.0	3.8	-8.7 - 35.0
	A	11	18.7 ± 25.7	24.4	-34.6 - 43.6
	B	12	33.3 ± 19.3	33.6	-12.5 - 56.8
	C	11	41.3 ± 16.7	40.2	19.0 - 71.1
t_{onset} (h)	P	4	15.2 ± 13.8	14.7	0.4 - 31.3
	A	12	1.1 ± 1.3	0.7	0.2 - 4.9
	B	12	0.3 ± 0.2	0.3	0.1 - 0.8
	C	12	0.4 ± 0.2	0.3	0.1 - 0.8
t_{25} (h)	P	12	1.7 ± 3.0	0.0	0.0 - 9.0
	A	12	26.9 ± 18.2	29.6	2.2 - 47.7
	B	12	35.4 ± 13.1	35.4	5.2 - 47.9
	C	12	40.5 ± 13.1	47.3	10.2 - 47.9

Table 4. Summary of the pharmacokinetic parameters of the diastolic blood pressure response to angiotensin II challenge as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)

P = placebo A = 20 mg B = 40 mg C = 80 mg

parameter	treatment	n	geometric mean	median	range
c_{max} (ng.mL^{-1})	A	12	10.2	9.9	5.8 - 17.0
	B	12	46.0	47.2	21.7 - 108.0
	C	12	127.9	143.5	44.8 - 260.0
t_{max} (h)	A	12	-	1.75	0.25 - 6.00
	B	12	-	0.50	0.25 - 2.00
	C	12	-	1.00	0.50 - 1.00
k_el (h^{-1})	A	12	0.0454	0.0487	0.0272 - 0.0669
	B	12	0.0442	0.0462	0.0271 - 0.0595
	C	12	0.0424	0.0426	0.0296 - 0.0766
$t_{½}$ (h)	A	12	15.3	14.2	10.4 - 25.4
	B	12	15.7	15.0	11.7 - 25.6
	C	12	16.3	16.3	9.1 - 23.4
AUC_{0-24} (ng.mL^{-1}.h)	A	12	104.3	110.1	42.0 - 234.3
	B	12	314.7	321.4	113.7 - 690.9
	C	12	539.6	563.3	290.7 - 1291.3
$AUC_{0-\infty}$ (ng.mL^{-1}.h)	A	12	148.0	147.8	53.8 - 331.4
	B	12	426.6	403.3	182.3 - 974.9
	C	12	709.8	721.8	373.6 - 1759.0

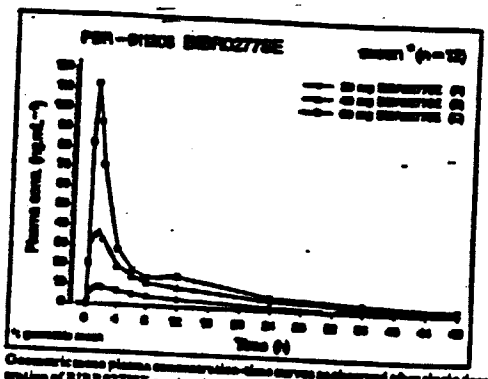


Figure 1 Geometric mean plasma concentration-time curves as observed after single dose administration of BIBR02778E or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

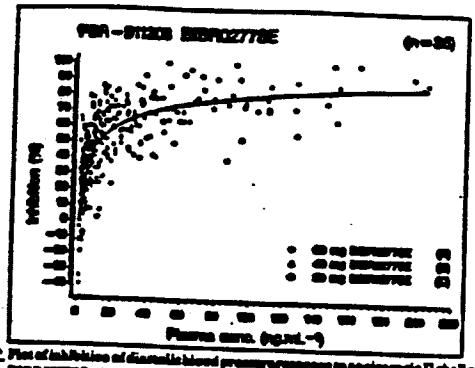


Figure 2 Plot of inhibition of diastolic blood pressure response to angiotensin II challenge versus BIBR02778E plasma concentrations as observed after single dose administration of BIBR02778E or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

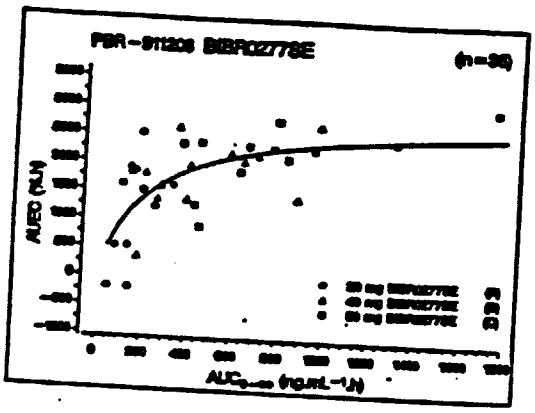


Figure 3 Plot of AUEC versus $AUC_{0-\infty}$ of BIBR02778E as observed after single dose administration of BIBR02778E or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

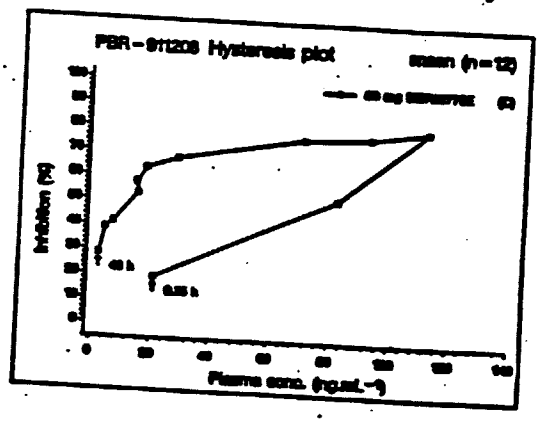


Figure 4 Plot of mean inhibition of diastolic blood pressure response to angiotensin II challenge versus geometric mean plasma concentrations of BIBR02778E at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36 and 48 h as observed after single dose administration of BIBR02778E or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

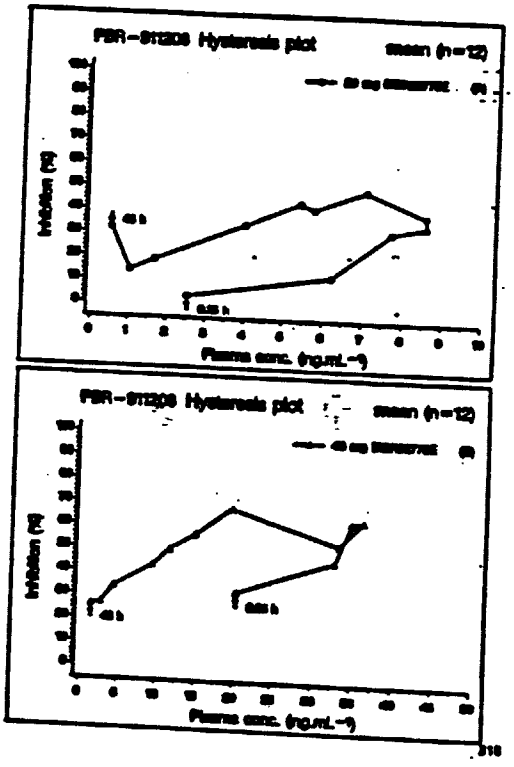


Figure 5 Plot of mean inhibition of diastolic blood pressure response to angiotensin II challenge versus geometric mean plasma concentrations of BIBR02778E at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36 and 48 h as observed after single dose administration of BIBR02778E or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

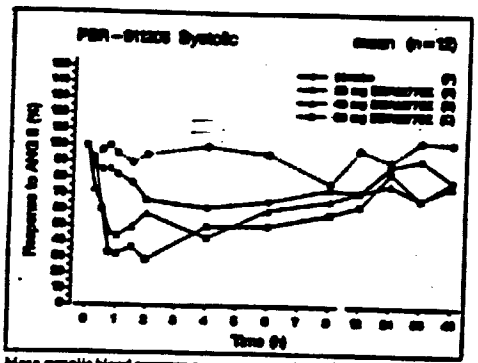


Figure 6 Mean systolic blood pressure response to angiotensin II challenge as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

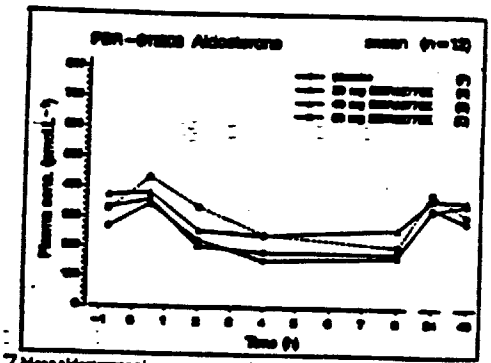


Figure 7 Mean aldosterone plasma concentrations as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

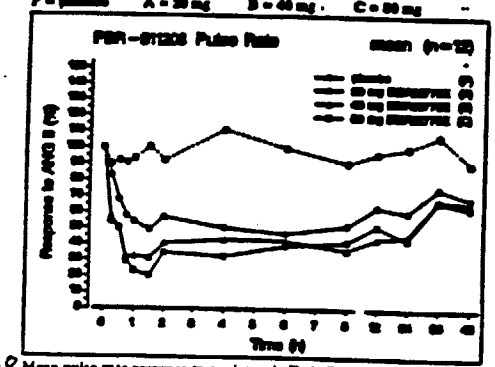


Figure 8 Mean pulse rate response to angiotensin II challenge as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

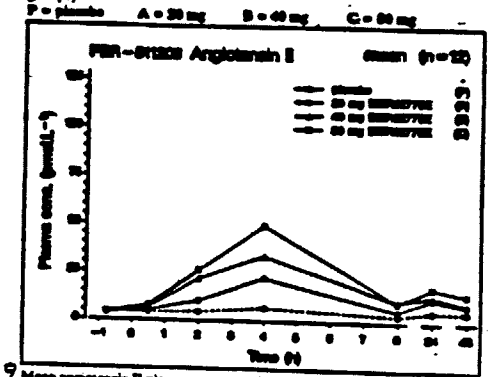


Figure 9 Mean angiotensin II plasma concentrations as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

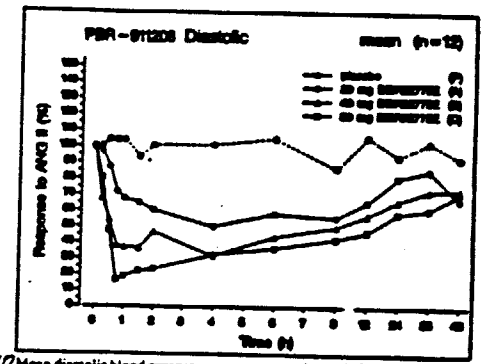


Figure 10 Mean diastolic blood pressure response to angiotensin II challenge as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

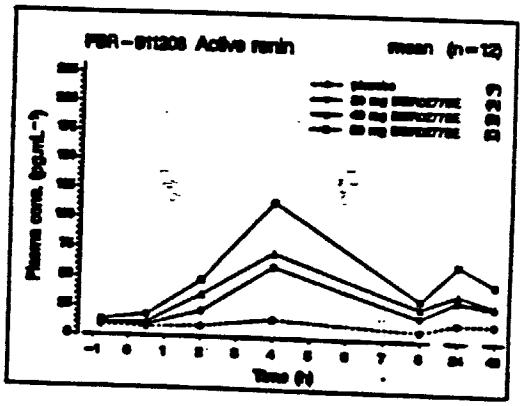


Figure 12 Mean data of active renin plasma concentrations as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

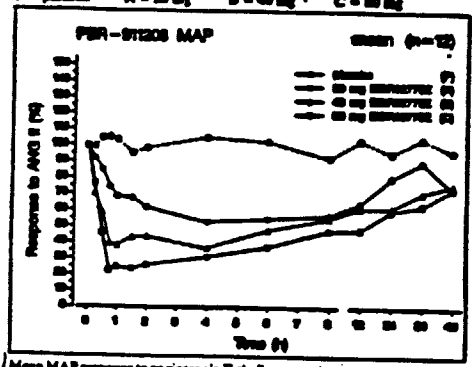


Figure 11 Mean MAP response to angiotensin II challenge as observed after single dose administration of BIBR0277SE or placebo as a drinking solution to 48 healthy male volunteers (4 parallel groups)
P = placebo A = 20 mg B = 40 mg C = 80 mg

CONCLUSIONS: The results obtained from the study show that:

1. Telmisartan dose-dependently inhibits the pressor and pulse rate response to angiotensin II infusion, with a virtually maximum inhibition of diastolic blood pressure already occurring at the middle dose level (40 mg). The inhibitory effect has a fast onset of action and a long duration of action and once daily treatment seems feasible.
2. As a compensation for the angiotensin II receptor blockade a rise in angiotensin II and active renin plasma concentrations is observed, whereas aldosterone concentrations remain unaffected.
3. The pharmacokinetics of telmisartan demonstrate a non-linearity, which is most prominent for c_{max}.
4. A hyperbolic pharmacodynamic-pharmacokinetic relationship is observed which can be described with the Hill equation.

SINGLE DOSE PHARMACOKINETICS

STUDY 502.105 **VOLUME: 1.090** **PAGES: 1 - 318**

INVESTIGATOR AND LOCATION:

STUDY DATE: March 1993.

OBJECTIVES: To investigate the tolerability and pharmacokinetics of an i. v. infusion over 30 minutes of 10, 20 and 40 mg telmisartan in healthy volunteers.

FORMULATIONS: Telmisartan injection (40 mg/ampoule), Pharmaceutical code ANT 0301A1A, Charge No 30106.
Placebo injection, Pharmaceutical code ANT 0301A0A Charge No 30105.

STUDY DESIGN: An open, group comparison, rising dose study with placebo randomized double blind in each dose group. Three groups of six healthy male volunteers were administered a single dose of telmisartan (10, 20 or 40 mg) or placebo formulated as an aqueous solution containing mannitol, hydrochloric acid (gaseous) and sodium hydroxide as excipients. The placebo formulation contained mannitol only. In each group, four volunteers were at random allocated to receive active drug and two volunteers to receive placebo. The doses were administered as an intravenous infusion over a time of 30 min. Blood samples of 5 ml volume were collected from all volunteers at baseline (pre-dose) and at 5, 7.5, 10, 15, 20, 25, 29 min during infusion and 1, 3, 6, 9, 15, 30, 45 min, 1, 1.25, 1.5, 2.5, 3.5, 6.5, 8.5, 12.5, 24.5 and 48.5 h after dosing. Plasma samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: $AUC_{0-\infty}$, C_{max}, t_{max}, $C_{(0.5h)}$ extr. and $AUD_{0-6.5h}$ Cmax, MRT, Tmax, $t_{1/2}$, Vss, V_z and CL_{tot} were calculated.

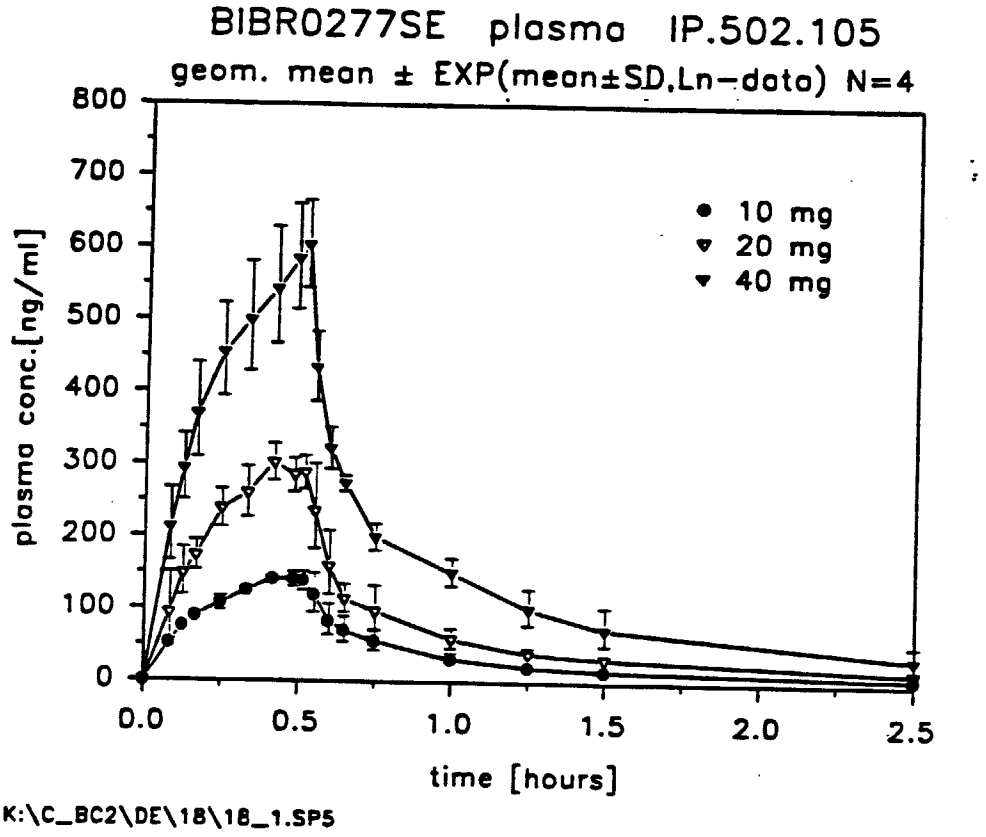
RESULTS: Table 1 and Figure 1 summarize the pharmacokinetic data obtained from the study.

Table 1: Summary of Pharmacokinetic Parameters (means ± % coefficient) for Telmisartan Following a 30 Minute Infusion to Healthy Volunteers

	dose	10 mg	20 mg	40 mg
parameter	unit	mean ± CV%	mean ± CV%	mean ± CV%
C_{max}	[ng/ml]	151 ± 5.27	310 ± 7.57	618 ± 10.5
$t_{1/2}$	[h]	n.a.	n.a.	18.6 ± 11.6
$AUD_{0\text{-}6.5h}$	[ng · h/ml]	126 ± 15.7	241 ± 4.17	544 ± 17.6
$AUC_{0\text{-}\infty}$	[ng · h/ml]	n.a.	n.a.	781 ± 34.9
$AUC_{tl\text{-}\infty}$	(%)	n.a.	n.a.	8.31 ± 14.7
$MRT_{0\text{-}\infty}$	[h]	n.a.	n.a.	10.2 ± 51.1
MRT_{disp}	[h]	n.a.	n.a.	9.93 ± 52.4
CL_{tot}	[ml/min]	n.a.	n.a.	942 ± 36.3
V_z	[l]	n.a.	n.a.	1485 ± 30.2
V_{ss}	[l]	n.a.	n.a.	483 ± 20.6

n.a.: not applicable

Figure 1: Plasma concentration-time profiles of telmisartan in healthy male volunteers after administration of 10, 20 and 40 mg (n = 4) as an intravenous infusion over 30 minutes. Data points represent geometric means ± exp(mean ± SD, ln.-data).



CONCLUSIONS: The results obtained from the study show that :

(i) Pharmacokinetics of telmisartan i. v. infusions were dose proportional over the dose range of 10 to 40 mg .

(ii) After i. v. infusions of 10 and 20 mg telmisartan plasma concentrations were below LOQ after 6.5 and 12.5 hours.

After i. v. infusion of 40 mg dose terminal $T_{1/2}$ was 18.6 hours, total clearance was 942 ml/min, V_z was 1485 liters and V_{ss} was 483 liters.

PHARMACOKINETICS STUDY IN HYPERTENSIVE PATIENTS

STUDY 502.201 **VOLUMES: 1.138 - 1.150**

INVESTIGATOR AND LOCATION:

STUDY DATE: November 1992 - May 1993.

OBJECTIVES: To define the efficacy (dose response), tolerability and pharmacokinetics of 7 day treatment with 10, 20, 40, 60, 80, 100, 120 and 160 mg telmisartan once daily in patients with mild to moderate hypertension.

FORMULATIONS: Telmisartan Solution
Placebo Solution

STUDY DESIGN: A group comparison, open rising dose study with placebo and active control. The patients of each dose group were at random allocated to receive either telmisartan (N = 6) , placebo or enalapril (N = 2 each). In total 80 patients were treated with 10 patients per dose group. Plasma levels of telmisartan were determined at the following time points: on day 1 before administration and 0.25, 0.5, 1, 1.5, 2, 3, 6, 8, 12, 16, 20 and 24 hours after administration of the test drug. During days 2 to 6, plasma levels were determined each day before administration and 1 h after administration. On day 7, plasma levels of telmisartan were determined at the following time points: before administration and at 0.25, 0.5, 1, 1.5, 2, 3, 6, 8, 12, 16, 20, 24, 32 and 48 hours after administration of the test drug. Plasma samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: $C_{max,day\ 1}$, $C_{max,ss}$, t_{max}, $AUC_{day\ 1}$ and AUC_{ss} (in the steady state interval 144-168 h) were calculated.

RESULTS : Tables 1 - 2 and Figures 1 - 4 summarize the pharmacokinetic data obtained from the study.

Table 1: Summary of Pharmacokinetic Parameters (means ± CV %) for Telmisartan Following Oral Administration on Day 1 and at Steady State

dose	C_{max}	$C_{max,ss}$	$AUC_{day\ 1}$	AUC_{ss}	$t_{max,ss}$ *	R_A (AUC)
[mg]	[ng/ml]	[ng/ml]	[ng·h/ml]	[ng·h/ml]	[h]	
10	8.94 ± 44	12.89 ± 36	81.77 ± 52	152.9 ± 47	2.0 (0.25 , 2.0)	2.0
20	29.7 ± 47	46.3 ± 59	276.1 ± 42	527.5 ± 56	2.0 (1.50 , 2.0)	1.8
40	70.4 ± 45	88.2 ± 44	485.5 ± 47	729.1 ± 47	1.5 (0.50 , 2.0)	1.5
60	159 ± 33	328 ± 41	1249 ± 38	2556 ± 43	0.51 (0.25 , 1.0)	2.0
80	366 ± 50	601 ± 84	1044 ± 38	2248 ± 81	0.50 (0.50 , 0.50)	2.0
100	767 ± 56	1041 ± 27	2284 ± 37	3403 ± 33	0.50 (0.50 , 0.50)	1.5
120	1131 ± 57	2017 ± 21	2946 ± 26	5743 ± 41	0.50 (0.25 , 1.0)	1.9
160	1520 ± 47	2871 ± 85	3177 ± 57	5357 ± 72	0.50 (0.25 , 0.50)	1.6

* median (min , max)

The accumulation ratio, $R_A = AUC_{ss} / AUC_{day\ 1}$.

Table 2: Summary table (mean ± CV%) of $t_{1/2}$, MRT_{ss}, V_z/f and Cl_{tot}/f at day 7

dose	$t_{1/2}$	MRT_{ss}	Cl_{tot}/f	V_z/f
[mg]	[h]	[h]	[ml/min]	[l]
10	25.23 ± 18	40.13 ± 8.5	1307 ± 44	2956 ± 66
20	27.77 ± 34	39.80 ± 30	917.6 ± 71	2043 ± 66
40	36.94 ± 58	39.94 ± 53	1396 ± 101	2589 ± 70
60	55.32 ± 82	50.48 ± 60	468.2 ± 49	2969 ± 118
80	26.75 ± 51	27.34 ± 30	982.1 ± 84	1779 ± 51
100	43.11 ± 77	29.81 ± 76	557.4 ± 46	1789 ± 55
120	23.13 ± 23	21.30 ± 39	410.8 ± 47	784.2 ± 41
160	18.37 ± 32	18.59 ± 27	1148 ± 99	1817 ± 106

Figure 1: Individual plasma concentration-time plots of BIBR0277SE in mild to moderate hypertensive patients during administration of 10 mg BIBR0277SE once daily for seven days. Day 1 and day 7. Geometric mean indicated by solid

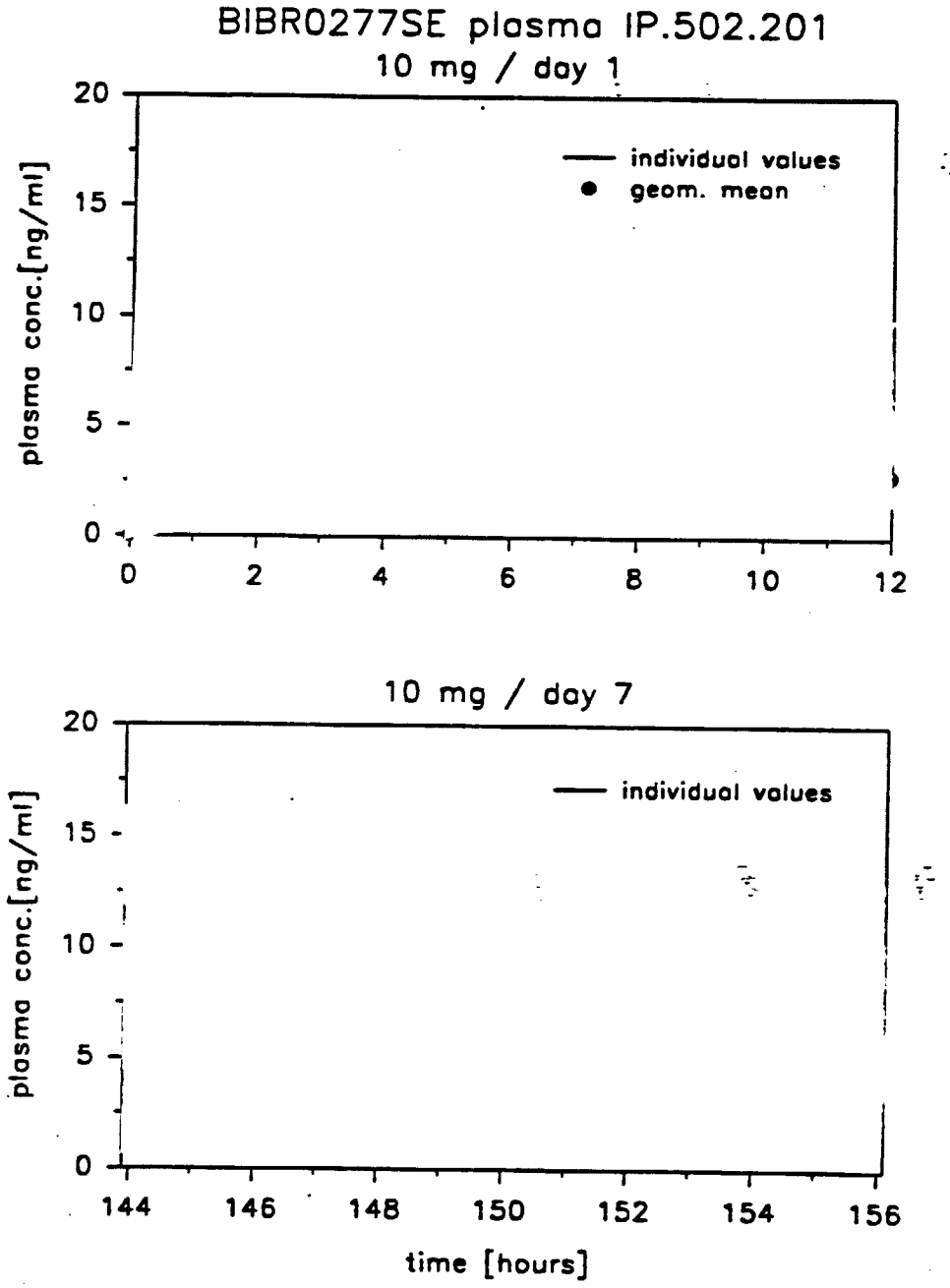


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Figure 2: Individual plasma concentration-time plots of BIBR0277SE in mild to moderate hypertensive patients during administration of 120 mg BIBR0277SE once daily for seven days. Day 1 and day 7. Geometric mean indicated by solid

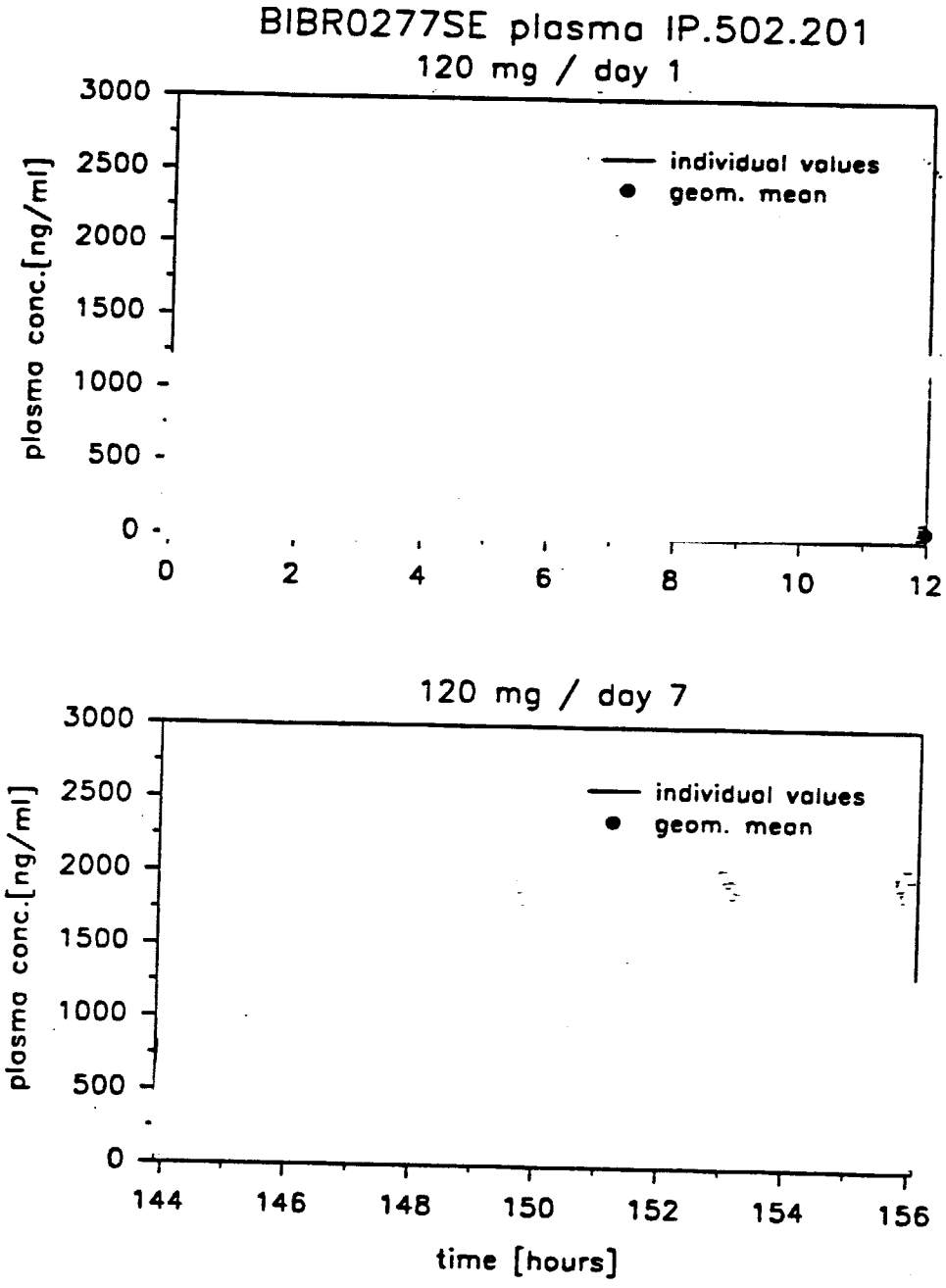

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Figure 3: Individual trough levels after administration of 10 mg (upper figure) and 20 mg BIBR0277SE to mild to moderate hypertensive patients.

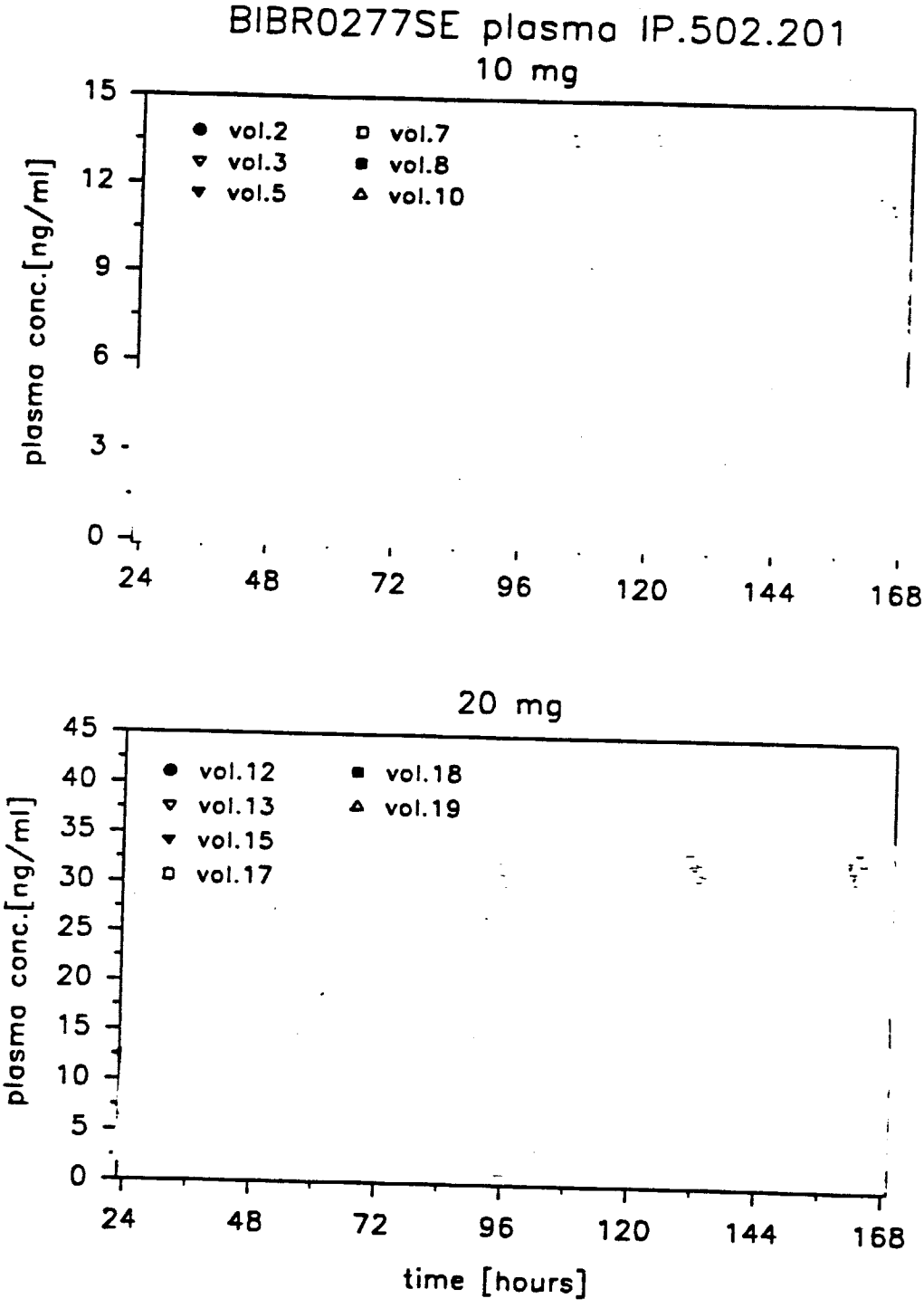

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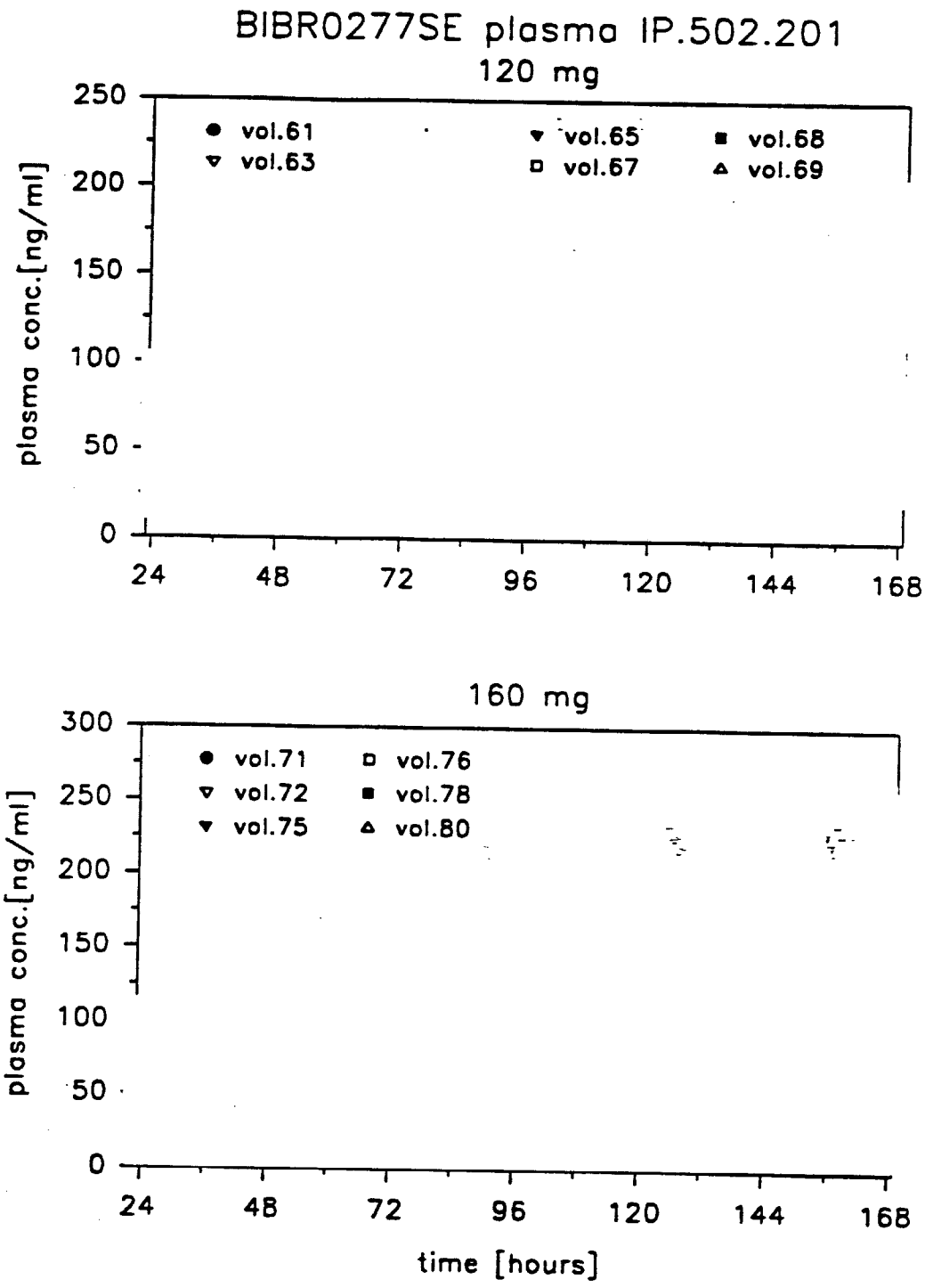
Figure 4: Individual trough levels after administration of 120 mg (upper figure) and 160 mg BIBR0277SE to mild to moderate hypertensive patients. Patient ID 80 was excluded from further treatment after 96 h due to increasing blood pressure.



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CONCLUSIONS: The results obtained from the study show that :

1. Administration of telmisartan as a solution resulted in a rapid and nonproportional increase in C_{max} with a very high variability within the dose . There is also a nonproportional increase in AUC_{ss} and $AUC_{day\ 1}$ with dose.
2. Administration of repeated doses of telmisartan over a one week period did not result in plasma level accumulation factors greater than 2.
3. Despite a long terminal half-live of the drug and persistent drug levels in plasma, telmisartan is cleared rapidly from the circulation.
4. It is estimated that with a once daily dose regimen steady state will be reached not before day 5 in most patients and that with some patients, it will need even longer to attain steady state conditions.
5. The mean terminal half-life after multiple dosing over a period of seven days ranged from 18 h to 55 h and was independent of dose.

PHARMACOKINETICS STUDY IN HYPERTENSIVE PATIENTS

STUDY 502.203 **VOLUMES: 1.164 - 1.171**

INVESTIGATOR AND LOCATION:

STUDY DATE : January to July, 1995.

OBJECTIVES: To evaluate the efficacy and safety of telmisartan 20, 40, 80, 120 and 160 mg, q.d. in comparison to placebo and to assess the dose-response relationship in patients with mild-to-moderate hypertension.

FORMULATIONS: Telmisartan Tablet, 20, 40 and 80 mg (Lots PD-1464 - 1466)
Matching Placebo (Lots PD-1467 - 1469)

STUDY DESIGN: This study consisted of a four-week Placebo Run-In Period, a four-week Double-Blind Period and a one-week Post Double-Blind Period (washout, at four centers). Eligible patients were randomized to: placebo, or telmisartan 20, 40, 80, 120, or 160 mg q.d. Trough blood pressures (BP) and heart rates (HR) were measured weekly in the Placebo Run-In and Double-Blind Periods, and daily during the Post Double-Blind Period. To assess the 24-hr BP effect, supine and standing BP and HR were measured hourly for 12 hrs and then again at 24 hrs post-dose at baseline and at the end of the Double-Blind Period. Plasma samples for telmisartan concentrations were obtained prior to the first double-blind dose, and at one hour after the dose on Days 1, 7, and 28 of the Double-Blind Period. Plasma samples were collected once daily during washout. Plasma samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: C_{1h}, C_{min}, $t_{1/2}$ were calculated.

The sigmoidal E_{max} equation was used to model the change from baseline in DBP (treated as a positive number) as a function of the plasma telmisartan concentration:

$$E = \frac{E_{max} \cdot C^n}{(EC_{50})^n + C^n}$$

where E is the effect (DBP reduction), E_{max} is the maximum effect attributable to the drug, C is the plasma telmisartan concentration, EC_{50} is the plasma telmisartan concentration producing 50% of the maximal effect, and n is the sigmoidicity factor that influences the shape of the curve.

RESULTS : Tables 1 - 5 and Figures 1- 5 summarize the pharmacokinetic / pharmacodynamic data obtained from the study.

TABLE 1. Descriptive Statistics for Telmisartan C_{min} (ng/mL) on Day 28 by Gender

Telmisartan		Female			
		Arithmetic	Geometric		
Dose (mg)	N	Mean	Mean	gCV(%)	Median
20	13	16.49	13.60	70.85	13.45
40	15	35.18	26.97	88.21	21.76
80	12	125.31	67.61	139.63	53.01
120	14	145.43	82.90	173.64	101.91
160	12	137.67	95.18	118.80	103.31
		Male			
		Arithmetic	Geometric		
Dose (mg)	N	Mean	Mean	gCV(%)	Median
20	29	14.34	9.97	112.30	10.83
40	31	34.17	25.17	90.55	25.75
80	28	70.03	43.27	139.98	40.74
120	29	94.80	50.88	138.78	51.89
160	31	141.57	99.87	111.31	119.71

gCV geometric coefficient of variation

TABLE 2. Descriptive Statistics for Day 28 $C_{1\ hr}$ (ng/mL) by Gender

Telmisartan Dose (mg)	Female				
	N	Arithmetic Mean	Geometric Mean	gCV(%)	Median
20	12	32.81	30.00	50.11	33.28
40	14	167.25	121.12	95.72	97.46
80	12	971.08	718.88	91.45	752.98
120	14	1496.20	805.09	282.75	1176.36
160	12	2905.69	2220.44	99.85	2529.50
Dose (mg)	Male				
	N	Arithmetic Mean	Geometric Mean	gCV(%)	Median
20	29	28.12	24.29	58.07	21.90
40	30	107.07	78.73	92.40	74.21
80	27	391.01	248.40	162.78	333.55
120	29	969.74	584.24	155.47	683.81
160	31	1685.42	1095.87	175.16	1429.03

gCV geometric coefficient of variation

TABLE 3. Descriptive Statistics for Telmisartan $t_{1/2}$ (hr)

Telmisartan Dose (mg)	Arithmetic Mean	N	%CV	Geometric Mean	Median
20	37.72	8	28.46	36.43	37.58
40	29.26	12	33.06	27.96	27.12
80	33.38	11	30.82	31.60	34.98
120	25.28	13	26.70	24.42	23.57
160	27.89	13	34.72	26.23	28.06

TABLE 4. Parameter Estimates for the Sigmoidal E_{max} Model for Responders

Dose Group	Parameter	Estimate	Approx. S.E.	Approx. P > |T|
20 mg	E_{max} (mmHg)	19.8	2.84	0.0001
	EC_{50} (ng/mL)	3.53	1.70	0.0016
	Sigmoidicity factor	1.17	0.51	0.0252
20 and 40 mg	E_{max} (mmHg)	18.7	2.30	0.0001
	EC_{50} (ng/mL)	2.32	0.93	0.0133
	Sigmoidicity factor	0.74	0.34	0.0333

TABLE 5. Mean Observed E_{max} on Day 28 for All Patients

Dose Group (mg)	Mean Observed E_{max} (mmHg)	S.D.	N
20	16.9	6.1	39
40	18.8	8.4	44
80	18.9	6.7	39
120	20.6	9.0	43
160	21.0	9.7	42
All	19.3	8.2	207

FIGURE 1. Telmisartan Trough Concentration as Geometric Means on Days 2, 7, 28 and 29 (Double-Blind Period) for All Patients Who Received Telmisartan

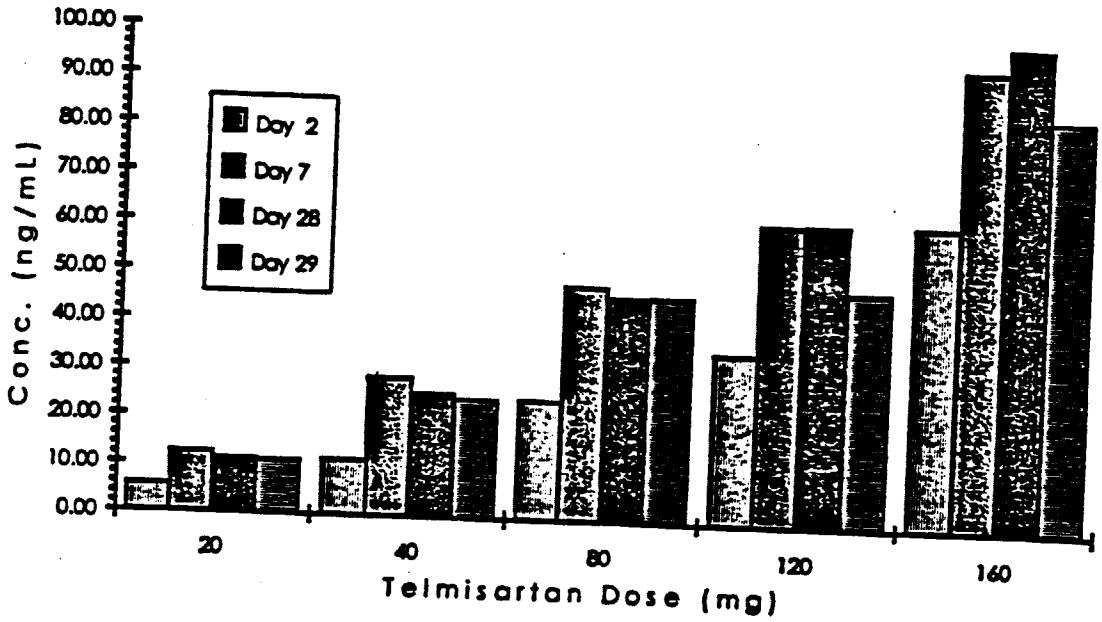

FIGURE 2. Sigmoidal E_{max} Model for Supine DBP Reduction and Telmisartan Plasma Concentration as Observed in Responder Patients in the 20 mg Dose Group (Solid Line: Fitted Line, Dotted Lines: Approximate 95% Confidence Bands,*: Observed Data)

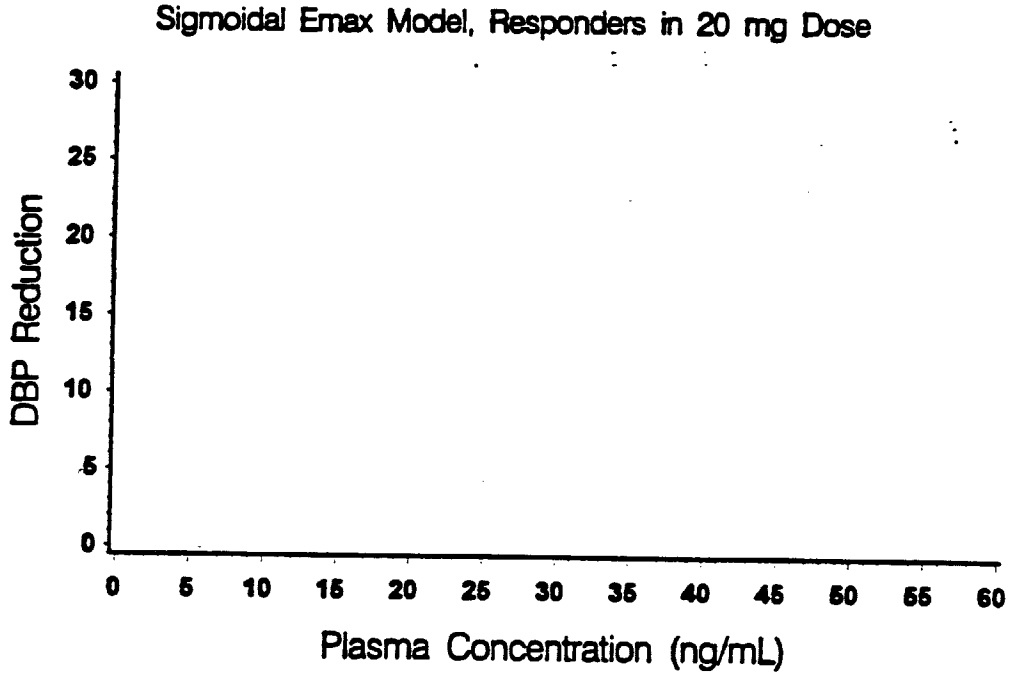

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FIGURE 3. Sigmoidal E_{max} Model for Supine DBP Reduction and Telmisartan Plasma Concentration as Observed in Responder Patients in the Pooled 20-mg and 40-mg Dose Groups (Solid Line: Fitted Line, Dotted Lines: Approximate 95% Confidence Bands,*: Observed Data)

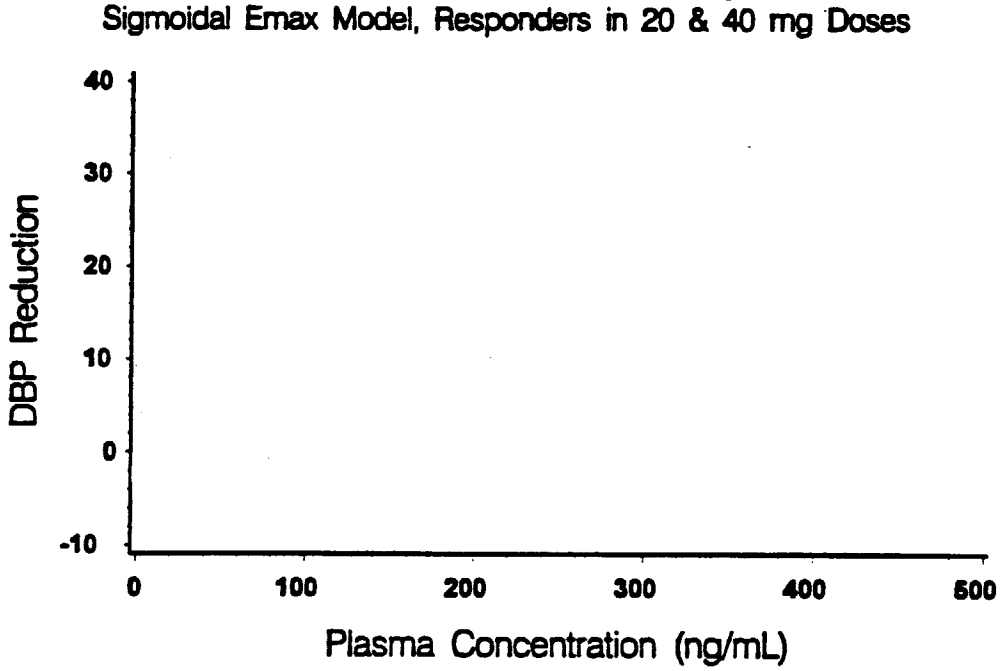


FIGURE 4 Comparisons of C_{min} on Day 28 Between Gender for Each Telmisartan Dose Group

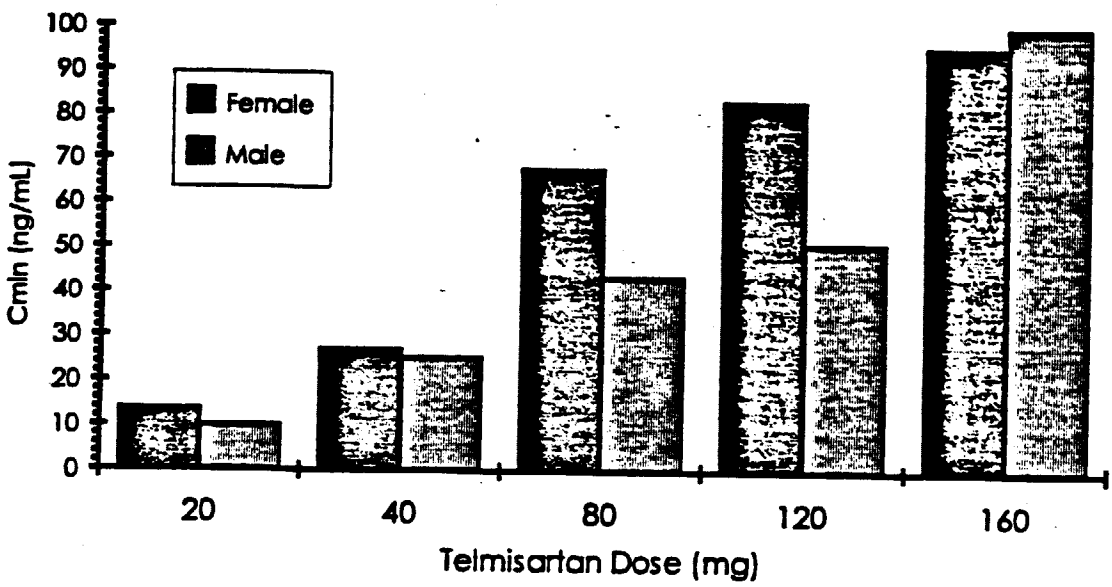
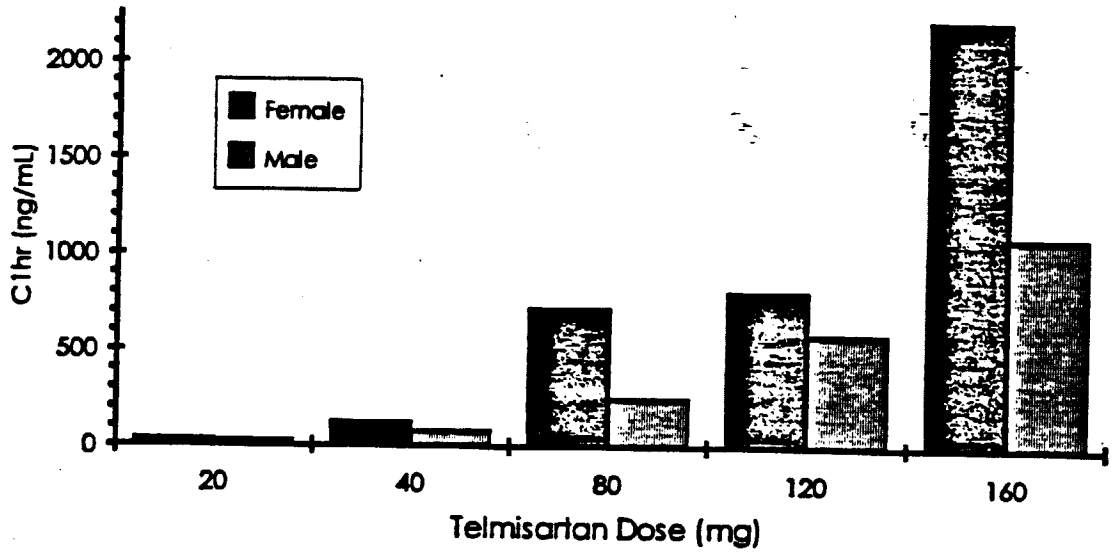


FIGURE 5. Comparison of One-Hour Telmisartan Concentration on Day 28 by Gender



CONCLUSIONS: The results obtained from the study show that:

1. Mean plasma telmisartan concentrations (Cp) at trough appeared to be dose proportional whereas, mean one-hour Cp were more than proportional to dose. High interpatient variability was observed for trough Cp (coefficient of variation >65%).
2. Telmisartan mean elimination half life ranged from 25.3 to 37.7 hours with no apparent dose-response relationship. The trough concentrations on Day 29 along with additional concentrations from study centers participating in the washout period were used to calculate the elimination half life of telmisartan.
3. When considering all patents who received telmisartan, no strong relationship was found between effect (supine DBP reduction) and plasma telmisartan concentration. For responders (defined as having supine DBP ≥10 mmHg reduction and/or trough ≤ 90 mmHg) in the 20 mg dose group and in the pooled 20 mg and 40 mg dose groups, a sigmoidal E_{max} model best described the relationship between the supine diastolic blood pressure lowering effect and plasma telmisartan concentration; the respective estimated E_{max} (maximal effect) was 19.8 and 18.7 mmHg, and the respective EC_{50} (concentration at half maximal effect) was 3.53 and 2.32 ng/mL.
4. Independent of dose, females tended to have higher plasma concentrations than males.

PHARMACOKINETICS STUDY IN HYPERTENSIVE PATIENTS

STUDY 502.202 **VOLUMES: 1.150 - 1.156**

INVESTIGATOR AND LOCATION:

STUDY DATE : August 30 1993 to March 31, 1994.

OBJECTIVES: The objective of this study was to assess the dose response relationship of the antihypertensive effect of telmisartan over the dose range of 40 to 120 mg and to identify doses of telmisartan which, administered once daily, lowered diastolic blood pressure at the end of the dosing interval when compared with placebo after 28 days of dosing. A related objective was to assess the safety of telmisartan over this dose range relative to placebo and enalapril 20 mg. Evaluation of the pharmacokinetics and pharmacodynamics of telmisartan following the 4-week treatment in these hypertensive patients was also planned

FORMULATIONS: Telmisartan Tablet, 40, 80 and 120 mg (Lots PD-1326 , PD-1327)
Matching Placebo (Lots PD-1323 , PD-1329, PD-1328)

STUDY DESIGN: This study was designed as a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study. After a 4-week placebo run-in period, patients were randomized to one of five treatment groups (placebo, enalapril 20 mg or telmisartan 40, 80 or 120 mg). Study drug was administered once daily in the morning for 4 weeks. To assess the antihypertensive effects of telmisartan over a 24-hour period, supine and standing blood pressures and heart rate were measured at baseline (Day 0), Day 1 and Day 28 of dosing approximately hourly for 12 hours and then again at 24 hours post-dosing. Trough blood pressure and heart rate were also measured on Days 7, 14 and 21. Serial blood samples for the determination of plasma telmisartan concentrations were collected following the last dose administration of Day 28. Pre-dose and 30 minute post-dose samples were also collected on Days 1, 7, 14, 21 and 28.

ASSAYS:

DATA ANALYSIS: $AUC_{0-\tau}$, $C_{30\,min}$, C_{max}, Cmin , t_{max}, $t_{1/2}$, and CL/F were calculated.

The plasma concentration-effect relationship was assessed by correlating:

- the trough plasma concentration with the change from baseline in trough supine diastolic (or systolic) blood pressure on Day 28 (Eff_{min}). Eff_{min} was calculated as the average of the pre-dose and 24-hour post-dose trough measurements.
- the observed peak plasma concentration (C_{max}) to the maximum decrease (Eff_{max}) from baseline for supine diastolic (or systolic) blood pressure on Day 28.
- $AUC_{0-\tau}$ with the time-integrated-area-under-the-effect vs time curve ($AUEC_{0-24\ hr}$).

These correlations were assessed using linear regression with untransformed and log transformed data.

RESULTS : Tables 1-9 and Figures 1- 2 summarize the pharmacokinetic / pharmacodynamic data obtained from the study.

Table 1. Pharmacokinetic Parameters (Mean ± SD) Following the three Doses on Day 28

Dose	Kel	$C_{max,ss}$	$t_{max,ss}$	$t_{½}$	$AUC_{0-\tau}$	CL/F
mg	hr^{-1}	ng/mL	hr	hr	hr·ng/mL	L/hr/lb
40	0.034 ±0.0223	159 ± 104	1.6 ± 1.0	25.2 ± 11.3	1655 ± 1169	0.226 ± 0.183
80	0.038 ± 0.016	693 ± 606	1.3± 1.3	21.6 ± 11.1	3728 ± 3356	0.230 ± 0.186
120	0.040 ± 0.021	1635 ± 1406	1.4 ± 1.5	21.8 ± 13.0	5657 ± 4578	0.209 ± 0.143

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TABLE 2. Mean ± SD for Pharmacokinetic Parameters by Race

Parameter	White (N=78)	Hispanic (N=24)	Black (N=10)	Other (N=2)
$AUC_{0-\tau}$ /Dose	33.7 ± 24.4	78.6 ± 47.1	54.9 ± 40.8	34.3 ± 11.7
C_{max}/Dose	6.4 ± 6.6	13.6 ± 11.1	15.3 ± 13.0	5.1 ± 2.5
$t_{1/2}$	23.3 ± 13.3	20.8 ± 5.2	21.2 ± 5.4	39.3 ± 24.5

Table 3. Mean ± SD for Pharmacokinetic Parameters for All Males and Females

Parameter	Males (N = 69)	Females (N = 45)	Female/Male Ratio
$AUC_{0-\tau}$ /Dose	37.6 ± 27.8	56.4 ± 44.8	1.50
C_{max}/Dose	6.4 ± 5.9	12.3 ± 11.6	1.92
$t_{1/2}$	21.7 ± 11.4	24.6 ± 12.4	1.13

Table 4. Mean ± SD (Median) for Pharmacokinetic Parameters for White Males and Females

Parameter	Males (N = 52)	Females (N = 26)	Female/Male Ratio
$AUC_{0-\tau}$ /Dose	32.5 ± 23.1	36.0 ± 27.3	1.11
	(24.9)	(27.3)	(1.10)
C_{max}/Dose	5.65 ± 5.27	8.05 ± 8.66	1.42
	(3.9)	(4.7)	(1.21)
$t_{1/2}$	21.6 ± 12.9	26.7 ± 13.8	1.24
	(20.3)	(24.3)	(1.20)

TABLE 5. Mean ± SD (Median) for Pharmacokinetic Parameters for Hispanic Males and Females

Parameter	Males (N = 12)	Females (N = 12)	Female/Male Ratio
$AUC_{0-\tau}$ /Dose	53.7 ± 23.7	103.5 ± 50.3	1.93
	(60.6)	(110.6)	(1.83)
C_{max}/Dose	7.6 ± 3.9	19.7 ± 12.7	2.59
	(7.5)	(21.6)	(2.88)
$t_{1/2}$	22.2 ± 4.9	19.5 ± 5.4	0.90
	(22.9)	(20.1)	(0.88)

TABLE 6. Mean ± SD (Median) for Pharmacokinetic Parameters for Black Males and Females

Parameter	Males (N = 5)	Females (N = 5)	Female/Male Ratio
$AUC_{0-\tau}$ /Dose	51.2 ± 54.5	58.6 ± 27.3	1.14
	(27.5)	(72.4)	(2.63)
C_{max}/Dose	10.9 ± 12.5	19.6 ± 13.4	1.80
	(9.0)	(18.7)	(2.08)
$t_{1/2}$	22.3 ± 5.8	20.0 ± 5.3	0.88
	(21.9)	(18.9)	(0.86)

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TABLE 7. Mean Trough Concentrations of Telmisartan[1]

Telmisartan Dose	Mean ± SD	%CV	Median	Range
40 mg	47.0 ± 38.5	82	32	5- 143
80 mg	70.4 ± 49.2	70	57	11- 217
120 mg	98.1 ± 65.6	67	80	17- 270

[1] Trough computed as the average of values collected pre-dose on Days 7, 14, 21, 28 and the estimated value for Day 29 (extrapolated 24-hour concentration for Day 28). Patients with two or more missing trough concentrations were not included in this analysis.

Units are ng/mL.

TABLE 8. Mean ± SD for $AUC_{0-\tau}$ and $AUEC_{0-24\ hr}$ for DBP and SBP

Dose Group	$AUC_{0-\tau}$ (ng • hr/mL)	SBP $AUEC_{0-24\ hr}$ (mm Hg x hr)	DBP $AUEC_{0-24\ hr}$ (mm Hg x hr)
Placebo	-	81 ± 248	80 ± 167
40 mg	1655 ± 1169	360 ± 270*	258 ± 207*
80 mg	3728 ± 3356	351 ± 211*	242 ± 161*
120 mg	5657 ± 4579	319 ± 258*	232 ± 167*
Enalapril	-	343 ± 280*	279 ± 183*

* Statistically significantly different from placebo group at $p<0.05$ (Tukey's multiple comparison test)

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TABLE 9 Adjusted Mean Changes in Supine Blood Pressure, by Race-Gender Subgroup and Treatment[1]

Variable	Race-Gender	No. Pts.[2]	Plac.	Telmisartan (mg) 40	80	120	Enal. 20 mg
Diastolic	Black Males	11	+5.5	-	-1.3	-2.7	-5.7
	Black Females	8	-1.2	-	-1.6	-3.4	-
	Hispanic Males	22	-2.2	-7.3	-4.5	-5.1	-3.7
	Hispanic Females	19	-3.8	-10.0	-9.2	-10.7	-12.2
	White Males	94	-2.6	-8.2	-10.7	-11.2	-10.4
	White Females	48	-1.9	-6.8	-12.4	-10.8	-8.8
Systolic	Black Males	11	+18.4	-	-0.9	-4.1	-2.2
	Black Females	8	+4.4	-	-10.8	+1.9	-
	Hispanic Males	22	-3.9	-9.4	-16.3	+4.4	-6.3
	Hispanic Females	19	+3.9	-22.8	-18.6	-15.4	-10.2
	White Males	94	+2.4	-9.7	-10.5	-18.0	-10.9
	White Females	48	+1.7	-6.5	-23.1	-5.8	-7.9

1 Means are adjusted for the effects of baseline response and body mass index. Units are mm Hg.

2 Five patients of 'other' race are not included in this table.

Figure 1. Mean Plasma Telmisartan Concentration Profiles and Change in DBP in Patients on Day 28

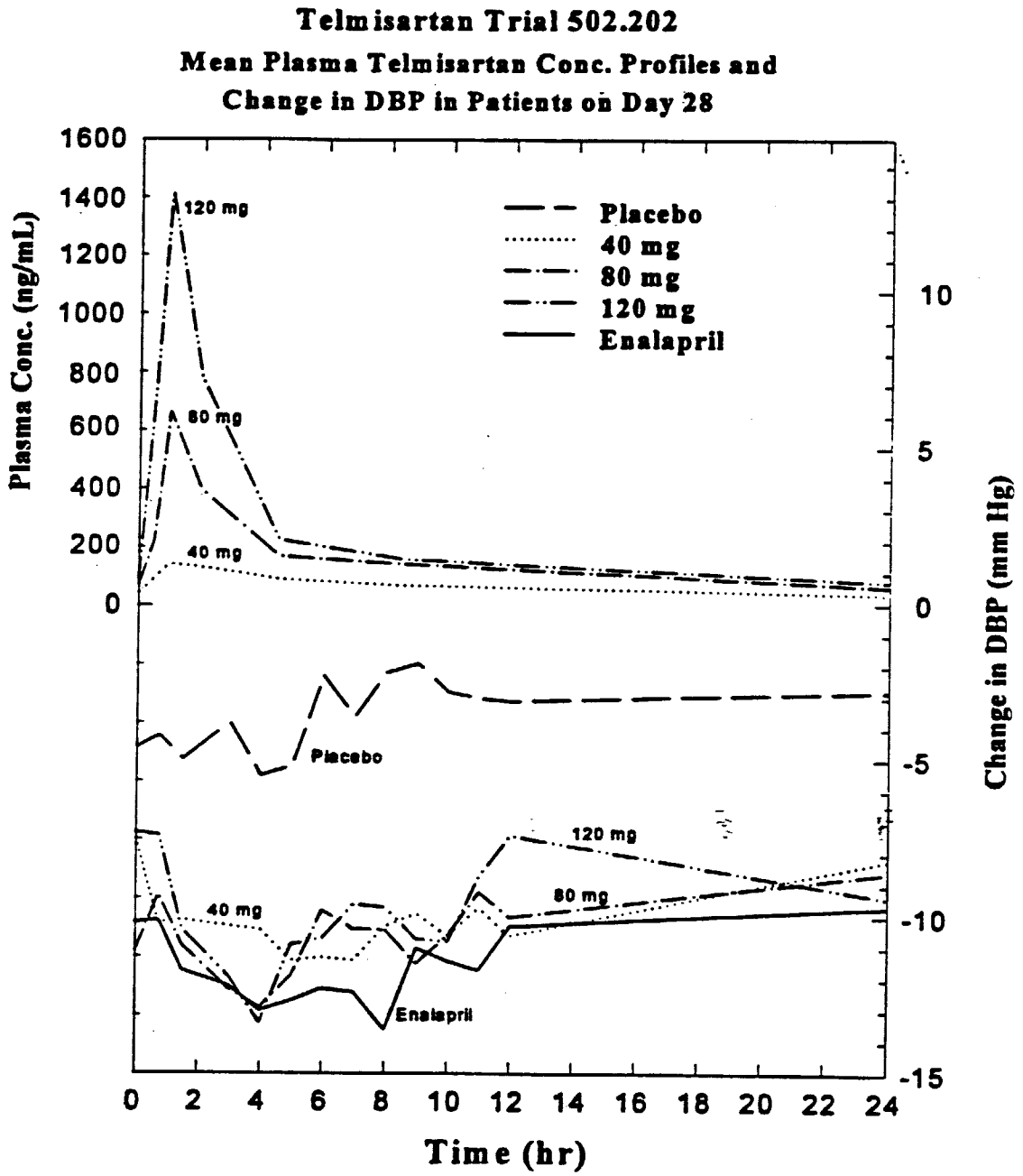
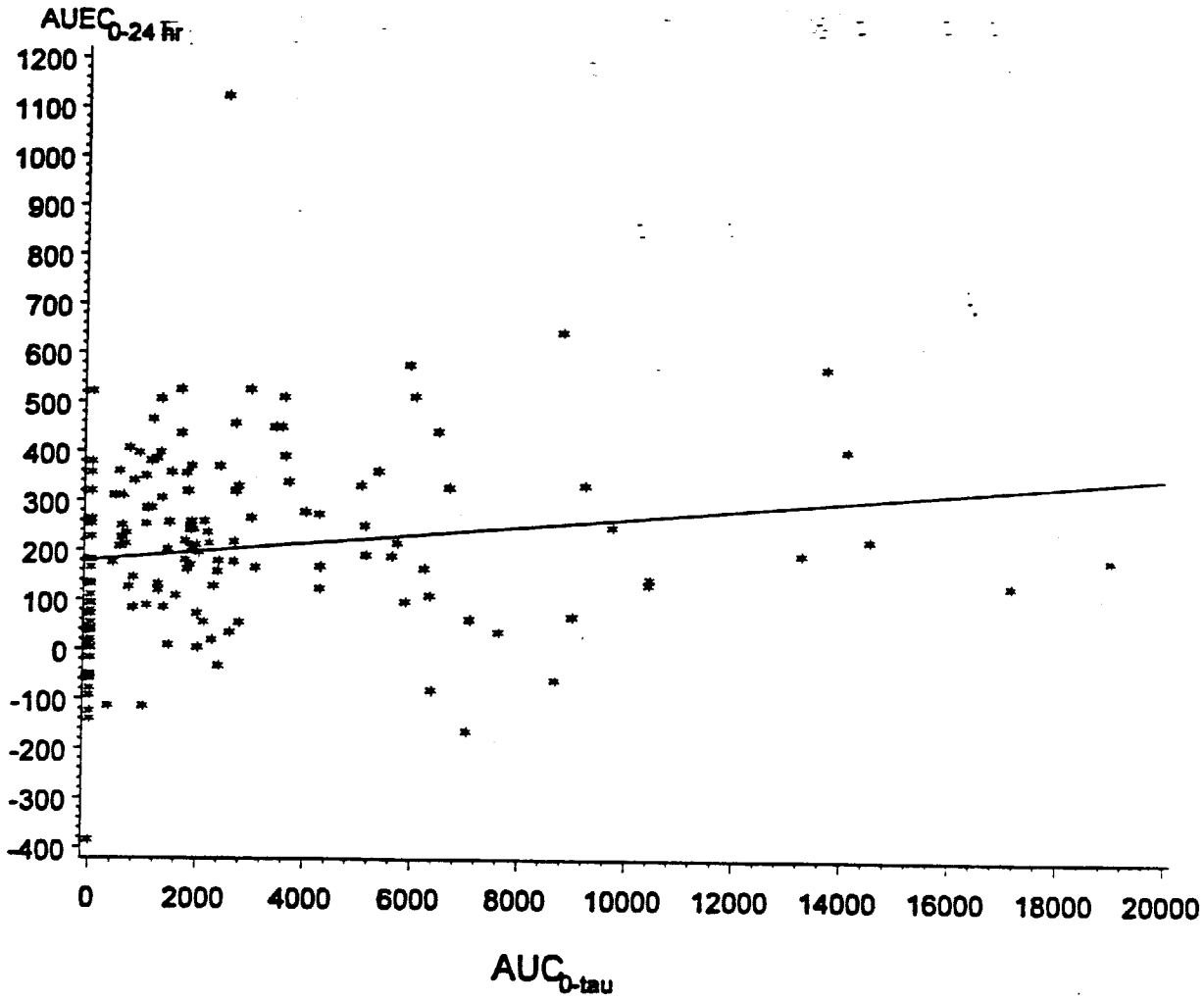


FIGURE 2 Plot of $AUEC_{0\text{-}24\ hr}$ for DBP vs $AUC_{0\text{-}\tau}$ on Day 28



CONCLUSIONS: The results obtained from the study show that:

1. Mean telmisartan Cmax and AUC were more than proportional to dose with about 10-fold increase in Cmax and 3.4-fold increase in AUC for a 3-fold increase in dose. High interpatient variability was observed in telmisartan plasma concentrations.
2. Telmisartan mean elimination half life ranged from 21.6 to 25.2 hours with no apparent dose-response relationship.
3. Steady state concentrations were achieved within seven days and steady state trough levels increased 2-fold with a 3-fold increase in dose.
4. There are gender and race differences in the disposition of temilsartan. Hispanics and Blacks generally had 2 to 3-fold higher mean Cmax, Cmin, and AUCs compared to

Whites. Females had higher plasma mean concentrations compared to males. Mean peak diastolic or systolic effect did not correspond with the mean peak plasma telmisartan concentration in any of the three dose groups (Figure 1) and there were no corresponding increases in mean peak effect with many fold increase in mean telmisartan plasma concentrations. Weak correlations were observed between plasma levels and effects and the concentration-effect relationship showed that at the three dose levels (40, 80 and 120 mg) were near the plateau region of the dose-response curve.

5. There are appears to be both gender and race differences in the effect of temilsartan on supine blood pressure (Table 9) with females showing greater effect and males and Hipanics showing greater effect than Blacks and Whites.

MULTIPLE DOSE PHARMACOKINETICS

STUDY 502.115 **VOLUME: 1.091** **PAGES: 1 - 382**

INVESTIGATOR AND LOCATION:

STUDY DATE: DECEMBER 1993.

OBJECTIVES: To investigate the safety and tolerability as well as pharmacokinetics of 320 mg BIBR 277 SE administered once daily over 7 days in healthy volunteers.

FORMULATIONS: Telmisartan Tablet (80 mg), Pharmaceutical code
BIBR 277 SE TA 030 2A 1A
Placebo injection, Pharmaceutical code BIBR 277 SE TA 030 2A 0A

STUDY DESIGN: The study was performed in a single-center, placebo-controlled, randomized, double blind parallel-group design with twelve (12) volunteers. Ten of them received telmisartan (4 x 80 mg), the remaining two volunteers received placebo. The study drug was applied once daily for a time period of seven (7) days. Blood samples for determination of content of telmisartan in plasma were taken before and after each drug administration, respectively more frequently after first and last administration of the study drug. Plasma samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

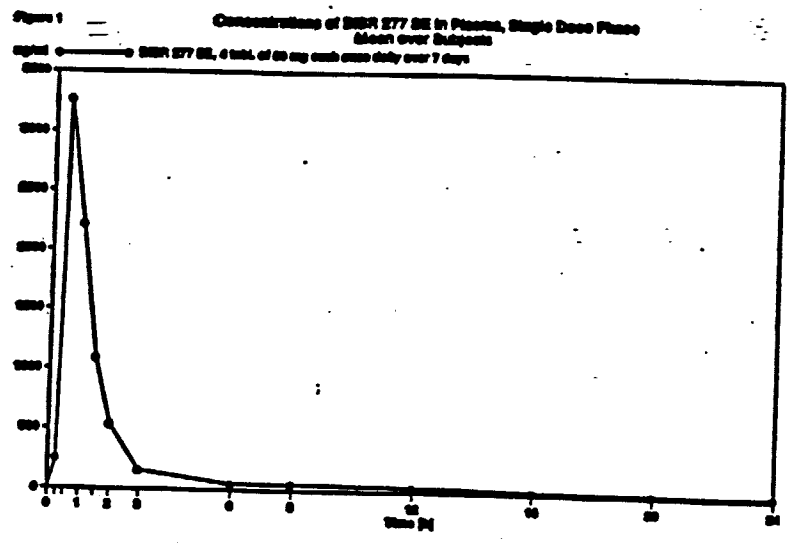
DATA ANALYSIS: AUC_{day1}, AUC_{SS}, $C_{max,\ day1}$, $C_{max,\ SS}$, R_A, $t_{1/2}$, MRT, V_Z/f, $CL_{(tot)}/f$, t_{max} and $t_{max,\ SS}$ were calculated.

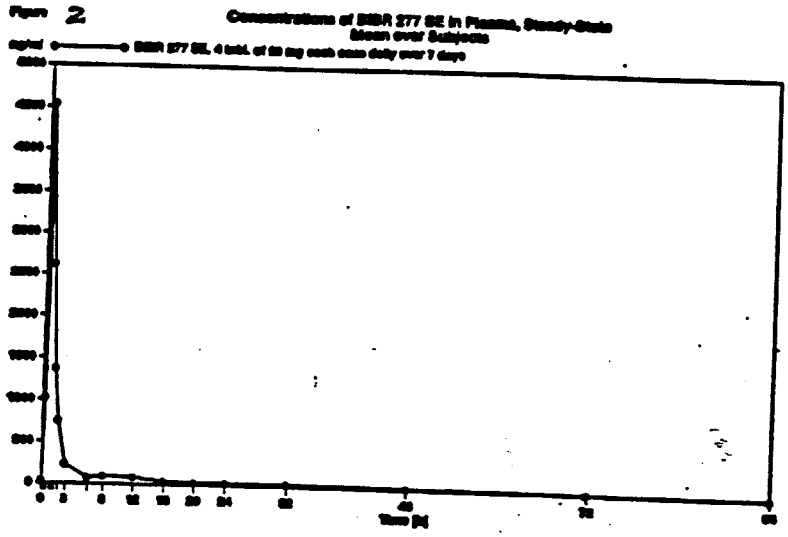
RESULTS: Table 1 and Figures 1-2 summarize the pharmacokinetic data obtained from the study.

Table 1: Summary of pharmacokinetic parameters (Mean ± SD%) for telmisartan following oral administration of 320 mg tablet healthy volunteers

Parameter	Day 1	Day 7
C_{max} [ng/ml]	3338.2 ± 1954.4	4640.6 ± 2618.6
Cmin [ng/ml]	-	26.5 ± 23.4
t_{max} [h]	0.65 ± 0.24	0.60 ± 0.21
$t_{1/2}$ [h]	-	25.3 ± 10.1
AUC_{0-24} [ng · h/ml]	4288.2 ± 2290.6	-
$AUC_{0-\infty}$ [ng · h/ml]	4285.2± 2295.5	-
AUC_{ss} [ng · h/ml]	-	6123.6 ± 3189.3
MRT_{tot} [h]	-	7.6 ± 2.7
CL/F [ml/min]	-	1390.2 ± 1349.7
Vz/F (l)	-	1821.1 ± 1217
λ_z	-	0.025 ± 0.016
R_A	-	1.55 ± 0.46

The accumulation ratio, $R_A = AUC_{ss} / AUC_{day\ 1}$





CONCLUSIONS: The results obtained from the study show that following oral administration of 320 mg telmisartan (Table 1) maximum concentrations were achieved within 1 hour and then declines exponentially with a half-life of about 25 hours. The acculation index is about 1.5 after 7 doses (similar to that in Study 502.201).

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 502.102 **VOLUME: 1.087** **PAGES: 1 - 349**

INVESTIGATOR AND LOCATION:

STUDY DATE : January - February 1993.

OBJECTIVES: The primary objective was the assessment of the relative bioavailability of a capsule compared to the γ-cyclodextrin solution.

FORMULATIONS:

Pharmaceutical codes and batch numbers of the formulation:

Pharmaceutical code	batch-No.	Formulation
PL 30 6A 1A LO 30 1A 0A	21218 21002	20 mg solution
PL 30 9A 1A LO 30 1A 0A	21217 21015	160 mg solution
KAH 30 2B1A	21225	20 mg capsule
KAH 30 1A 1A	21114	80 mg capsule

STUDY DESIGN: The study was designed as a randomized, open 4-way cross over study with 12 healthy male volunteers per dose group and formulation (either 20 mg or 160 mg). The reference was a freshly prepared drinking solution containing the excipient γ–cyclodextrin and the test formulations were telmisartan capsules (20 mg and 80 mg). Blood samples of 5 ml volume were collected from all volunteers at baseline (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48 and 72 h after dosing. Plasma samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: AUC_{0-12h}, $AUC_{0-\infty}$, Cmax, MRT_{tot} and tmax were calculated.

RESULTS: Tables 1-3 and Figure 1 summarize the data obtained from the study.

Table 1: AUC_{0-12h}, C_{max}, t_{max} and MRT values of 20 mg telmisartan (mean ± % CV) of solution and capsule

parameter	unit	solution mean ± % CV	capsule mean ± % CV
AUC_{0-12h}	[ng·h/ml]	96.1 ± 52.2	116 ± 65.8
C_{max}	[ng/ml]	12.8 ± 44.2	15.3 ± 61.5
t_{max}	[h]	3.88 ± 57.7	4.00 ± 52.2
MRT_{tot}	[h]	18.9 ± 75.0	22.6 ± 62.9

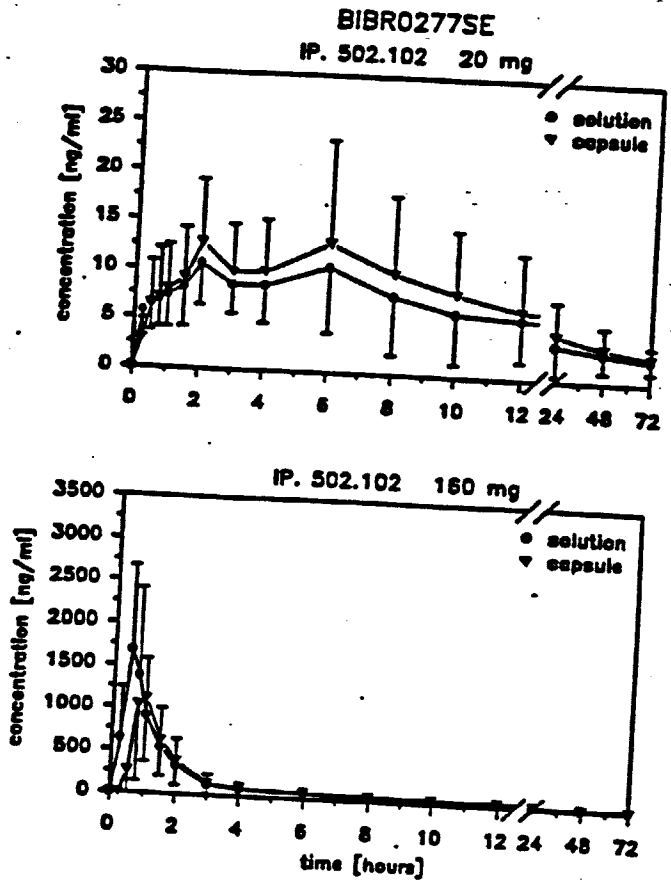
Table 2: $AUC_{0-\infty}$, C_{max}, t_{max} and MRT values of 160 mg telmisartan (mean ± %CV) of solution and capsule.

parameter	unit	Solution mean ± % CV	capsule mean ± % CV
$AUC_{0-\infty}$	[ng·h/ml]	3410 ± 72.4	3000 ± 69.1
C_{max}	[ng/ml]	1920 ± 51.9	1370 ± 55.8
t_{max}	[h]	0.50 ± 21.3	0.85 ± 31.7
MRT_{tot}	[h]	13.0 ± 63.5	13.1 ± 41.7

Table 3: Relative Bioavailability: (test/reference) Statistical analysis of AUC_{0-oo} and C_{max} levels.

Parameter	comparison	20 mg		160 mg	
		point estimate	confidence interval [90 %]	point estimate	confidence interval [90 %]
AUC	Anova	120.55	102.61 - 138.48	88.07	78.07 - 98.07
	Wilcoxon	113.37	102.62 - 126.95	90.15	85.18 - 97.26
$C_{max,}$	Anova	119.21	99.97 - 138.46	71.26	57.24 - 85.27
	Wilcoxon	109.34	101.32 - 123.50	69.55	58.50 - 87.59

Figure 1: Mean Plasma Concentration-Time Profiles of Telmisartan After Administration a 20 mg and 160 mg Dose as Solution and Capsules (Mean ± SD).



CONCLUSIONS: The results obtained from the study showed that:

1. With the 20 mg capsule, the ratios (test/reference) for the parameters C_{max} and $AUC_{0\text{-}12h}$ were 1.19 and 1.21. The ratios for C_{max} and $AUC_{0\text{-}oo}$ at 160 mg were 0.71 and 0.88.
2. There is a nonlinear increase in C_{max} and AUC with dose for both formulation.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 502.106 **VOLUME: 1.096** **PAGES: 1 - 348**

INVESTIGATOR AND LOCATION:

STUDY DATE : November - December, 1995

OBJECTIVES: The objective was the assessment of absolute and relative bioavailability of 40 mg telmisartan given as a 30-minute i. v.-infusion, single doses oral solution and tablet in healthy volunteers.

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A 1A
Telmisartan Solution (40 mg/24 ml), Pharmaceutical codes BIBR 277 SE PL 030 7A 1A, BIBR 277 SE LO 030 1A 0A
Telmisartan injection (40 mg/10 ml), Pharmaceutical code BIBR 277 SE AMT 030 1A 1A.

STUDY DESIGN: The study was designed as a randomized, open 3-way cross over study with 12 healthy male volunteers. Each subject was administered single doses of telmisartan (40 mg) formulated as a tablet , as 30 minute intravenous infusion and as an oral solution. Blood samples were withdrawn at the following time points: For the oral administrations (solution and tablet): before administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48 and 72 hours after administration of the drug. For the 30 minute infusion: before administration and during the infusion period at 0.0833, 0.125, 0.167, 0.250, 0.333, 0.417, 0.483 h, as well as at 0.517, 0.550, 0.600, 0.650, 0.750, 1.0, 1.25, 1.5, 2.5, 3.5, 6.5, 8.5, 12.5, 24.5, 48.5 and 72.5. Plasma samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: $AUC_{0-\infty}$ and C_{max}, t_{max}, MRT, Cl_{tot}, $t_{1/2}$, V_z/f, V_{ss} and V_z were calculated.

RESULTS: Tables 1-4 and Figure 1 summarize the data obtained from the study.

Table 1: Summary table of pharmacokinetic parameters of telmisartan after intravenous administration of 40 mg.

ampoule i.v.			arithm.		geom.		
parameter	unit	N	mean	% CV	mean	min	max
C_{max}	ng/ml	12	634	19.0	623	471	820
t_{max}	h	12	0.489	7.61	0.488	0.417	0.517
$C_{0.5\ (extr.)}$	ng/ml	12	756	22.1	740	539	1110
$t_{½}$	h	12	24.2	41.4	22.6	13.5	45.7
$AUC_{0-48.5h}$	ng·h/ml	12	667	21.8	653	448	897
$AUC_{0-\infty}$	ng·h/ml	12	726	24.3	706	454	1030
$AUC_{t_f-\infty}$	%	12	4.94	68.7	3.49	0.400	10.8
MRT_{tot}	h	12	11.7	43.0	10.4	3.49	19.3
MRT_{disp}	h	12	11.5	43.9	10.1	3.24	19.0
CL_{tot}	ml/min	12	970	24.7	944	647	1470
V_z	l	12	2040	49.9	1850	1020	3920
V_{ss}	l	12	620	36.9	574	228	978

Table 2: Summary table of pharmacokinetic parameters of telmisartan after administration of 40 mg as an oral solution.

solution p.o.			arithm.		geom.		
parameter	unit	N	mean	% CV	mean	min	max
C_{max}	ng/ml	12	38.5	56.4	34.8	21.6	101
t_{max}	h	12	1.38	49.3	1.17	0.250	2.00
$t_{½}$	h	12	22.7	37.7	21.7	15.5	46.7
AUC_{0-48h}	ng·h/ml	12	364	80.8	285	101	1130
$AUC_{0-\infty}$	ng·h/ml	12	428	82.1	334	149	1340
$AUC_{t_f-\infty}$	%	12	8.32	69.0	6.92	2.91	22.9
MRT_{tot}	h	12	22.6	37.0	21.5	14.7	45.1
CL_{tot}/f	ml/min	12	2430	57.4	2000	498	4460
V_z/f	l	12	5060	92.0	3740	894	18000

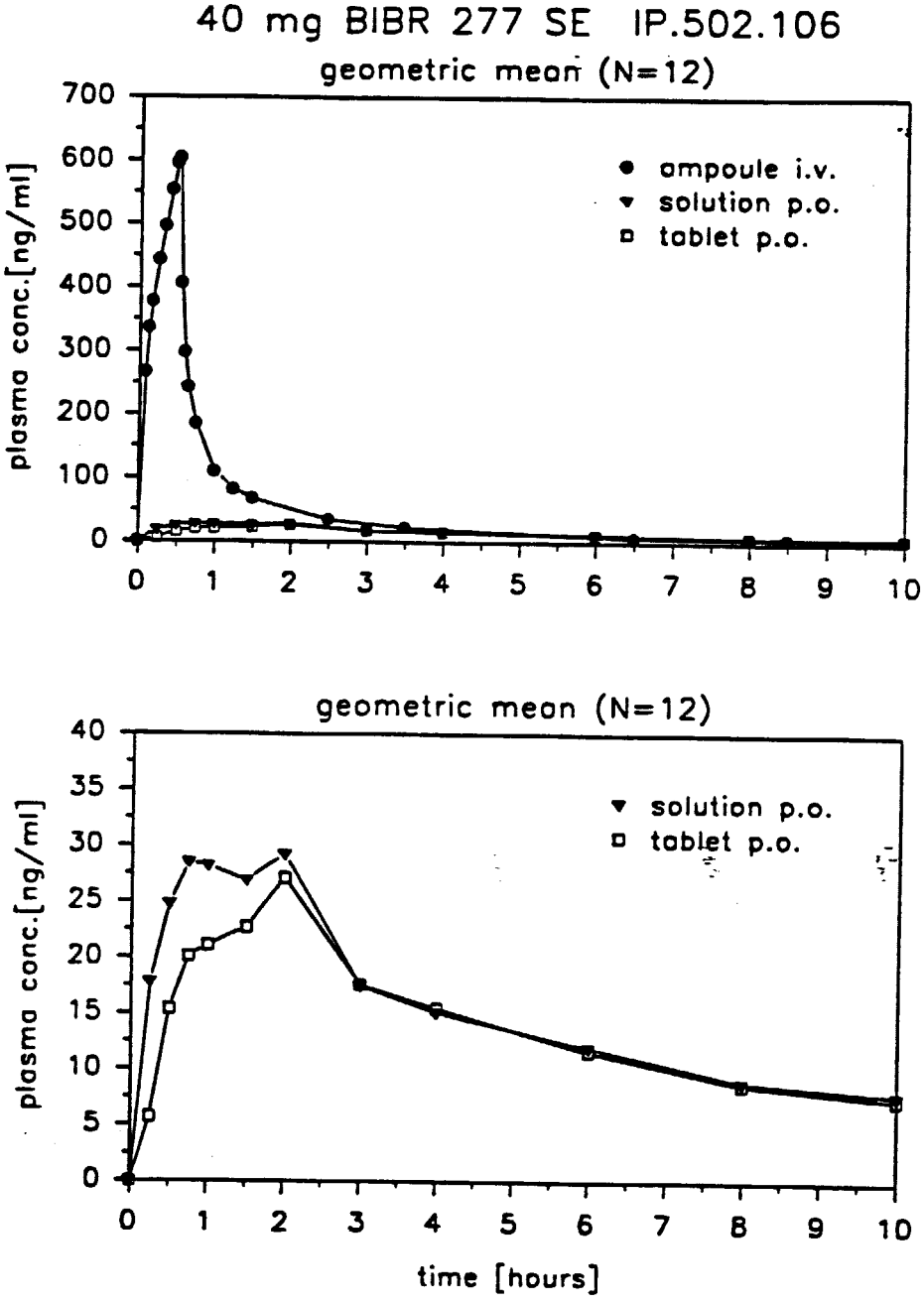
Table 3: Summary table of pharmacokinetic parameters of telmisartan after administration of a 40 mg tablet.

tablet p.o.			arithm.		geom.		
parameter	unit	N	mean	% CV	mean	min	max
C_{max}	ng/ml	12	32.1	44.9	29.5	14.3	67.1
t_{max}	h	12	1.75	27.9	1.66	0.750	2.00
$t_{½}$	h	12	19.6	36.8	18.6	9.92	36.4
AUC_{0-48h}	ng·h/ml	12	305	55.8	260	88.9	574
$AUC_{0-\infty}$	ng·h/ml	12	360	61.5	299	111	726
$AUC_{t_z-\infty}$	%	12	8.79	65.0	6.67	1.70	17.2
MRT_{tot}	h	12	21.3	34.8	20.2	11.8	37.6
CL_{tot}/f	ml/min	12	2670	61.4	2230	919	5980
V_z/f	l	12	4490	84.9	3580	1520	15300

Table 4: Absolute and relative bioavailability (test/reference ratios of the $AUC_{0-\infty}$) for the tablet, the oral solution, and the intravenous infusion

test	reference	alpha-level	lower limit	point estimator	upper limit
solution p.o.	ampoule i.v.	0.05	0.353	0.473	0.634
tablet p.o.	ampoule i.v.	0.05	0.316	0.424	0.569
tablet p.o.	solution p.o.	0.1	0.703	0.896	1.143

Figure 1: Mean (geometric mean) plasma concentration-time profiles of BIBR 277 SE after administration of a 40 mg dose either as oral solution, tablet or intravenous infusion. The plasma concentration - time profiles observed with the oral dosage forms are shown at a different y-axis scale in the lower figure



CONCLUSIONS: The results obtained from the study showed that:

1. The absolute bioavailability of the 40 mg tablet was therefore 42.4 %.
2. The absolute bioavailability of the solution was 47.
3. The relative bioavailability of the tablet compared to the solution of 89.7 % .

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 502.109 **VOLUME: 1.089** **PAGES: 1 - 346**

INVESTIGATOR AND LOCATION:

STUDY DATE : May - June, 1993.

OBJECTIVES: The objective was the assessment of the relative bioavailability of a tablet compared to the capsule.

FORMULATIONS: Pharmaceutical codes and lot numbers of the formulationa are:

Pharmaceutical code	lot-No.	Formulation
TA 30 1A 1A	30416	20 mg tablet
KAH 30 1A 1A	30403	80 mg capsule
TA 30 2A 1A	30430	80 mg tablet

STUDY DESIGN: The study was designed as a randomized, open 3-way cross over study with 12 healthy male volunteers with one week washout period. Each subject was administered single doses of telmisartan capsule (80 mg, reference formulation), telmisartan tablet (80 mg , test formulation) and telmisartan tablet (20 mg , test formulation). Plasma samples of approximately 5 ml volume were collected from all volunteers at baseline (pre-dose) and at 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 24 h after dosing and were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: $AUC_{0-\infty}$ and C_{max} , t_{max}, MRT, Cl_{tot}, $t_{1/2}$, V_z/f, V_{ss} and V_z were calculated.

RESULTS: Tables 1-4 and Figure 1 summarize the data obtained from the study.

Table 1: AUC_{0-24h}, C_{max}, t_{max} and MRT values of 20 mg BIBR 277 SE (mean ± % CV) administered as a tablet, * median.

parameter	unit	tablet, 20 mg mean ± % CV
AUC_{0-24h}	[ng·h/ml]	124 ± 50.9
C_{max}	[ng/ml]	15.5 ± 52.5
t_{max}	[h]	2.00 *
MRT_{tot}	[h]	14.6 ± 30.8

Table 2: AUC_{0-24h}, C_{max}, t_{max} and MRT values of 80 mg BIBR 277 SE (mean ± %CV) of solution and capsule, * median.

parameter	unit	capsule, 80 mg mean ± % CV	tablet, 80 mg mean ± % CV
AUC_{0-24h}	[ng·h/ml]	818 ± 60.2	867 ± 68.5
C_{max}	[ng/ml]	247 ± 59.5	209 ± 52.4
t_{max}	[h]	1.00 *	0.75 *
MRT_{tot}	[h]	12.3 ± 84.4	14.8 ± 44.3

Table 3: Statistical analysis of AUC_{0-24h} and C_{max} levels and intraindividual coefficient of variation, CV %, (Anova, log-transformed data).

C_{max}:

Lower Lim. Conf.Intv.	Quotient	Upper Lim. Conf.Intv.	intraindividual CV %
0.71879	0.85729	1.02246	25

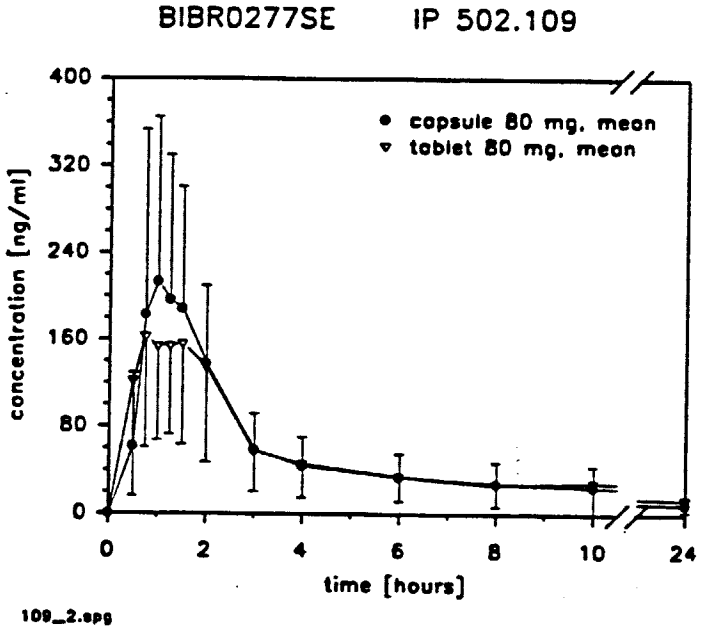
AUC_{0-24h}:

Lower Lim. Conf.Intv.	Quotient	Upper Lim. Conf.Intv.	intraindividual CV %
0.90213	1.03394	1.18500	20

Table 4: Summary of mean values (± CV%) of other pharmacokinetic parameters

dose	formulation	N	MRT_{tot} ± CV % [h]	$t_{½}$ ± CV % [h]	CL/f ± CV % [ml/min]	V_z/f ± CV % [l]
20 mg	tablet	12	14.6 ± 30.8	9.95 ± 40.1	3150 ± 78.1	2170 ± 44.3
80 mg	tablet	12	14.8 ± 44.3	13.2 ± 49.4	1800 ± 68.1	1820 ± 63.3
80 mg	capsule	12	12.3 ± 84.4	10.8 ± 78.8	1940 ± 59.0	1490 ± 51.6

Figure 1: Mean plasma concentration/time profiles (mean ± SD) of telmisartan after administration of a 80 mg dose as a capsule (filled dots) and tablet (open triangels)



CONCLUSIONS: The results obtained from the study showed that relative bioavailability of the 80 mg tablet compared to the the 80 mg capsule formulationis 1.03. The two formulations are bioequivalent with respect to AUC but not with Cmax.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 502.127 **VOLUMES: 1.122 - 1.125**

INVESTIGATOR AND LOCATION:

STUDY DATE : October to November, 1996.

OBJECTIVE: To compare the single-dose bioavailability of clinical batches of 80 mg telmisartan tablet with the final formulation from the production site.

FORMULATIONS:
Telmisartan tablets production batch, batch no. PD - 1727 (manufacturer lot # 601816)
Telmisartan tablets clinical batch, batch no. PD - 1552 (manufacturer lot # 50211)

STUDY DESIGN: The study a randomized, single dose, open-label, 2 sequence (TRRT and RTTR), 4-period crossover replicate study in normal, healthy subjects (16 male and 13 female). Each subject received, in replicate, a single-dose of the assigned formulation (80 mg telmisartan tablets clinical batch, reference formulation) and 80 mg telmisartan tablets production batch, test formulation). Blood samples of (approximately 7 mL) for plasma telmisartan determinations was obtained prior to study drug administration on each dosing day and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 8, 12, 24, 48, 72, and 96 hours post dose and plasma samples were stored at -20°C until assayed.

ASSAYS:

DATA ANALYSIS: AUC_{0-t}, $AUC_{0-\infty}$), C_{max} and t_{max} were calculated.
Bioequivalence between the production batch (test formulation) and the clinical batch (reference formulation) of telmisartan 80 mg tablets was assessed using conventional average

bioequivalence, and assessments of average scaled bioequivalence and individual bioequivalence using the moment-based scaled approach as described by Schall and Williams.

RESULTS: Tables 1-3 and Figure 1 summarize the data obtained from the study.

TABLE 1 Summary Statistics (Assessment of Average Bioequivalence, n=29)

Variable (Units)	Clinical (B) (Reference) Geometric Mean	Production (A) (Test) Geometric Mean	Mean Ratio (%)	90% Confidence Interval (%)
AUC_{0-t}[1] (ng*hr/mL)	1678	1723	102.7	97.9 - 107.7
AUC_{0-t}[3] (ng*hr/mL)			104.7	97.9 - 112.1
$AUC_{0-\infty}$[2] (ng*hr/mL)	1889	1907	100.9	93.9 - 108.5
$AUC_{0-\infty}$[3] (ng*hr/mL)			102.5	95.1 - 110.4
C_{max}[1] (ng/mL)	212.8	216.6	101.8	90.7 - 114.1
C_{max}[3] (ng/mL)			103.1	90.6 - 117.4

1 Geometric least-squares means, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data (no adjustment for carry-over effect).

2 Geometric least-squares means, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from mixed model analysis of variance of log-transformed data (no adjustment for carry-over effect).

3 Geometric least-squares means, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from mixed model analysis of variance of log-transformed data (adjustment for carry-over effect).

TABLE.2: Summary Statistics (Assessment of Individual Bioequivalence n=29)

Variable (Units)	Estimate of M_{as}[1]	Upper bound (U) of one-sided 95% confidence interval for M_{ms}[2]	Upper bound (U*) of one-sided 95% confidence interval for M_{ms} on ratio scale (%)[3]
AUC_{0-t} (ng*hr/mL)	-0.492	0.407	110.0
$AUC_{0-\infty}$(ng*hr/mL)	-0.473	0.644	112.8
C_{max} (ng/mL)	-1.173	3.323	131.4

1 Moment-estimate of moment-based, scaled bioequivalence measure

$$M_{ms} = \left[(\mu_T - \mu_R)^2 + \sigma_D^2 + \sigma_{WT}^2 - \sigma_{WR}^2\right] / \sigma_{WR}^2$$

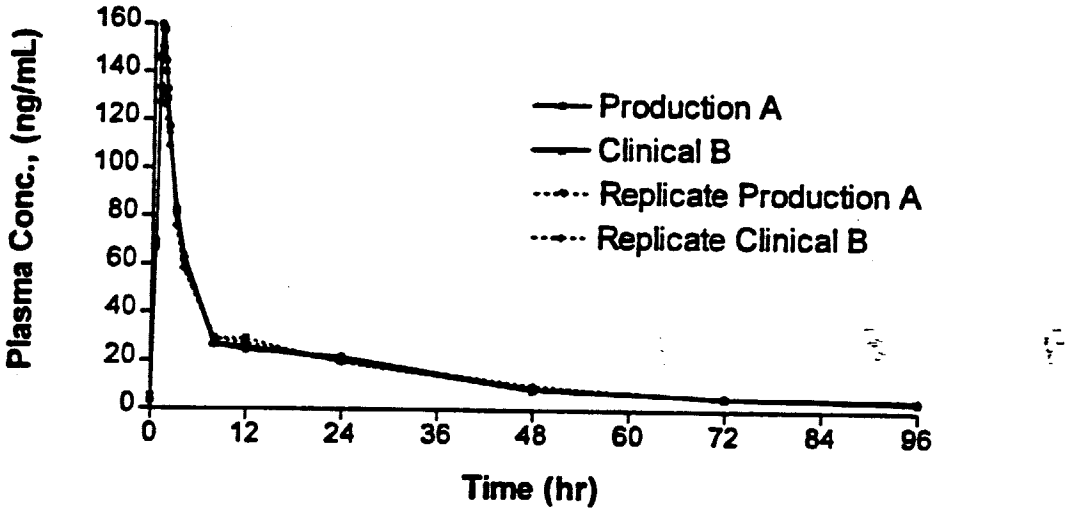
2 Bootstrap percentile interval; upper bound of bioequivalence range: $\Delta^2_{ms} = \left[\log(1.25)\right]^2 / \sigma^2_{wo} = 2.213$ for $\sigma^2_{wo} = 0.15^2$

3 $U^* = 100\% \cdot \exp\left(\sigma_{ms} \cdot \sqrt{U}\right)$; upper bound of bioequivalence range: 125%

TABLE 3. Geometric Means of Telmisartan Pharmacokinetic Parameters ($AUC_{0-\infty}$ and C_{max}) by Gender and Treatment Period.

	$AUC_{0-\infty}$ (ng*hr/mL)		C_{max} (ng/mL)	
Treatment	Female	Male	Female	Male
Production A	2336	1459	296	162
Clinical B	2581	1288	325	146
Replicate Production A	3330	1173	371	144
Replicate Clinical B	2789	1277	322	159

FIGURE 1. Mean Plasma Telmisartan Concentration - Time Profiles (All Subjects)



CONCLUSIONS: The results obtained from the study showed that:

1. the clinical batches and the final formulation from the production site were bioequivalent based on conventional average bioequivalence.
2. Individual bioequivalence was demonstrated with respect AUC_{0-t} and $AUC_{0-\infty}$, but not with respect to C_{max}. The failure to show individual bioequivalence with respect to C_{max} was solely due to the fact that for C_{max} the observed within-subject variability for the reference formulation (CV=31%) was smaller than the observed

within-subject variability of the test formulation (CV=48%). (*NOTE*: The within-subject CV of the test (production) formulation was in fact consistent with the within-subject variability observed in previous studies with the reference (clinical) formulation (CV=50% and CV=57%, respectively, in studies 128 and 114) (U96-2526, U96-3069), while the within-subject CV of the reference (clinical) formulation in the present study was lower (CV=31%) than in the previous studies).

3. There are gender differences in the disposition of telmisartan, with the female displaying higher concentrations than the males.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 502.128 **VOLUME: 1.106 - 1.107**

INVESTIGATOR AND LOCATION:

STUDY DATE : August - September, 1995.

OBJECTIVES: (i) to assess the bioavailability of a newly developed 120 mg oblong tablet of telmisartan (the final formulation) relative to two round tablets of 40 and 80 mg dose strength used in earlier clinical trials, (ii) to assess a possible gender difference in the pharmacokinetics of telmisartan.

FORMULATIONS:
Telmisartan tablets 120 mg (oblong), Pharmaceutical code: BIBR 277 SE TA 030 6A1A
Telmisartan tablets 40 mg (round), Pharmaceutical code: BIBR 277 SE TA 030 3A1B
Telmisartan tablets 80 mg (round), Pharmaceutical code: BIBR 277 SE TA 030 2A1B

STUDY DESIGN: The study was designed as a randomized, two way cross-over, randomised, open trial in 24 healthy subjects (12 male and 12 female). Each subject received seven morning doses of 120 mg telmisartan round tablets (40 + 80 mg) and, after a washout period of at least seven days, seven morning doses of 120 mg telmisartan oblong tablets or vice versa. Medication sequence was randomly allocatedwith one week washout period. Plasma samples of approximately 5 ml volume were collected on day 1: before administration, 0.5, 1, 1.5, 2, 3, 4, 8, 12 h; day 2 - day 6: trough levels and on day 7: before administration, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 48, 72 and 96 hours after the last drug administration. Plsama samples were stored at -20°C until assayed for telmisartan.

ASSAYS:

DATA ANALYSIS: $AUC_{0-\infty}$ and C_{max}, t_{max}, MRT, Cl_{tot}, $t_{1/2}$, V_z/f, V_{ss} and V_z were calculated.

RESULTS: Tables 1-3 and Figure 1 summarize the data obtained from the study.

TABLE 1: Summary statistics on individual pharmacokinetic parameters in male and female subjects derived from plasma concentration-time profiles obtained after administration of 120 mg telmisartan as a single oblong tablet.

Oblong tablet		male		geom.		female		geom.	
Parameter	unit	min	max	mean	gCV (%)	min	max	mean	gCV (%)
C_{max}	ng/ml			355	75.7			981	106
t_{max}	h			0.750*				0.500*	
$C_{max,ss}$	ng/ml			289	118			899	110
$t_{max,ss}$	h			0.500*				0.750	
$C_{pre,ss}$	ng/ml			10.8	76.2			25.3	61.0
$t_{½}$	h			16.6	33.8			24.7	37.3
AUC_{0-24h}	ng.h/ml			773	52.4			1780	73.9
AUC_{ss}	ng.h/ml			858	74.0			2040	74.8
MRT_{tot}	h			14.2	37.8			17.5	29.7
Cl_{tot}/f	ml/min			2330	74.0			982	74.9
V_z/f	l			3350	71.8			2100	80.7
R_A (AUC)				1.11	38.3			1.14	25.2
R_A (C_{max})				0.815	96.2			0.917	71.6
$C_{max,ss}/AUC_{ss}$	1/h			0.337	42.5			0.442	38.5

TABLE 2: Summary statistics of individual pharmacokinetic parameters in male and female subjects derived from plasma concentration-time profiles after administration of 120 mg telmisartan as 2 round tablets of 80 and 40 mg.

round tablets		male		geom.		female		geom.	
parameter	unit	min	max	mean	gCV (%)	min	max	mean	gCV (%)
C_{max}	ng/ml			308	76.6			752	76.7
t_{max}	h			0.500*				0.500*	
$C_{max,ss}$	ng/ml			320	70.4			883	100
$t_{max,ss}$	h			1.00*				1.25*	
$C_{pre,ss}$	ng/ml			10.1	71.9			31.9	101
$t_{½}$	h			16.1	21.7			24.3	29.9
AUC_{0-24h}	ng.h/ml			720	74.1			1560	64.9
AUC_{ss}	ng.h/ml			930	61.1			2380	87.1
MRT_{tot}	h			12.8	29.7			19.3	36.4
CL_{tot}/f	ml/min			2150	61.0			840	87.1
V_z/f	l			3000	60.0			1770	79.8
R_A (AUC)				1.29	26.4			1.53	41.0
R_A (C_{max})				1.04	48.8			1.17	77.0
$C_{max,ss}$/ AUC_{ss}	1/h			0.344	41.0			0.371	34.5

TABLE 3: Assessment of Bioequivalence.

Confidence interval alpha=0.1 / model=sex + sequ + vol(sequ) + tre + per

parameter	lower limit	point estimator	upper limit
C_{max}	0.98	1.23	1.53
$C_{max,ss}$	0.76	0.96	1.21
AUC_{0-24h}	0.98	1.11	1.25
AUC_{ss}	0.79	0.89	1.00

FIGURE 1: Individual and geometric mean plasma concentration-time profiles of telmisartan after administration of 120 mg telmisartan as a single oblong tablet and as two round tablets with 40 and 80 mg telmisartan.