CONCLUSIONS: The results obtained from the study showed that the 120 mg telmisartan oblong tablet was bioequivalent to one 40 mg plus one 80 mg round tablet with respect to AUC but not with Cmax.. Plasma concentrations demonstrated high intra- and inter-individual variability. The pharmacokinetic profiles of male and female subjects were characterised by 2 to 3 fold higher values of C_{max} and AUC in the latter.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 502.112 **VOLUME: 1.102** **PAGES: 1 - 359**

INVESTIGATOR AND LOCATION:

STUDY DATE : February - May, 1994

OBJECTIVES: The objective was the assessment absolute and relative bioavailability of 160 mg telmisartan given as a 30-minute i.v.-infusion, single doses oral solution and tablet in healthy volunteers.

FORMULATIONS:
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE TA 2A1A (round tablet)
Telmisartan Solution (160 mg/98 ml), Pharmaceutical codes BIBR 277 SE LO 1A0A
Telmisartan injection (40 mg/10 ml), Pharmaceutical code BIBR 277 SE AMT 1A1A (ampoule); BIBR 277 SE PL 9A1A (dry powder).

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 (160 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 Blood samples were withdrawn at the following time points: For the oral administrations (solution and tablet): before administration and at before administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48, 72 and 96 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, 1.50, 2.50, 3.50, 6.50, 8.50, 12.5, 24.5, 48.5, 72.5 and 96.5 hours after the end of the infusion period. 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} , V_z , F and F_{rel} % (using the ratio $AUC_{0-\infty}$) were calculated. The ANOVA was performed by the SAS procedure GLM.

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

Table 1: Summary table of pharmacokinetic parameters of telmisartan

		i.v. infusion		solution		tablet	
parameter	unit	mean	% CV	mean	% CV	mean	% CV
C_{max}	ng/ml	3290	24.3	1240	50.0	1330	57.0
t_{max}	h	0.500*		0.500*		0.500*	
$C_{0.5\ (extr.)}$	ng/ml	3710	25.1	–	–	–	–
$t_{½}$	h	18.3	27.8	18.9	35.5	20.0	35.2
$AUC_{0-\infty}$	ng·h/ml	3590	45.0	2180	52.1	2220	57.7
MRT_{tot}	h	9.00	51.7	13.1	40.3	13.9	34.1
MRT_{disp}	h	8.74	53.1	–	–	–	–
CL_{tot}/f	ml/min	–	–	1600	54.1	1630	55.8
Cl_{tot}	ml/min	859	35.8	–	–	–	–
V_z	l	1380	53.7	–	–	–	–
V_z/f	l	–	–	2630	71.7	2960	77.6
V_{ss}	l	393	36.2	–	–	–	–

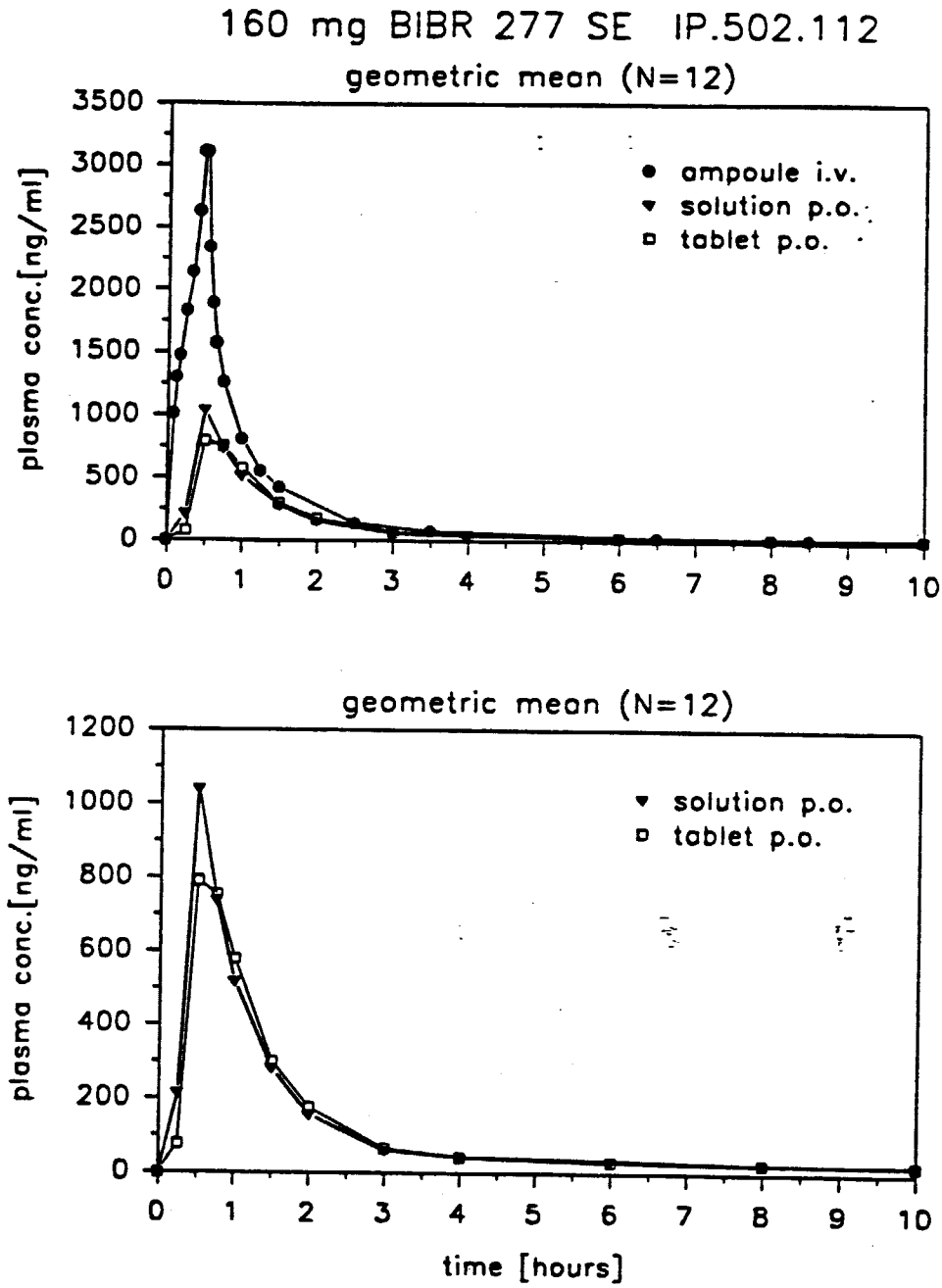
*median

data rounded to 3 sign. digits

Table 2: Absolute and relative bioavailability (test/reference ratios of the $AUC_{0-\infty}$) for the tablet, the oral solution, and the intravenous infusion (point estimates and the confidence intervals obtained by analysis of variance using log-transformed)

test	reference	alpha-level	lower limit	point estimator	upper limit
solution p.o.	ampoule i.v.	0.05	0.507	0.575	0.652
tablet p.o.	ampoule i.v.	0.05	0.506	0.574	0.650
tablet p.o.	solution p.o.	0.10	0.900	0.998	1.108

Figure 1: Geometric mean plasma concentration - time plots of BIBR 277 SE after administration of 160 mg as tablets (2 x 80 mg), oral solution and intravenous infusion.



CONCLUSIONS: The results obtained from the study showed that:

1. The absolute bioavailability of the 80 mg tablet was approximately 57 %.
2. The absolute bioavailability of the solution was approximately 57 %
3. The relative bioavailability of the tablet compared to the solution of 99.8 %.

(**NOTE**: 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)

FOOD EFFECT STUDY

STUDY 502.113 **VOLUMES**: 1.093 - 1.094

INVESTIGATOR AND LOCATION:

STUDY DATE : November to December, 1993.

OBJECTIVES: The objective was the assessment of influence of food on the bioavailability of single oral doses of 40 mg and 160 mg BIBR 277 SE in healthy volunteers

FORMULATIONS:
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE TA 030 2A 1A
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A 1A

STUDY DESIGN: The study was designed as a randomized, open 4-way crossover study with 12 healthy male volunteers and a washout period of 1 week. Each subject was administered 40 and 160 mg (2x80 mg) telmisartan as tablets either in the fasted state or after administration of a high caloric fat meal. Blood samples (5 ml) 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, 2.5, 3, 4, 6, 8, 10, 24, 48 and 72 hours after administration of the drug. Plasma samples were stored at -20°C until assayed for telmisartan.
The meal consisted of 2 eggs à 57 g, 20 g butter, 500 g potatoes, 25 g bacon, 10 g lard, 2 toast bread (50 g), 200 ml milk (equivalent to 1067 **Kcal** consisting of 105.94 g carbohydrate, 31.24 g protein and 29.6 g fat).

ASSAYS:

DATA ANALYSIS: $AUC_{0-\infty}$ and C_{max}, C_{max}/ AUC, t_{max}, MRT, $t_{1/2}$, CL_{tot}/f and V_z/f were calculated. The ANOVA was performed by the SAS procedure GLM.

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

Table 1: Summary table of pharmacokinetic parameters (mean ± CV%) of telmisartan after administration of 40 mg either in the fasted and non-fasted state.

40 mg			fasted		non fasted	
parameter	unit	N	mean	% CV	mean	% CV
C_{max}	[ng/ml]	12	21.0	38.4	16.3	49.0
t_{max}	[hour]	12	2.2	81.6	2.7	51.3
$t_{½}$	[hour]	12	19.2	27.6	23.3	39.6
AUC_{0-48h}	[ng·h/ml]	12	242	50.7	220	59.9
$AUC_{0-\infty}{}^{+}$	[ng·h/ml]	12	288	56.3	280	61.1
C_{max}/AUC	[1/h]	12	0.0864	52.3	0.0687	44.8
MRT_{tot}	[hour]	12	23.3	27.4	29.9	36.2
CL_{tot}/f	[ml/min]	12	2960	45.6	3280	53.7
V_z/f	[l]	12	4950	58.1	6720	70.8

+: calculated with inclusion of BQL data

Table 2: Summary table of pharmacokinetic parameters (mean ± CV %) of BIBR 277 SE after administration of 160 mg either in the fasted and non-fasted state.

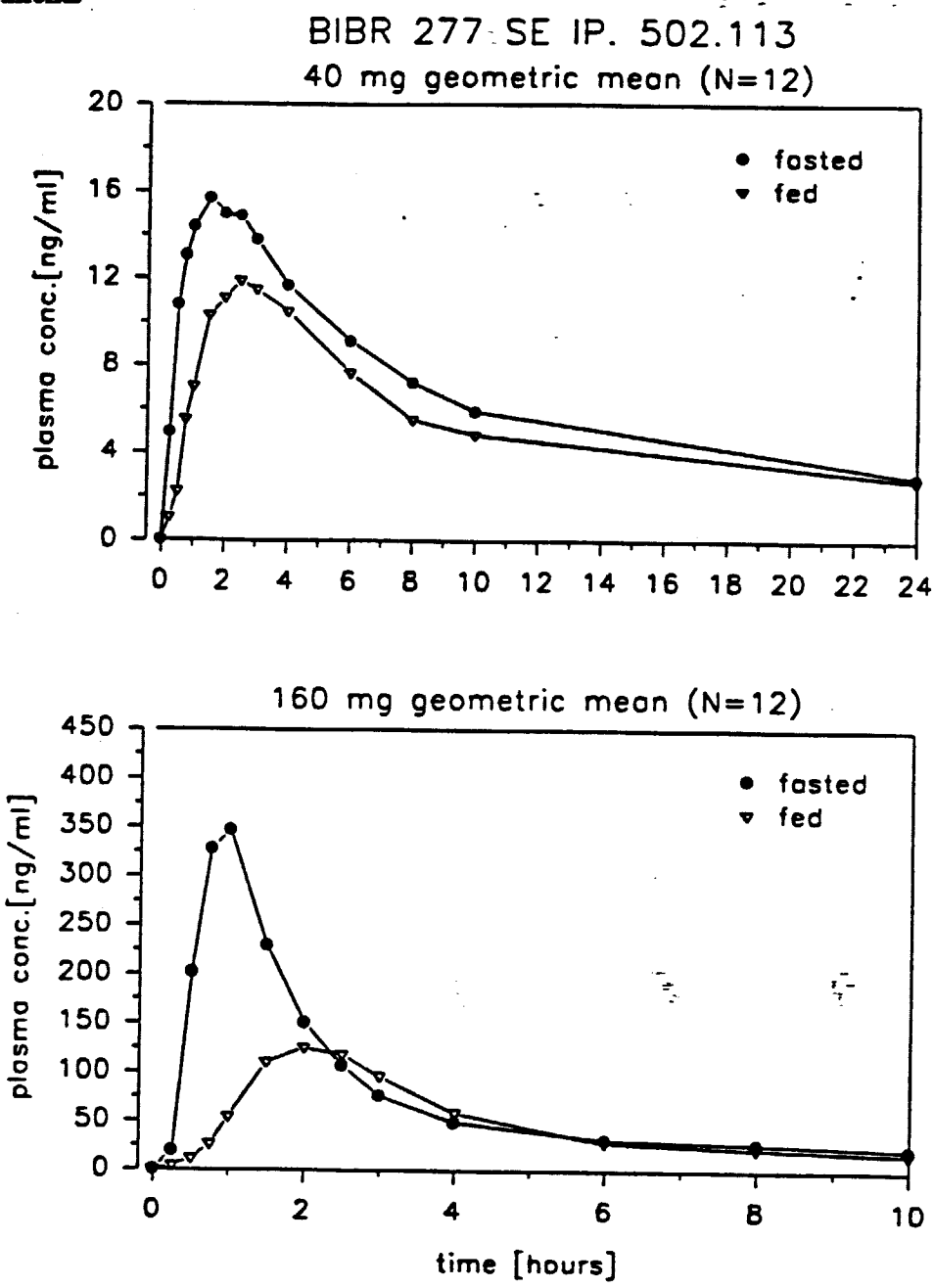
160 mg			fasted		non fasted	
parameter	unit	N	mean	% CV	mean	% CV
C_{max}	[ng/ml]	12	624	69.6	268	62.9
t_{max}	[hour]	12	0.69	31.4	1.78	47.2
$t_{½}$	[hour]	12	17.8	26.6	20.5	27.9
AUC_{0-48h}	[ng·h/ml]	12	1440	47.3	1110	50.8
$AUC_{0-\infty}{}^{+}$	[ng·h/ml]	12	1560	46.0	1280	49.4
C_{max}/AUC	[1/h]	12	0.400	41.2	0.224	52.7
MRT_{tot}	[hour]	12	14.7	26.8	20.9	35.1
CL_{tot}/f	[ml/min]	12	2130	51.7	2630	48.1
V_z/f	[l]	12	3350	57.3	4740	59.2

+: calculated with inclusion of BQL data

Table 3: 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})*

parameter	40 mg fed/ fasted			160 mg fed/ fasted		
	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

Figure 1: Geometric mean plasma concentration - time plots of telmisartan for all 4 treatments



CONCLUSIONS: The results obtained from the study showed that there is a dose-dependent food effect on the pharmacokinetics of telmisartan:

1. 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).
2. 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 %. While t_{max} was delayed and occurred at 1.8 h after concomitant food intake compared to 0.7 h in the fasted . (*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).

AGE / GENDER EFFECT STUDY

STUDY 502.124 **VOLUMES: 1.111 - 1.112**

INVESTIGATOR AND LOCATION:

STUDY DATE : October 1994 - Febrary 1995.

OBJECTIVES: To investigate the pharmacokinetics and safety of single and repeated doses of telmisartan (20 and 120 mg) in elderly healthy subjects

FORMULATIONS:
Telmisartan Tablet (200 mg), Pharmaceutical code BIBR 277 SE TA 030 1A1A
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A1A
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE 030 2A1A

STUDY DESIGN: The study was a single-centre, open, randomised, two-way cross-over study with 12 healthy volunteers (6 male, 6 female, age 65 to 78 years) and a washout period of 14 days. Each subject was administered 20 or 120 mg (40 mg + 80 mg) telmisartan tablets daily for 7 days during each period of the study. Blood samples were collected before and 0.5, 1, 1.5, 2, 3, 6, 9 and 12 hours after dosing on Day 1, before and 0.5, 1 and 3 hours after dosing on Days 2 to 6 and before and 0.5, 1, 1.5, 2, 3, 6, 9, 12, 24, 48 and 72 hours after dosing on Day 7 (steady state). Plasma samples were stored at -20°C until assayed for telmisartan. A sample was taken at 0.5 hours on Day 7 of each period for determination of plasma protein binding.

ASSAYS:

DATA ANALYSIS: C_{max}, $C_{max,ss}$, AUC_{0-24}, AUC_{ss}, t_{max}, $t_{max,ss}$, $t_{1/2}$, MRT_{tot}, and R_A (the ratio of accumulation for C_{max} and AUC); plasma protein binding were calculated.

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

Table 1: Summary statistics of model free pharmacokinetic parameter after administration of 20 mg telmisartan

20 mg		arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	19.2	35.9	19.8	7.94	29.3	17.9	41.9
t_{max}	h	12	1.50	161	0.500	0.500	9.00		
AUC_{0-24h}	ng·h/ml	12	187	65.6	170	53.4	527	159	64.1
$C_{max,ss}$	ng/ml	12	34.0	72.8	25.8	10.7	98.6	28.3	66.0
$t_{max,ss}$	h	12	1.42	112	0.500	0.500	6.00	0.953	105
$C_{pre,ss}$	ng/ml	12	12.6	174	6.99	1.21	81.5	6.90	127
$t_{½}$	h	12	39.2	39.2	39.3	19.4	64.1	36.4	42.5
AUC_{ss}	ng·h/ml	12	402	123	268	97.6	1940	287	85.1
MRT_{tot}	h	12	43.9	35.4	42.8	21.9	67.8	41.3	38.5
Cl_{tot}/f	ml/min	12	1410	60.8	1260	172	3410	1160	85.0
V_z/f	l	12	4370	68.5	3570	887	12900	3660	70.0
$R_A(AUC)$		12			1.68	1.03	3.68	1.80	38.5
$R_A(C_{max})$		12			1.43	0.894	3.40	1.58	41.0

Table 2: Summary statistics of model free pharmacokinetic parameter after administration of 120 mg telmisartan

120 mg		arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	751	99.6	468	115	2850	533	102
t_{max}	h	12	0.875	55.2	0.750	0.500	2.00		
AUC_{0-24h}	ng·h/ml	12	1770	71.8	1570	356	4740	1420	79.5
$C_{max,ss}$	ng/ml	12	966	98.6	501	105	2700	592	147
$t_{max,ss}$	h	12	1.00	56.4	1.00	0.500	2.00	0.870	59.1
$C_{pre,ss}$	ng/ml	12	49.1	130	31.7	9.62	248	33.6	94.4
$t_{½}$	h	12	41.9	51.9	36.2	18.0	91.8	37.2	53.9
AUC_{ss}	ng·h/ml	12	2920	98.2	1990	545	11500	2200	86.3
MRT_{tot}	h	12	31.7	58.9	25.4	12.0	72.8	27.1	63.8
Cl_{tot}/f	ml/min	12	1150	77.8	1020	173	3670	909	86.5
V_z/f	l	12	4720	103	2120	572	16800	2930	140
$R_A(AUC)$		12			1.64	0.929	2.43	1.55	27.6
$R_A(C_{max})$		12			0.999	0.271	3.27	1.11	85.4

Table 3: Gender effects

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

Table 4: Percentage of telmisartan bound to plasma protein.

Subject	% bound, 20 mg dose	% bound, 120 mg dose
1	> 99.5	> 99.5
2	> 99.5	> 99.5
3	> 99.5	97.6
4	> 99.5	> 99.5
5	> 99.5	97.9
6	> 99.5	> 99.5
7	> 99.5	97.4
8	97.5	99.5
9	*	> 99.5
10	> 99.5	drop out
11	no sample	> 99.5
12	> 99.5	no sample
13	drop out	drop out
14	not done	not done

* value was out of acceptance range, no plasma left for reanalysis

FIGURE 1: Individual and Geometric Mean Plasma Concentration-time Profiles for 20 mg BIBR 277 SE on Day 1 and Day 7

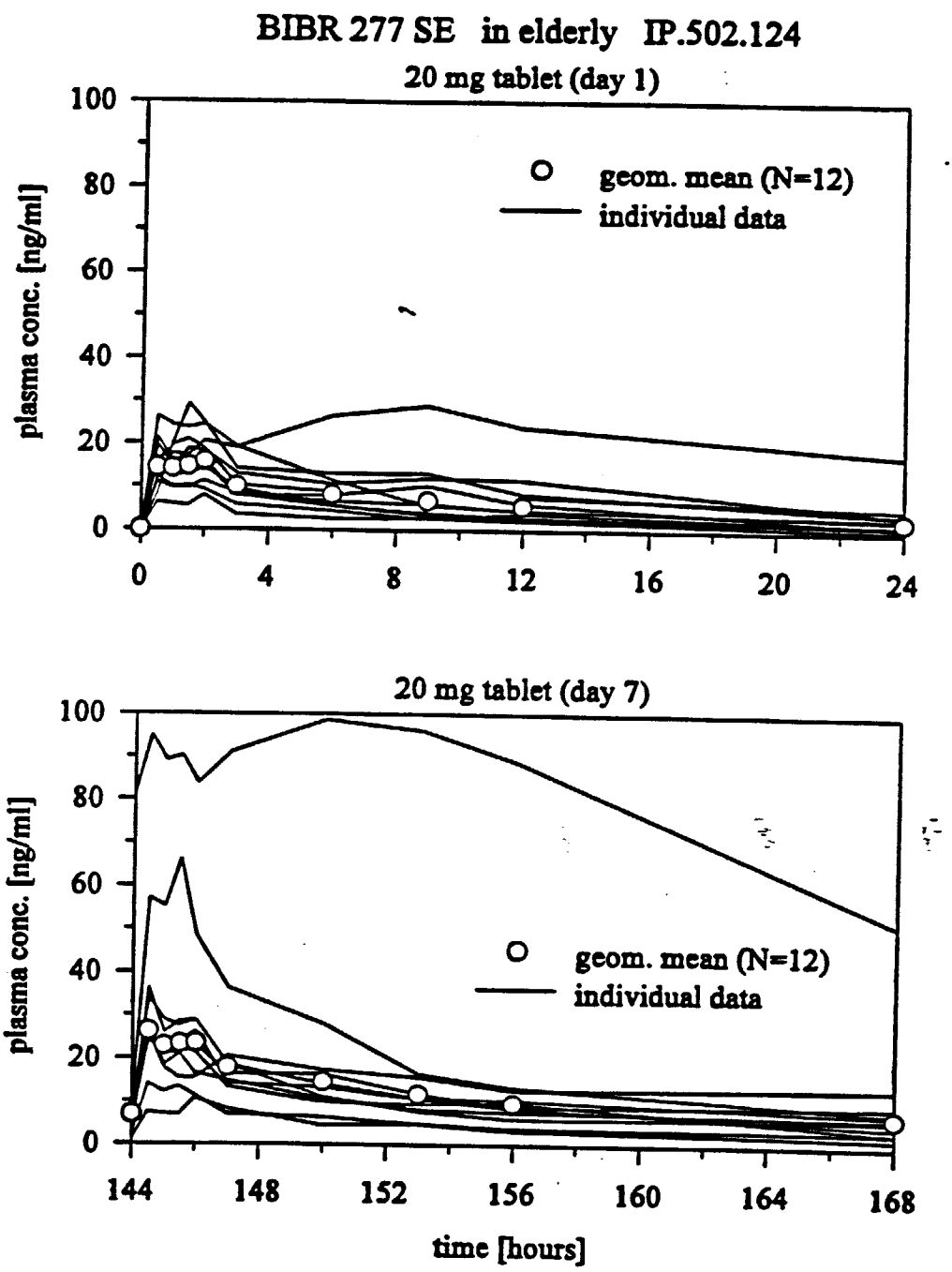


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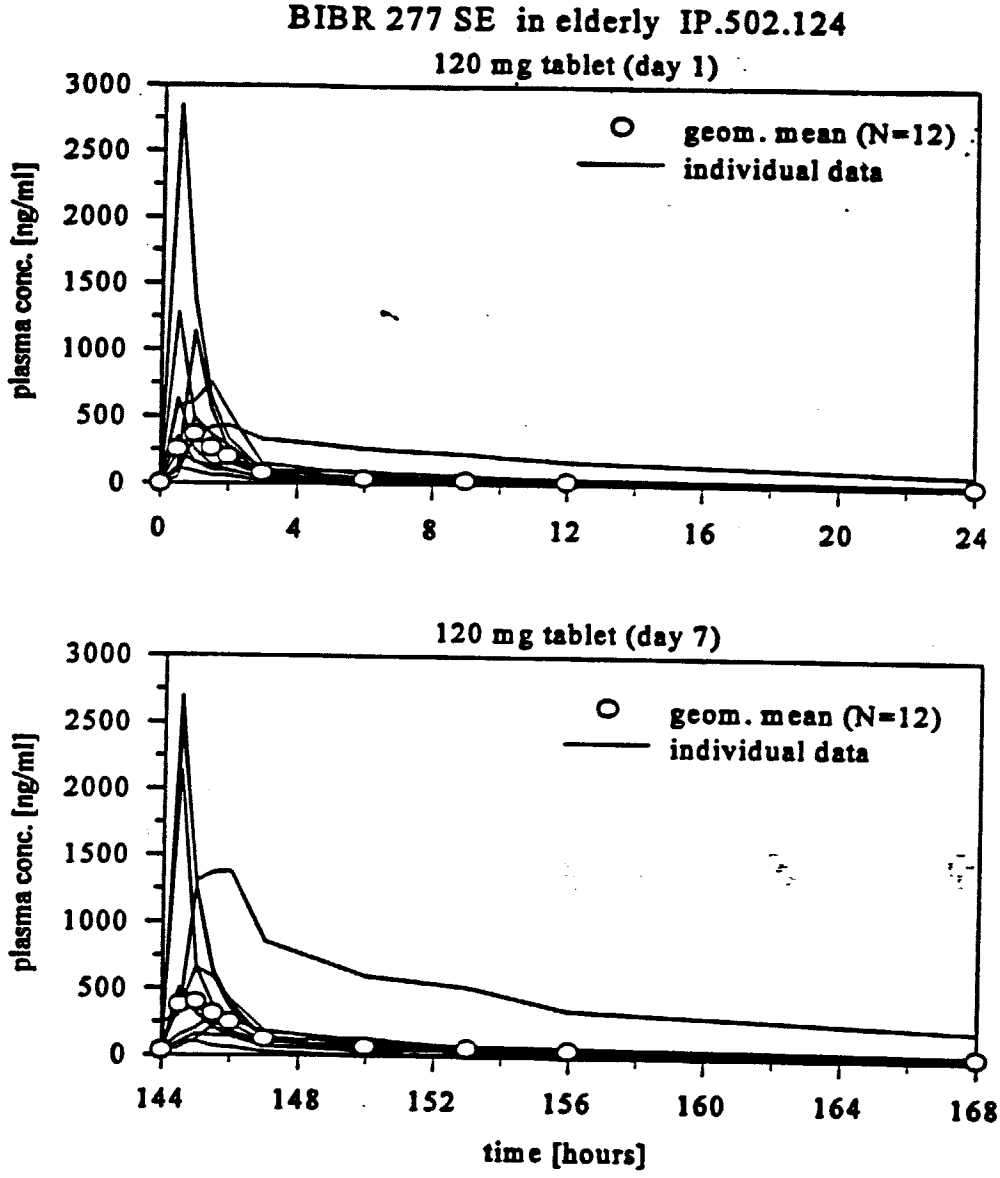
FIGURE 2: Individual and Geometric Mean Plasma Concentration-time Profiles for 120 mg BIBR 277 SE on Day 1 and Day 7



CONCLUSIONS: The results obtained from the study showed that

1. 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 - 1918 ng/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.
2. 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.
3. No decrease in protein binding of telmisartan was present in elderly subjects.

HEPATIC IMPAIRMENT STUDY

STUDY 502.123 **VOLUMES: 1.115 - 1.117**

INVESTIGATOR AND LOCATION:

STUDY DATE : October - December 1994.

OBJECTIVES: To investigate the pharmacokinetic variables after single oral dosing of telmisartan administered as 20 and 120 mg tablets to subjects with impaired liver function compared to healthy controls and, for the oral part of the study, to generate additional data on safety and tolerance. The subsequent administration of 60 and 120 mg BIBR 277 SE as intravenous infusion to subjects with impaired liver function should provide further information on the pharmacokinetic profile in the group of hepatically impaired subjects with regard to the significantly increased pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$.

FORMULATIONS:
Telmisartan Tablet (20 mg), Pharmaceutical code BIBR 277 SE TA 030 1A1A
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A1A
Telmisartan Tablet (80 mg), BIBR 277 SE TA 030 2A1A

STUDY DESIGN: The study was an open label, two-period, group comparison (matched-pairs technique), single oral dose design with 12 hepatically impaired subjects (Child Pugh Score A or B) and 12 healthy controls and a washout period of 14 days. Each subject was administered single dose of 20 or 120 mg (40 mg + 80 mg) telmisartan tablets during each period of the study. Blood sampling time points for determination of telmisartan were as follows: pre dose and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0 h post dose. Additional blood samples were withdrawn for determination of telmisartan plasma protein binding at 0.5, 2.0 and 6.0 h post dose. Seven (7) male volunteers with impaired and compensated liver function out of the group of twelve (12) subjects who already received the 20 and 120 mg oral dose of telmisartan were included in the intravenous (30 minutes infusion 0f 120 mg) part of the study. Two out of seven subjects preceded the other participants as doseleaders for safety reasons and received only half of the intended dose (i.e. 60 mg telmisartan). Plasma levels of telmisartan were determined by a validated method at the following time points: at pre dose and at 5, 7.5, 10, 15, 20, 25, 29 minutes during infusion as well as at 31, 33, 36, 39, 45 minutes, and 1, 1.25, 1.5, 2.5, 3.5, 6.5, 8.5, 12.5, 24.5, 48.5, 72.5 h after start of infusion.

ASSAYS:

DATA ANALYSIS: AUC_{0-24h}, t_{max}, $t_{1/2}$, λ_z, MRT_{tot}, CL_{tot}/f, V_z/f after oral administration; $AUC_{0-24.5h}$, $t_{1/2}$, CL_{tot}, V_z, V_{ss}, MRT_{disp} after intravenous dosing.

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

TABLE 1: Summary statistics of model free pharmacokinetic parameter, 20 mg telmisartan administered to patients with hepatic impairment

20 mg patients		arithm.					Geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	105	84.5	80.4	10.5	265	68.7	141
t_{max}	h	12	1.25	94.2	0.500	0.500	4.00		
$t_{½}$	h	12	36.4	67.7	27.1	16.3	95.8	30.8	62.2
AUC_{0-24h}	ng·h/ml	12	492	49.5	466	112	836	425	67.2
$AUC_{tf-\infty}$	%	12	14.4	98.5	9.44	2.50	49.9	9.69	117
$AUC_{0-\infty}$	ng·h/ml	12	1290	93.7	1130	355	4930	996	81.2
MRT_{tot}	h	12	49.5	66.6	37.0	21.9	137	42.5	58.4
Cl_{tot}/f	ml/min	12	412	66.2	295	67.6	939	334	81.2
V_z/f	l	12	1130	85.2	889	386	3840	893	75.4

TABLE 2: Summary statistics of model free pharmacokinetic parameter, 20 mg telmisartan administered to healthy subjects.

20 mg healthy subj.		arithm.					Geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	16.2	35.2	15.3	7.73	26.7	15.3	37.2
t_{max}	h	12	2.50	57.8	3.00	0.500	4.00		
$t_{½}$	h	12	24.6	40.3	23.3	13.2	48.5	23.1	38.5
AUC_{0-24h}	ng·h/ml	12	208	41.6	194	105	409	194	40.4
$AUC_{tf-\infty}$	%	12	8.70	69.3	6.87	3.49	26.6	7.57	53.8
$AUC_{0-\infty}$	ng·h/ml	12	471	75.1	415	174	1530	401	58.6
MRT_{tot}	h	12	35.7	38.5	33.0	17.3	71.9	33.7	36.3
CL_{tot}/f	ml/min	12	934	46.7	804	217	1920	831	58.7
V_z/f	l	12	1780	42.4	1660	912	3830	1660	39.0

TABLE 3: Summary statistics of model free pharmacokinetic parameter, 120 mg telmisartan administered to patients with hepatic impairment.

120 mg patients		arithm.					geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	1520	54.9	1330	514	3280	1340	57.2
t_{max}	h	12	0.917	51.1	1.00	0.500	2.00		
$t_{½}$	h	12	31.8	88.7	24.5	12.6	119	26.3	60.1
AUC_{0-24h}	ng·h/ml	12	5420	53.1	5130	1470	11300	4700	63.6
$AUC_{tf-\infty}$	%	12	9.19	155	5.54	0.460	53.3	4.63	188
$AUC_{0-\infty}$	ng·h/ml	12	11300	107	7800	2760	48400	8490	80.4
MRT_{tot}	h	12	37.6	104	26.5	14.4	159	29.3	70.2
CL_{tot}/f	ml/min	12	285	61.3	257	41.3	724	236	80.4
V_z/f	l	12	599	43.3	612	188	1010	537	56.4

TABLE 4: Summary statistics of model free pharmacokinetic parameter, 120 mg telmisartan administered to healthy subjects.

120 mg healthy subj.		arithm.					geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	475	37.1	486	167	760	438	47.5
t_{max}	h	12	1.00	42.6	1.00	0.500	2.00		
$t_{½}$	h	12	27.1	32.4	25.4	18.5	46.4	25.9	30.6
AUC_{0-24h}	ng·h/ml	12	2170	50.3	1990	758	4790	1940	53.1
$AUC_{tf-\infty}$	%	12	6.52	81.9	4.20	1.65	16.8	4.94	88.2
$AUC_{0-\infty}$	ng·h/ml	12	3670	68.7	3230	1490	11100	3190	55.0
MRT_{tot}	h	12	28.8	39.1	25.0	14.4	47.8	26.9	39.1
CL_{tot}/f	ml/min	12	697	43.8	622	180	1340	627	55.0
V_z/f	l	12	1690	75.5	1420	590	5400	1410	64.9

TABLE 5: Summary statistics on model free pharmacokinetic after 30 minute infusion of 120 mg BIBR 277 SE to liver insufficient subjects.

120 mg infusion			arithm.					geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
$C_{29'}$	ng/ml	5	2680	29.3	2720	1740	3710	2590	31.0
$t_{½}$	h	5	30.3	41.9	28.5	17.7	49.7	28.3	42.8
$AUC_{0-24.5h}$	ng·h/ml	5	5540	27.5	5670	3850	7580	5370	28.5
$AUC_{0-\infty}$	ng·h/ml	5	8870	37.3	10500	4900	12200	8320	43.5
$AUC_{t_f-\infty}$	%	5	11.6	70.7	8.10	3.22	21.7	9.17	94.4
MRT_{tot}	h	5	28.5	49.2	20.2	14.8	44.1	25.8	52.8
MRT_{disp}	h	5	28.2	49.6	20.0	14.5	43.8	25.5	53.4
CL_{tot}	ml/min	5	258	43.3	190	164	408	240	43.6
V_z	l	5	620	33.6	625	344	857	589	38.1
V_{ss}	l	5	379	25.1	415	227	476	368	29.5

Assessment of telmisartan protein binding

Independent of the time of blood sampling, telmisartan is bound to plasma proteins to an extent of > 99%. The group of 12 healthy controls presents an extent of telmisartan protein binding of 99.2 - 99.6% for the treatment with 20 mg and a mean of 99.5% (arithm. mean) for the treatment with 120 mg telmisartan. In the group of subjects with hepatic impairment the extent of protein binding was > 99.5% after administration of 20 mg. The mean percentage binding at 120 mg was 99.5%. This indicates that there is no change in protein binding of telmisartan in subjects with hepatic impairment.

FIGURE 1: Plasma concentration-time plots of telmisartan after oral administration of 20 and 120 mg

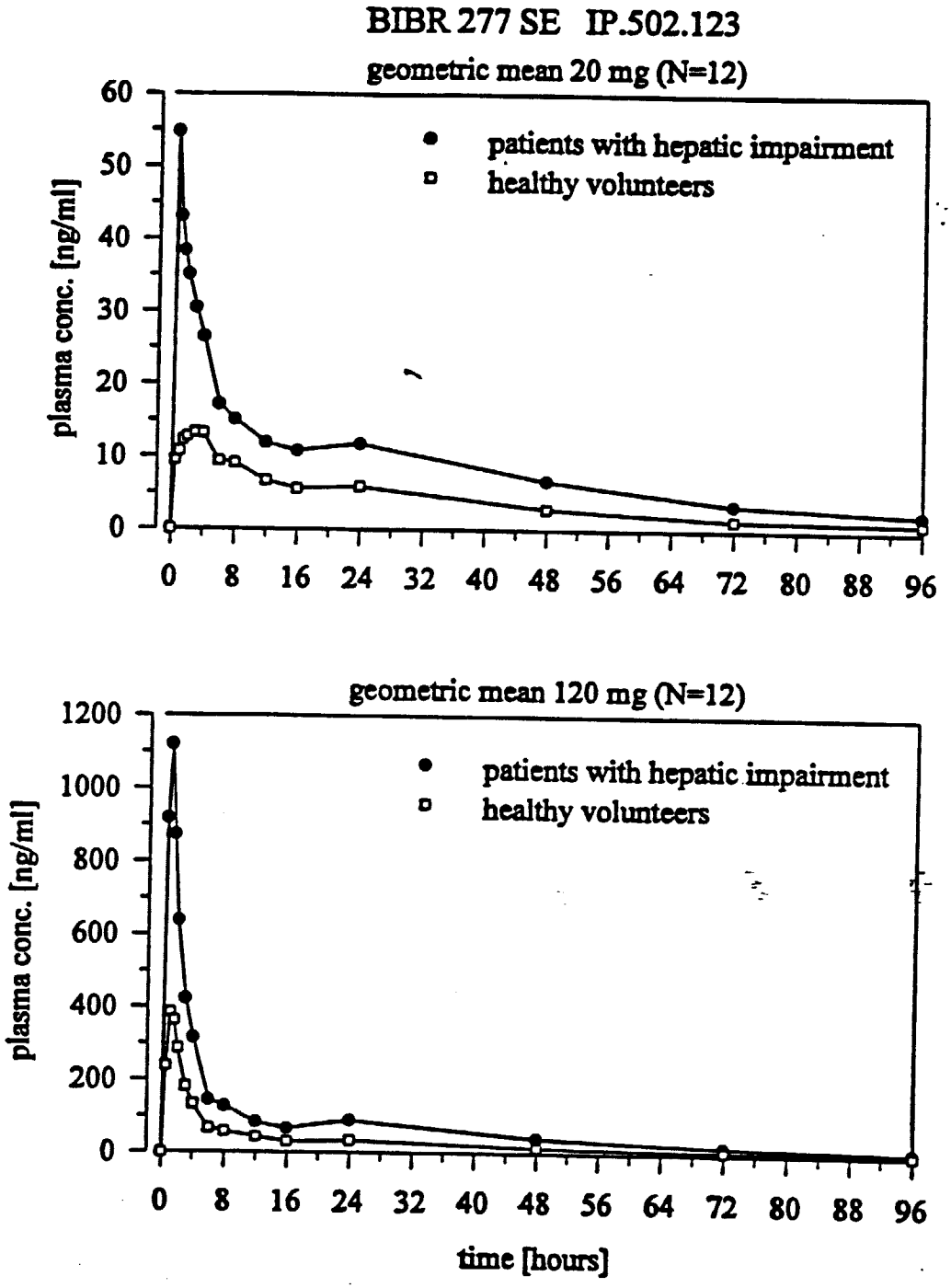
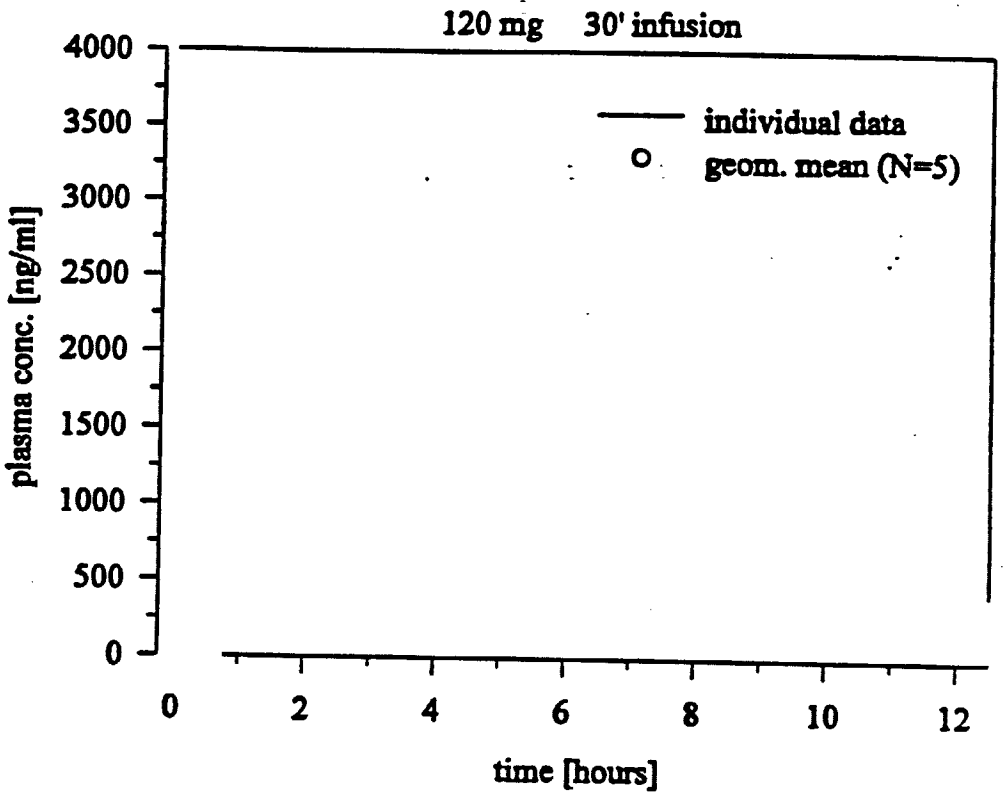


FIGURE 2: Individual plasma concentration-time plots of telmisartan after intravenous infusion of 120 mg



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CONCLUSIONS: The data obtainned from the study showed that:

1. 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.
2. At the 120 mg dose level, there was aapproximately 3 fold increase in C_{max} and $AUC_{0-\infty}$ and about 60% decrease in oral clearance 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.
3. The absolute bioavailability of telmisartan in hepatically impaired subjects was close to 100 %, whereas in healthy subjects absolute bioavailability was approximately 50 %.
4. As increase in bioavailability and decrease in hepatic clearance implicate a multiplicative effect on the $AUC_{0-\infty}$, a dose reduction of telmisartan should be considered when administered orally to patients with liver disease
5. Telmisartan is bound to plasma proteins to an extent of > 99% in the subjects with hepatic impairment as well as in the healthy controls.

RENAL IMPAIRMENT STUDY

STUDY 502.118 **VOLUMES: 1.113 - 1.114**

INVESTIGATOR AND LOCATION:

STUDY DATE : November - December 1994.

OBJECTIVES: To investigate the pharmacokinetics of telmisartan in subjects with severe renal insufficiency (drug administration between and during dialysis).

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A1A
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE 030 2A1A

STUDY DESIGN: Single-centre, open-label, non-randomised, two-way cross-over study. Fasting subjects (4 male and 2 female patients) were studied on two separate days, and received a single dose of 120 mg telmisartan on each day (either between [Period 1] or during dialysis [Period 2]). There was a washout phase of approximately 14 days between the two study days. Blood (5 ml) samples were taken at 0, 0.5, 1, 2, 3, 4, 6, 12, 24, and 48 hours on each study day.

ASSAYS:

DATA ANALYSIS: $AUC_{0-\infty}$, AUC_{0-24h}, Cmsx, t_{max}, $t_{1/2}$, MRT_{tot}, CL_{tot}/f, V_z/f and protein binding were determined.

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

TABLE 1: Plasma Concentration of telmisartan at the Dialyser Inlet and Outlet Lines

Time (h)	"in" Concentration (ng/ml)			"out" Concentration (ng/ml)		
	Arith. mean (CV,%)	Range	Geom. mean (gCV, %)	Arith. mean (CV,%)	Range	Geom. mean (gCV, %)
0.5	347.2 (175.6)	8.39-1587	117.6 (391.3)	268.4 (149.7)	10.43-1079	117.4 (289.7)
2.0	121.7 (68.9)	33.73-247.2	98.1 (85.48)	123 (70.34)	29.85-280	99.39 (86.22)
4.0	48.16 (38.67)	19.29-69.54	44.43 (49.94)	51.89 (49.13)	16.64-92.88	45.96 (63.01)

TABLE 2: Comparison of Pharmacokinetic Parameters (Arithmetic Means)*

Parameter	unit	Period 1 (Interdialysis)		Period 2 (During Dialysis)	
		Arith. mean (CV,%)	Range	Arith. mean (CV,%)	Range
C_{max}	ng/ml	142 (90.4)	20-387	314 (144)	68.5-1220
t_{max}	h	1.00+	0.5-2.0	0.50+	0.5-3.0
$t_{1/2}$	h	24.9 (48.2)	11.0-42.1	24.1 (56.6)**	9.79-42.5
AUC_{0-24h}	ng.h/ml	614 (57.4)	133-1200	793 (57.6)	228-1450
$AUC_{0-\infty}$	ng.h/ml	832 (49.1)	258-1440	971 (63.8)**	279-1570
MRT_{tot}	h	23.3 (50.8)	13.4-44.7	22.3 (40.0)**	12.4-33.0
Cl_{tot}/f	ml/min	3230 (72.1)	1390-7750	3270 (84.1)**	1270-7170
V_z/f	l	7960 (126)	2770-28300	5750 (75.8)**	2470-11800

+ Median

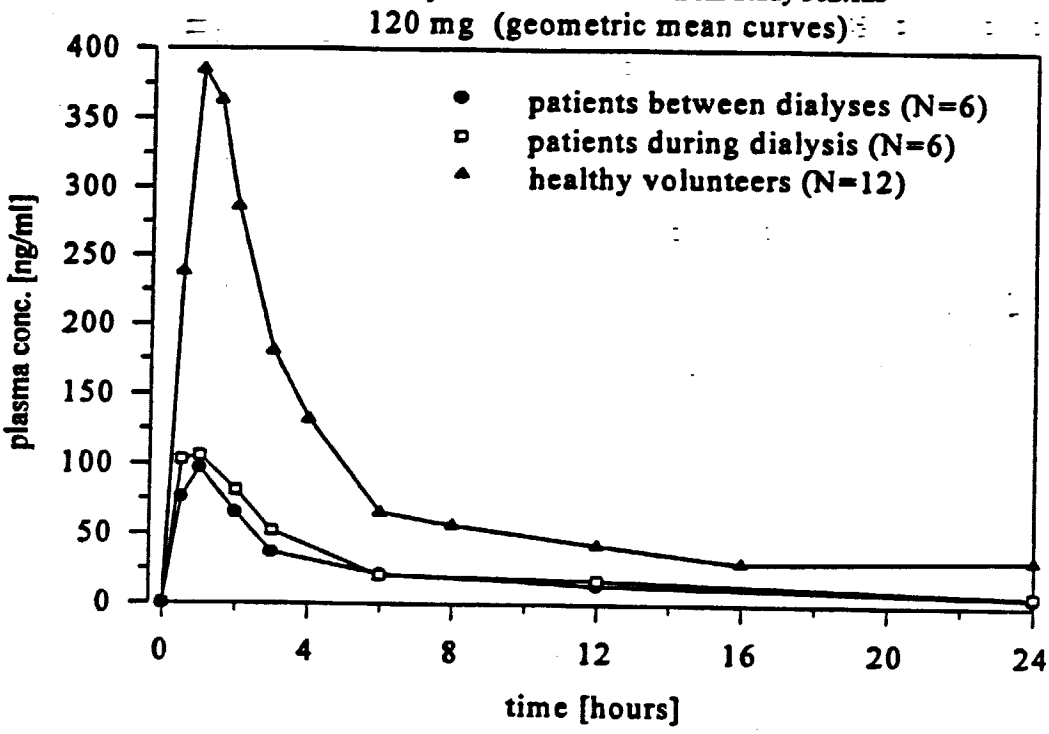
*: Model-free values with $t_{1/2}$ determination based on last two datapoints

** N = 4 (N = 6 for all other values)

Plasma Protein Binding

Plasma protein binding of telmisartan was almost 100%, both between dialyses (range 99.0 - 99.4%, mean 99.1 % [N = 5]), and during dialysis (range 97.8 - 99.4 %, mean 98.8 % [N = 5])

FIGURE 1: 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



CONCLUSIONS: The data obtainned from the study showed that:

1. The plasma concentration-time profile of telmisartan in subjects with severe renal insufficiency is characterised 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 compared to healthy volunteers (Study 502.123).
2. Telmisartan is not removed by haemofiltration.
3. Telmisartan is bound to plasma proteins to an extent of > 99% in the subjects with renal impairment as well as in the healthy controls.

TELMISARTAN-DIGOXIN INTERACTION STUDY

STUDY 502.119 **VOLUME: 1.095** **PAGES: 1 - 335**

INVESTIGATOR AND LOCATION:

STUDY DATE : August - October 1994.

OBJECTIVES: To study the effect of multiple dose administration of BIBR 277 SE on the steady state pharmacokinetics of digoxin.

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE tablets (lot 31123)
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE tablets (lot 31122)
0.25 mg digoxin (Lanoxin®) tablets (batch number 94B08-1).

STUDY DESIGN: Multiple dose, open label, two-period, randomized, cross over, study in 12 male subjects with a washout of at least two weeks between the periods. Each subject received 0.25 mg digoxin daily with loading doses of 0.5 mg digoxin in the morning and 0.25 mg digoxin in the evening of day 1 together with 120 mg of telmisartan daily for seven days (treatment A) and 0.25 mg digoxin daily for seven days with loading doses of 0.5 mg digoxin in the morning and 0.25 mg digoxin in the evening of day 1 (treatment B). Each period blood samples were taken regularly up to 24 h after drug administration in the morning of day 7 for the determination of digoxin in serum and telmisartan in plasma.In addition, blood sampling was performed pre-(morning) dose on days 1, 5, 6 and 7.

ASSAYS:

DATA ANALYSIS: $AUC_{144-168}$, c_{max} and c_{min} for digoxin , t_{max} and $c_{max}/AUC_{144-168}$ for digoxin and $AUC_{144-168}$, c_{max}, t_{max} and c_{pre} for BIBR 277 SE were determined.

RESULTS: Tables 1-3 and Figures 1-2 summarize the data obtained from the study.

Table 1: Pharmacokinetic parameters of digoxin as observed during multiple dose oral administration of digoxin with and without telmisartan for 7 days
Comparison of Pharmacokinetic Parameters (Arithmetic Means)*

Parameter	unit	Treatment A		Treatment B	
		Arith. mean (SD)	Range	Arith. mean (SD)	Range
C_{max}	$\mu g.L^{-1}$	2.54 (0.40)	1.94-3.17	1.70 (0.32)	1.37 - 2.38
t_{max}	h	0.5+	0.5 - 1.0	1.00+	0.5 - 1.00
c_{min}	$\mu g.L^{-1}$	0.48 (0.11)	0.31- 0.69	0.42 (0.07)	0.33 - 0.58
$AUC_{144-168}$	$\mu g.L^{-1}.h$	17.2 (2.9)	12.9 - 22.7	14.1 (2.0)	11.37 - 17.74
$c_{max}/AUC_{144-168}$	ng.h/ml	0.15 (0.03)	0.11 - 0.20	0.12 (0.02)	0.08 - 0.17

A = digoxin 0.25 mg o.d.• and BIBR 277 SE 120 mg o.d.
B = digoxin 0.25 mg o.d.•
• loading dose of 0.5 and 0.25 mg on day 1

Table 2: A summary table of the statistical results of the pharmacokinetic parameters is given below.

parameter	treatment	geometric mean	min - max	90% confidence interval and point estimate of ratio (%)*	
		digoxin			
$AUC_{144-168}$ ($\mu g.L^{-1}.h$)	A	16.97	12.89 - 22.65	116 - 128	122
	B	13.92	11.37 - 17.74		
c_{max} ($\mu g.L^{-1}$)	A	2.51	1.94 - 3.17	134 - 168	150
	B	1.67	1.37 - 2.38		
c_{min} ($\mu g.L^{-1}$)	A	0.470	0.305 - 0.695	105 - 122	113
	B	0.416	0.328 - 0.575		

* 90% confidence interval for the ratio of geometric means of A (digoxin+BIBR 277 SE) and B (digoxin) (from ANOVA on log-transformed data)

Table 3 Summary table of pharmacokinetic parameters of telmisartan after administration of 120 mg once daily for seven days.

Treatment A parameter	unit	N	arithm. mean	CV (%)	median
$C_{max,ss}$	$\mu g.L^{-1}$	12	741.6	73.11	576.0
$t_{max,ss}$	h	12	0.67	36.7	0.500
$C_{pre,ss}$	$\mu g.L^{-1}$	12	25.64	67.55	20.73
$AUC_{144-168}$	$\mu g.L^{-1}.h$	12	1817	65.07	1483

Figure 1. PLOT OF DIGOXIN GEOMETRIC MEAN SERUM CONCENTRATION-TIME

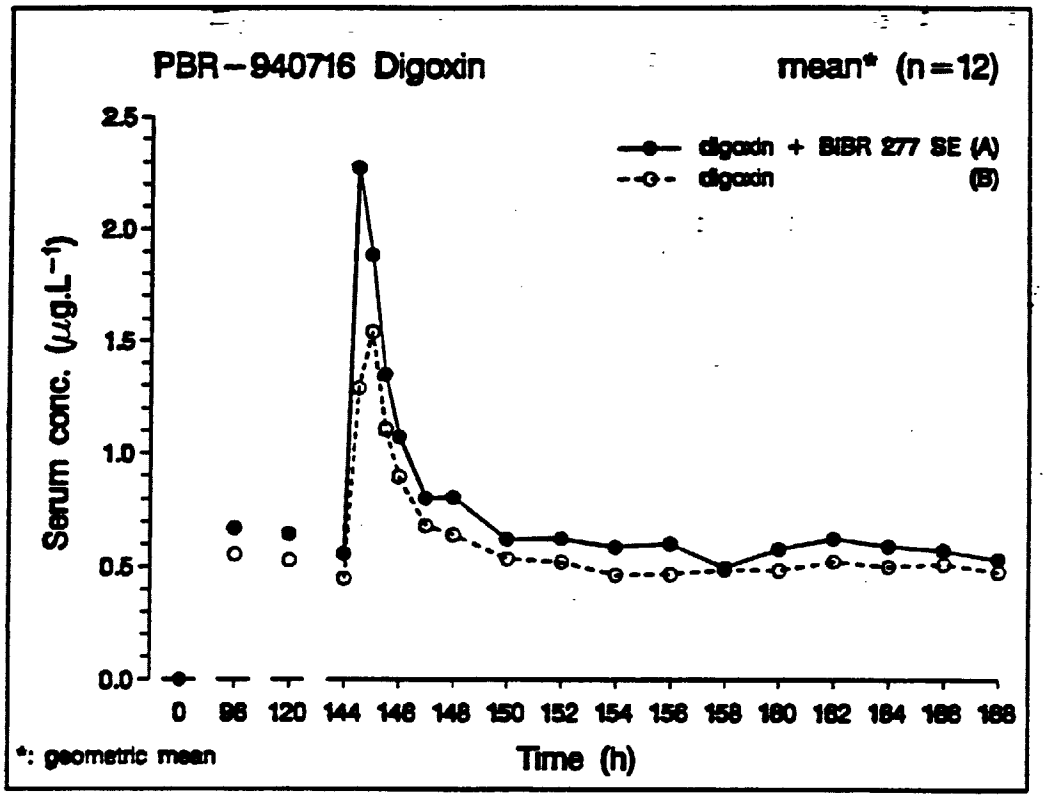


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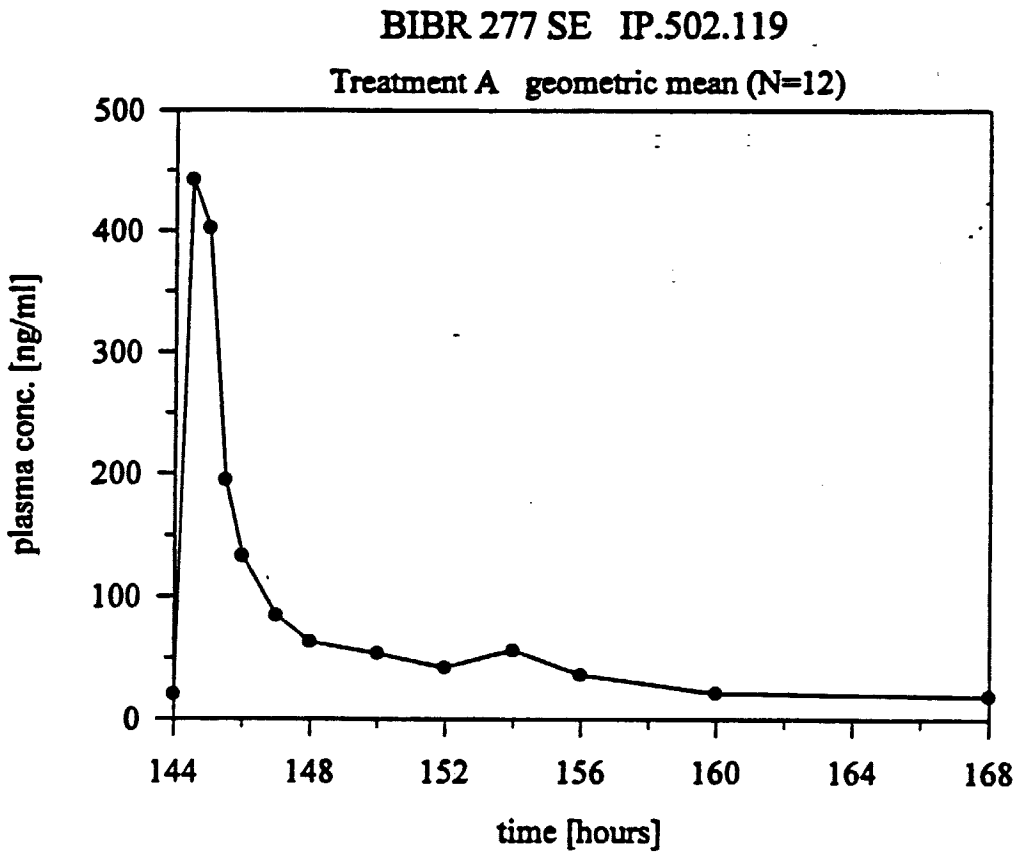
Figure 2: Geometric mean curve (Treatment A) of telmisartan plasma concentrations at day 7 of once daily oral dosage of 120 mg telmisartan



CONCLUSIONS: The data obtainned from the study showed that upon co-administration of telmisartan with digoxin:

1. 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.
2. The pharmacokinetics of telmisartan are similar to those in healthy subjects without concomitant drug administration (Study 502.124)

TELMISARTAN-WARFARIN INTERACTION STUDY

STUDY 502.120 **VOLUMES: 1.103 - 1.104**

INVESTIGATOR AND LOCATION:

STUDY DATE : August - November 1994.

OBJECTIVES: To study the effect of multiple dose administration of telmisartan on the steady state pharmacodynamics and pharmacokinetics of warfarin.

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code mg BIBR 277 SE tablets (lot 31123)
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE tablets (lot 31122)
1 mg warfarin (Warfarin Sodium BP) tablets, batch number BN 49435

STUDY DESIGN: Multiple dose, open label, two-period, randomized, cross over, study in 12 male subjects with a washout of at least two weeks between the periods. Each subject received warfarin daily for 30 days according to the following dose schedule: 10 mg on day 1, 5 mg on day 2, 4 mg on days 3 to 5 and individual dose adjustment on days 6 and/or 9 to attain a stable INR (International Normalized ratio) value between 1.2-1.8 (phase W_1); telmisartan 120 mg daily was co-administered from day 15 to 24 (phase W + B); on days 25-31 warfarin was administered alone again (phase W_2). Blood samples for the determination of INR_{pre} and c_{pre} were taken regularly throughout the study before the morning dose. In addition, blood samples for the determination of telmisartan were taken at regular intervals for a period of 24 hours on days 15 and 24. Plasma was analysed for warfarin and/or telmisartan using validated methods.

ASSAYS:

DATA ANALYSIS: AUC, C_{max}, t_{max} and C_{pre} for telmisartan, prothrombin time (INR_{pre}) and C_{pre} for warfarin were determined.

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

Table 1: A summary of the results of the pharmacodynamic parameter INR_{pre}

	INR_{pre}		
treatment phase	n	geometric mean	Arith. Mean (SD)
W_1	12	1.50	1.50 (0.14)
W+B	12	1.53	1.53 (0.26)
W_2	12	1.46	1.46 (0.22)

Table 2. A summary table of the results of the pharmacokinetic parameter c_{pre}

		c_{pre} warfarin		
	treatment phase	n	geometric mean	Mean (SD)
c_{pre} ($\mu g.L^{-1}$)	W_1	12	676	699 (196)
	W+B	12	602	631 (208)
	W_2	12	656	685 (223)

Table 3 Summary table of pharmacokinetic parameters of telmisartan

		Day 15	Day 24
Parameter	unit	Mean (SD)	Mean (SD)
C_{max}	ng/ml	495 (258)	415 (178)
t_{max}	h	1.00	1.00
Cpre	h	-	19.9 (13.7)
$AUC_{336-360}$	ng.h/ml	1330 (718)	-
$AUC_{552-600}$	ng.h/ml	-	1450 (805)

+ Median

FIGURE 1. LINEAR PLOT OF MEAN INR_{pre} VALUES VERSUS TREATMENT DAY

Linear plot of the mean INR_{pre} values versus treatment day as observed during multiple dose oral administration of warfarin on day 1-30 and telmisartan on days 15-24

FIGURE 1. LINEAR PLOT OF MEAN INR_{pre} VALUES VERSUS TREATMENT DAY

Linear plot of the mean INR_{pre} values versus treatment day as observed during multiple dose oral administration of warfarin on day 1-30 and telmisartan on days 15-24

phase W_1 = warfarin o.d. on days 1-14: 10 mg on day 1, 5 mg on day 2, 4 mg on days 3-5 and individual dose adjustment on day 6 and/or 9

phase W+B = individual warfarin dose o.d. and BIBR 277 SE 120 mg o.d. days 15-24

phase W_2 = individual warfarin dose o.d. on days 25-30

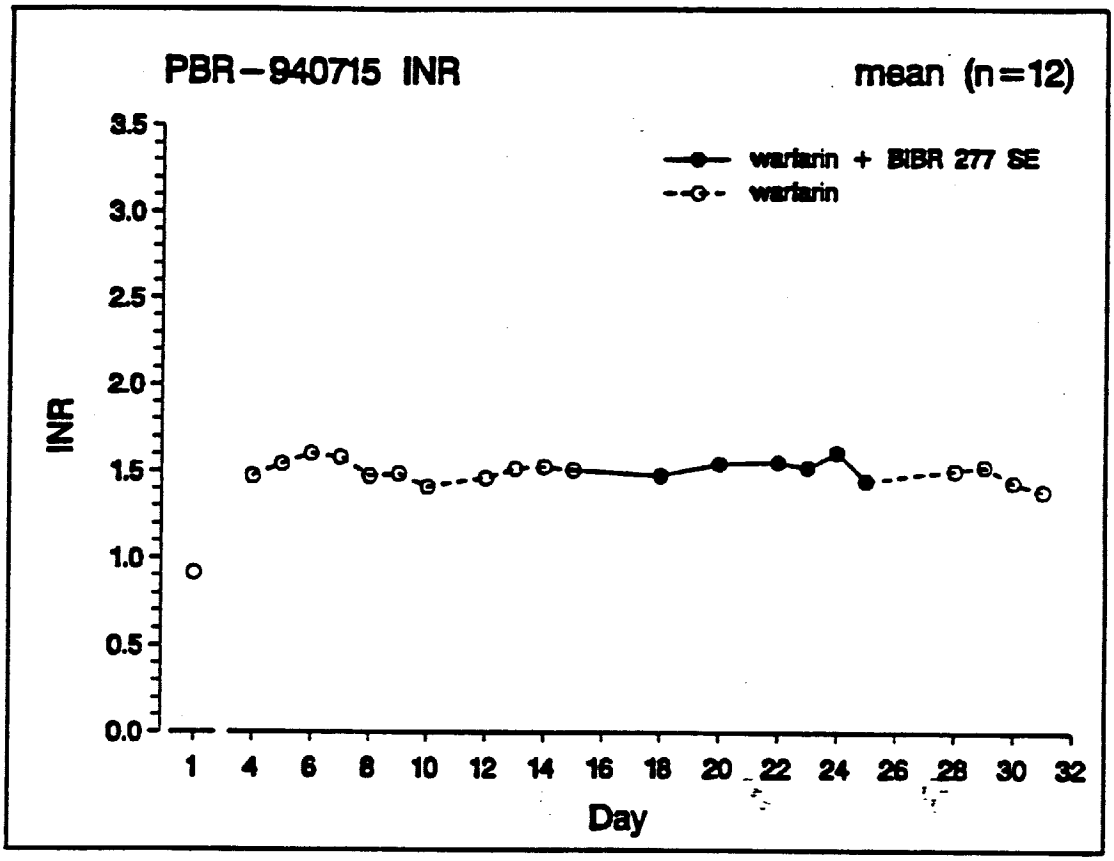


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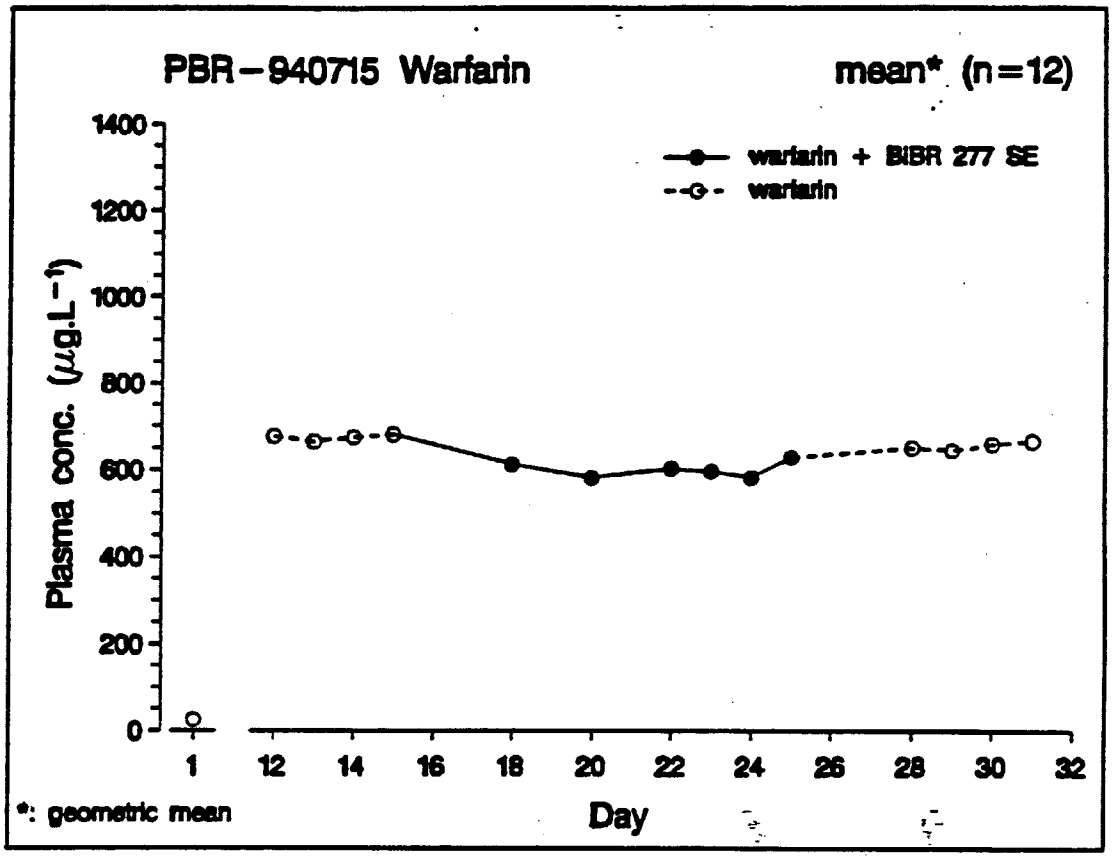
FIGURE 2. LINEAR PLOT OF GEOMETRIC MEANS OF WARFARIN TROUGH PLASMA CONCENTRATION VERSUS TREATMENT DAY PROFILES



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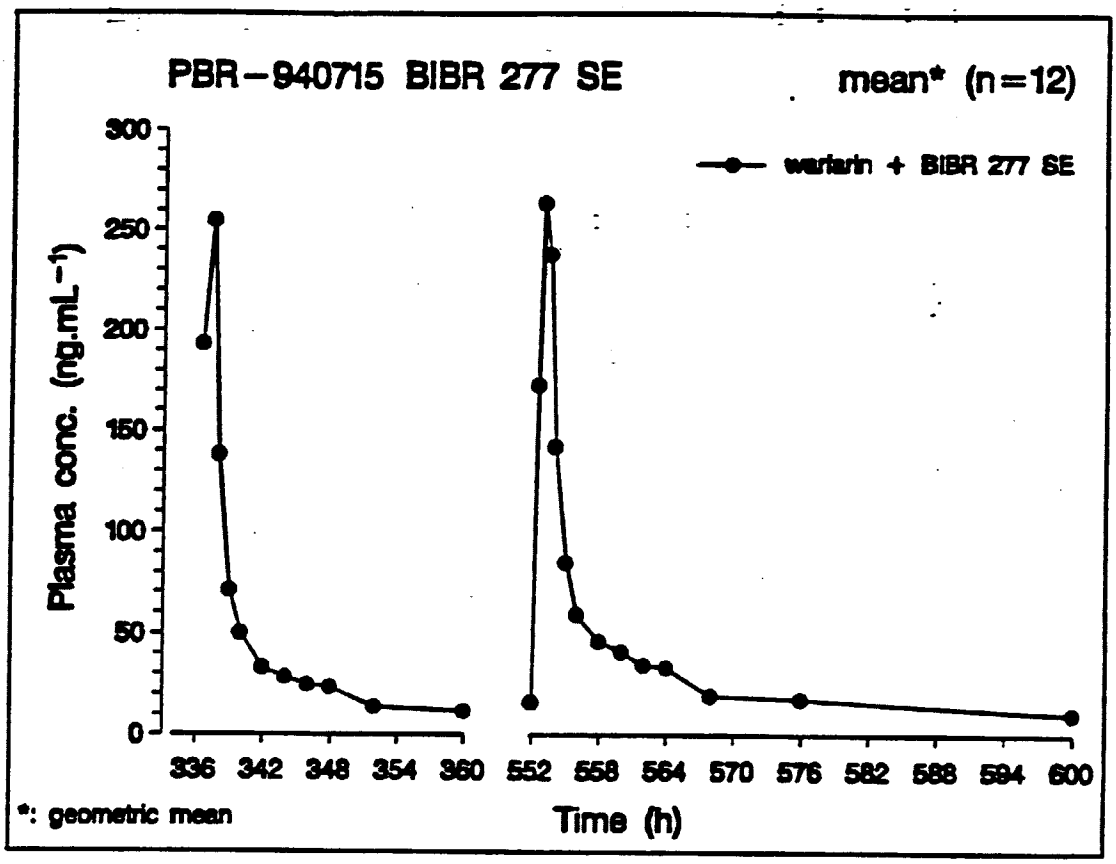
LINEAR PLOT OF GEOMETRIC MEAN BIBR 277 SE GEOMETRIC MEAN PLASMA CONCENTRATION-TIME PROFILES



CONCLUSIONS: The data obtainned from the study showed that upon co-administration of telmisartan with warfarin:

1. The mean INR_{pre} under steady state conditions remained unchanged during the treatment phases with warfarin alone, as well as during combined treatment; the difference between phase W_2 and phase W_1 being -0.04 (95% CI: -0.17 - 0.10) and between phase W+B and phase W_1 being 0.03 (95% CI: -0.11 - 0.10).
2. a small but statistically significant ($p=0.0006$) decrease in c_{pre} was observed when compared to the geometric mean of phase W_1; the corresponding point estimate of the ratio of phase W+B over phase W_1 amounted to 0.89 (95% CI: 0.84-0.95). The decrease in warfarin trough concentrations apparently 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
3. The pharmacokinetics of telmisartan are similar to those in healthy subjects without concomitant drug administration (Study 502.124)

TELMISARTAN- PARACETAMOL (ACETAMINOPHEN) INTERACTION STUDY

STUDY 502.121 VOLUMES: 1.097 - 1.098

INVESTIGATOR AND LOCATION:

STUDY DATE : November to December 1994.

OBJECTIVES: To assess the effect of concomitant administration of 120 mg telmisartan on the pharmacokinetics of 1 g 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.

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A1A
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE TA 030 2A1A
Paracetamol tablets (500 mg), Pharmaceutical code: Lonarid® mono.

STUDY DESIGN: This was a two way cross over, randomized, open, single oral dose design with 12 healthy male subjects and a wash out period of two weeks. Single doses of either 1.0 g paracetamol (2x500 mg) alone or 1.0 g paracetamol (2x500 mg) plus 120 mg telmisartan (40 + 80 mg) were orally administered the volunteers. Blood samples (9 ml) for determining the plasma levels of paracetamol and telmisartan were withdrawn at the following time points : before administration and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12, 24, 48 and 72hours after administration of test materials. Plasma was analysed for paracetamol and telmisartan using validated methods.

ASSAYS:

DATA ANALYSIS: $AUC_{0-\infty}$, C_{max}, t_{max}, 1/2, MRT_{tot}, CL_{tot}/f, V_z/f of paracetamol and BIBR 277 SE were determined.

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

Table 1: Summary Statistics of Model Free Pharmacokinetic Parameters of Paracetamol Administered Without Concomitant Medication

T1			arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	µg/ml	12	12.8	19.9	13.3	9.99	17.0	12.6	19.9
t_{max}	h	12	0.729	69.3	0.500	0.250	1.50	0.586	78.1
$t_{½}$	h	12	4.95	22.1	4.96	2.71	6.22	4.82	25.1
AUC_{0-24h}	µg·h/ml	12	48.4	20.6	47.3	37.6	73.9	47.6	19.1
$AUC_{0-\infty}$	µg·h/ml	12	49.6	21.6	48.4	37.6	76.9	48.7	20.2
$AUC_{t_f-\infty}$	%	12	3.12	42.6	2.98	1.40	5.83	2.85	47.8
MRT_{tot}	h	12	5.25	18.5	5.13	3.52	6.54	5.16	20.1
CL_{tot}/f	ml/min	12	349	18.9	345	217	444	343	20.2
V_z/f	l	12	146	20.9	144	104	210	143	20.7

Table 2 : Summary Statistics of Model Free Pharmacokinetic Parameters of Paracetamol Administered with 120 mg telmisartan

T2		arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	µg/ml	12	14.7	28.0	14.9	8.56	20.3	14.1	30.5
t_{max}	h	12	0.500	64.0	0.375	0.250	1.00	0.420	65.9
$t_{½}$	h	12	5.19	26.0	4.94	3.17	8.52	5.05	25.2
AUC_{0-24h}	µg·h/ml	12	48.9	18.2	49.7	39.4	69.8	48.2	17.5
$AUC_{0-\infty}$	µg·h/ml	12	50.2	18.7	50.9	39.4	72.5	49.5	17.9
$AUC_{t_f-\infty}$	%	12	3.47	59.1	2.33	1.60	7.07	2.99	60.3
MRT_{tot}	h	12	5.14	18.6	4.83	3.71	7.17	5.07	18.2
CL_{tot}/f	ml/min	12	342	16.9	328	230	423	337	17.8
V_z/f	l	12	152	30.1	136	116	278	147	25.9

Table 3: Summary statistics of telmisartan model free pharmacokinetic parameter

T2		arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	550	55.2	519	168	1200	469	68.3
t_{max}	h	12	0.750	34.8	0.750	0.500	1.00	0.707	37.4
$t_{½}$	h	12	16.6	30.7	17.6	10.9	26.9	15.9	31.1
AUC_{0-48h}	ng·h/ml	12	1510	49.2	1420	598	3020	1340	54.9
$AUC_{0-\infty}$	ng·h/ml	12	1660	51.1	1500	618	3400	1470	57.3
$AUC_{t_f-\infty}$	%	12	3.85	72.9	3.04	1.10	11.7	3.16	72.6
MRT_{tot}	h	12	15.3	38.7	14.2	8.14	28.7	14.3	38.7
Cl_{tot}/f	ml/min	12	1550	53.8	1340	588	3230	1360	57.2
V_z/f	l	12	2110	49.0	2040	880	4160	1880	53.5

Table 4: Statistical evaluation of bioequivalence for the parameter C_{max} $AUC_{0-\infty}$ and t_{max} Point estimates and 90 % confidence intervals after backtransformation of log-transformed C_{max} and $AUC_{0-\infty}$ data.

Model: sequence + vol(sequence) + per + tre			
parameter	lower limit	point estimator	upper limit
$AUC_{0-\infty}$	0.98400	1.01589	1.04881
C_{max}	0.95846	1.12081	1.31065

FIGURE 1: Geometric Mean Plasma Concentration-time Curves of Paracetamol alone or with Concomitant Administration of 120 mg Telmisartan

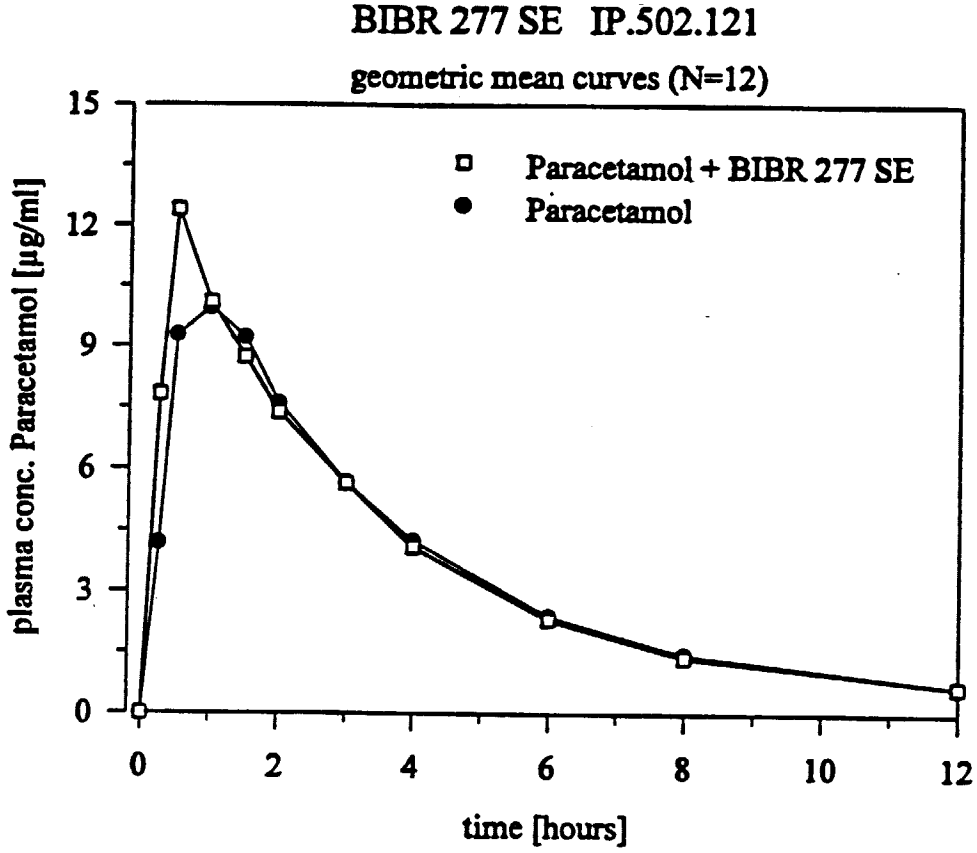


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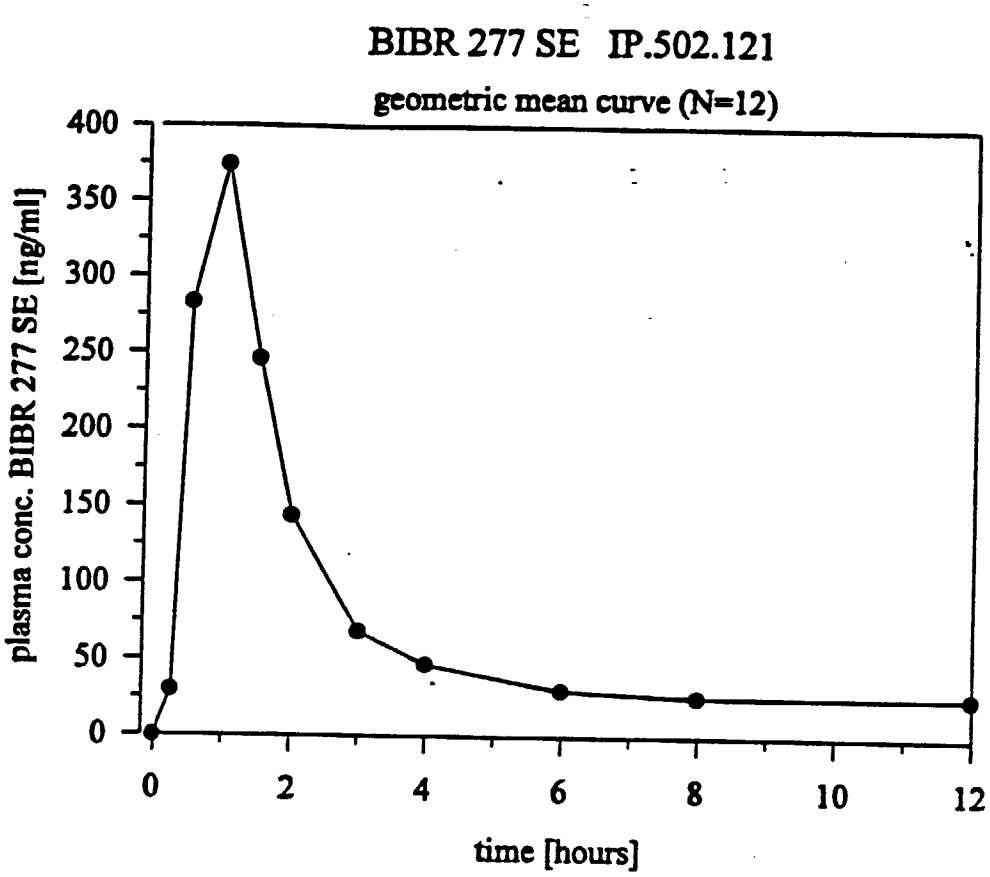
FIGURE 2 : Geom. Mean Plasma Concentration-time Plot of BIBR 277 SE (Treatment 2: Paracetamol and BIBR 277 SE).



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CONCLUSIONS: The data obtainned from the study showed that upon co-administration of telmisartan with paracetamol:

1. 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).
2. The pharmacokinetics of telmisartan are similar to those in healthy subjects without concomitant drug administration.

TELMISARTAN-HYDROCHLOROTHIAZIDE INTERACTION STUDY

STUDY 502.114 = VOLUMES: 1.118 - 1.120

INVESTIGATOR AND LOCATION:

S TUDY DATE : March to May 1995.

OBJECTIVES: To compare the steady state pharmacokinetics of telmisartan with and without the co-administration of hydrochlorothiazide (HCTZ), and to compare the steady state pharmacokinetics of HCTZ with and without the co-administration of telmisartan.

FORMULATIONS:
Telmisartan 80 mg Tablets Lot PD-1466
HCTZ 25 mg Tablets: Lot PD-1506

STUDY DESIGN: Open-label, randomized, 3-way complete crossover design with 14 subjects (9 male and 5 female) and a wash out period of two weeks. Each subject received the following treatments: Treatment A: HCTZ alone, 25 mg once a day orally for seven days, Treatment B: Telmisartan alone, 160 mg administered once a day orally for seven days. and Treatment C: Telmisartan 160 mg plus HCTZ 25 mg both administered once a day orally for seven days. Blood samples for plasma telmisartan determination were obtained (Treatments B and C) five minutes prior to study drug administration on dosing Days 1 (Visit 2), 6 and 7 (troughs) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 6, 8, 12, 16, 24 (trough), 36, 48, 60, 72, and 84 hours after the last dose on dosing Day 7. Blood samples for plasma HCTZ determination were obtained (Treatments A and C) five minutes prior to study drug administration on dosing Days 1 (Visit 2), 6 and 7 (troughs) and at 0.5, 1.0, 2, 2.5, 3, 4, 6, 9, 12, 16, 24 (trough), 30 36, and 48 hours after the last dose on dosing Day 7. Urine specimens for HCTZ determination were collected (Treatments A and C) before study drug administration on dosing Day 1, and at 0-6, 6-12 and 12-24 hours following the last dose on dosing Day 7.

ASSAYS:

DATA ANALYSIS: AUC, C_{max} , t_{max}, $t_{1/2}$, C_{min}, $t_{1/2}$, T_{max}, CL/F, CLr (for HCTZ), C_{ss}, and MRT were determined. analysis of variance (ANOVA) for crossover design was done, and 90% confidence intervals were calculated.

RESULTS: Tables 1-8 and Figures 1-4 summarize the data obtained from the study.

TABLE 1. Primary Statistical Comparisons Between Telmisartan Treatments

Parameter	Telmisartan Treatment	Arithmetic Mean (% CV)	Adjusted Geometric Mean	% Diff. (C-B)/B	90% CI in %
AUC_{0-24} (hr x ng/mL)	C	4464.0 (89.4)	3408.0	7.2	-4.5, 20.3
	B	4202.7 (89.0)	3179.3		
C_{max} (ng/mL)	C	2052.9 (101.2)	1315.3	7.3	-19.2, 35.3
	B	2093.0 (102.3)	1226.3		

TABLE 2. Secondary Statistical Comparisons Between Telmisartan Treatments

Parameter	Telmisartan Treatment	Arithmetic Mean (% CV)	Adjusted Means	% Diff. (C-B)/B	90% CI in %
C_{min} (ng/mL)	C	51.6 (108.4)	37.1#	0.3	-13.3, 15.9
	B	1.7 (98.3)	37.0#		
$t_{1/2}$ (hr)	C	22.0 (40.1)	22.0*	-1.2	-15.5, 13.1
	B	22.3 (29.3)	22.3*		

Geometric means, log transformed data were used

* Arithmetic means, original data were used.

TABLE 3. Other Mean* Plasma Pharmacokinetic Parameters for Telmisartan

Telmisartan Treatment		T_{max} (hr)	CL/F (L/hr)	C_{ss} (ng/mL)	MRT (hr)
B (Alone)	Mean	0.88	63.01	175.11	16.68
	% CV	48.30	67.42	89.00	45.28
C (Concurrent)	Mean	0.90	58.56	186.00	15.18
	% CV	25.13	66.77	89.41	50.24

TABLE 4. Mean HCTZ Trough Concentrations (ng/mL) on Days 6, 7 and 8

Treatment	Day 6	Day 7	Day 8	Pairwise Differences		
				Pair	% Diff.	90% CI in %
A (Alone)	11.63	12.20	13.10	Day 6 vs. Day 7	4.9	0.55, 9.32
				Day 6 vs. Day 8	12.6	8.25, 17.02
				Day 7 vs. Day 8	7.3	3.16, 11.52
C (Concurrent)	11.62	10.84	12.02	Day 6 vs. Day 7	-6.7	-13.18, -0.29
				Day 6 vs. Day 8	3.4	-3.08, 9.81
				Day 7 vs. Day 8	10.8	3.91, 17.73

TABLE 5 Primary Statistical Comparisons Between HCTZ Treatments

Parameter	HCTZ Treatment	Arithmetic Mean (% CV)	Adjusted Mean*	% Diff. (C-A)/A	90% CI in %
AUC_{0-24} (hr x ng/mL)	C	1095.2 (30.1)	1066.9	-5.3	-11.6, 0.9
	A	1130.2 (19.9)	1127.0		
C_{max} (ng/mL)	C	159.6 (30.3)	153.5	-9.4	-17.7, -1.1
	A	170.0 (26.4)	169.5		

* Arithmetic adjusted mean, original data were used.

TABLE 6 Secondary Statistical Comparisons between HCTZ Treatments

Parameter	HCTZ Treatment	Arithmetic Mean (% CV)	Adjusted Mean or Median	% Diff. (C-B)/B	90% CI in %
C_{min} (ng/mL)	C	11.4 (34.9)	10.7#	-13.3	-20.3, -5.7
	A	12.7 (21.1)	12.4#		
$t_{1/2}$ (hr)	C	10.0 (18.6)	9.9ψ	2.8§	-2.6, 11.3
	A	9.5 (16.9)	9.4ψ		

Geometric means

ψ Median of rank transformed data.

§ Median of paired difference.

TABLE 7. Other Mean* Plasma Pharmacokinetic Parameters for HCTZ

HCTZ Treatment		T_{max} (hr)	CL/F (L/hr)	C_{ss} (ng/mL)	MRT (hr)
A (Alone)	Mean	2.35	22.84	47.09	11.01
	% CV	16.03	17.54	19.91	12.68
C (Concurrent)	Mean	2.31	24.53	45.63	10.73
	% CV	29.67	26.48	30.12	14.30

* Arithmetic mean.

TABLE 8. Mean* Urine HCTZ Pharmacokinetic Parameters

Treatment		Cumulative Amount (mg) (A_{0-24})	% Dose	CL_T (mL/min.)
A (Alone)	Mean	16.1	80.5	244.7
	% CV	14.9	14.9	22.4
C (Concurrent)	Mean	16.8	84.2	278.6
	% CV	11.8	11.8	34.4

* Arithmetic mean.

TABLE 9 Comparisons of HCTZ Urinary Excretion Between Treatments

Parameter	HCTZ Treatment	Adjusted Mean*	% Difference	90% CI in %
Cumulative Amount Excreted in 24 hr (mg) (A_{0-24})	C	16.6	3.2	-4.0, 10.4
	A	16.1		

* Arithmetic mean, original data was used.

FIGURE 1: Mean Plasma HCTZ Concentration-Time Profiles

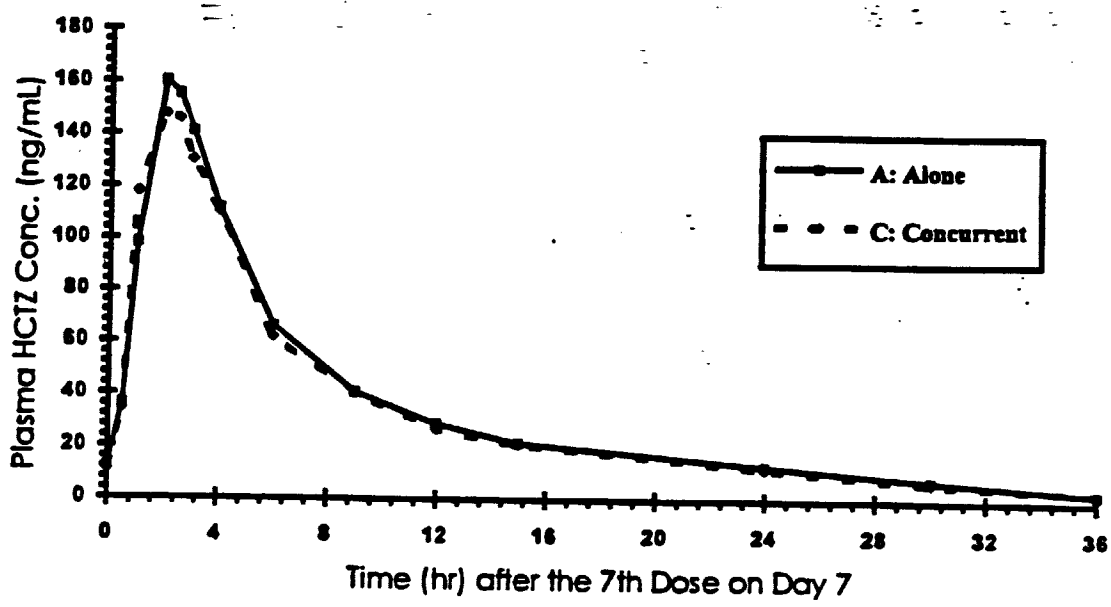
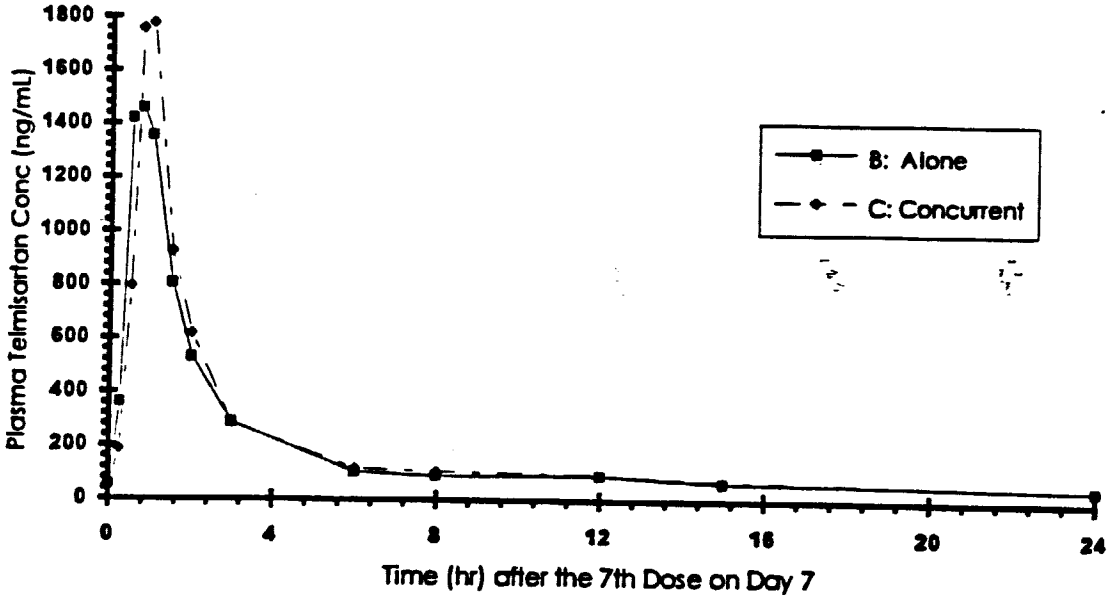


FIGURE 2. Mean Plasma Telmisartan Concentration-Time Profiles



FIGU RE 3. Telmisartan Plasma AUC_{0-24} and C_{max} by Gender in Terms of Geometric Means

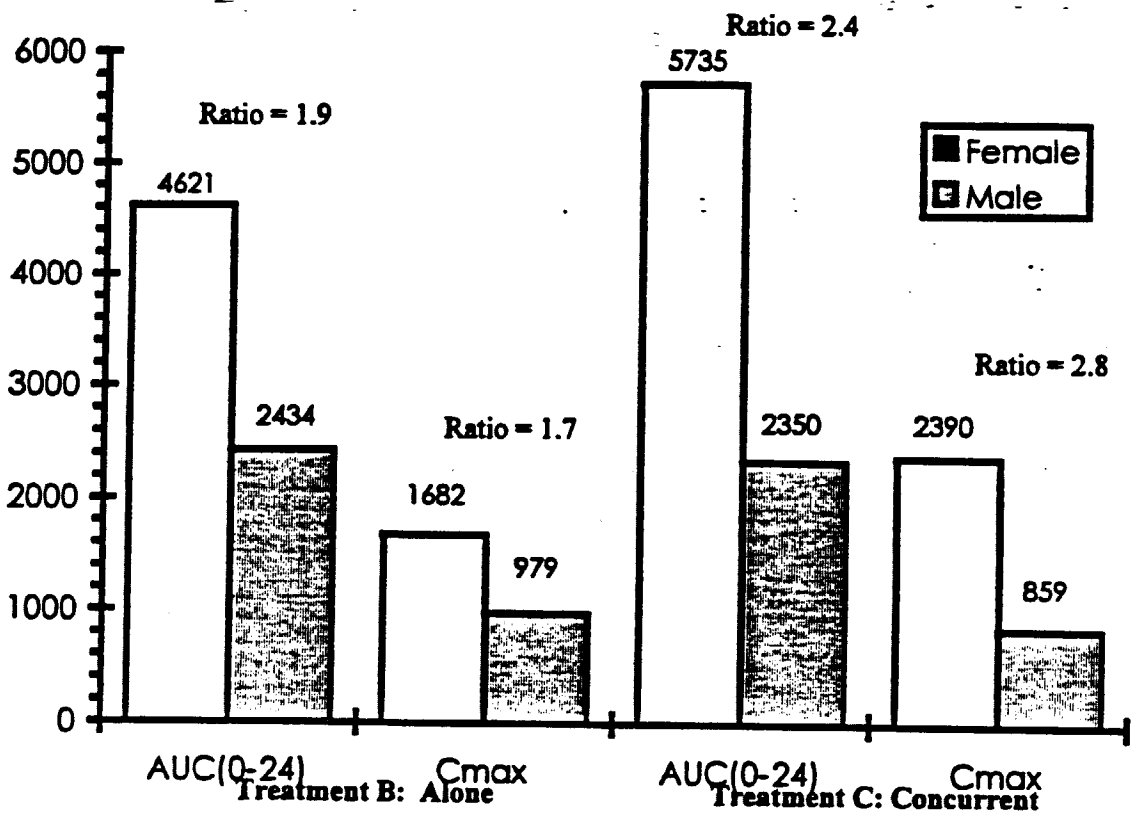


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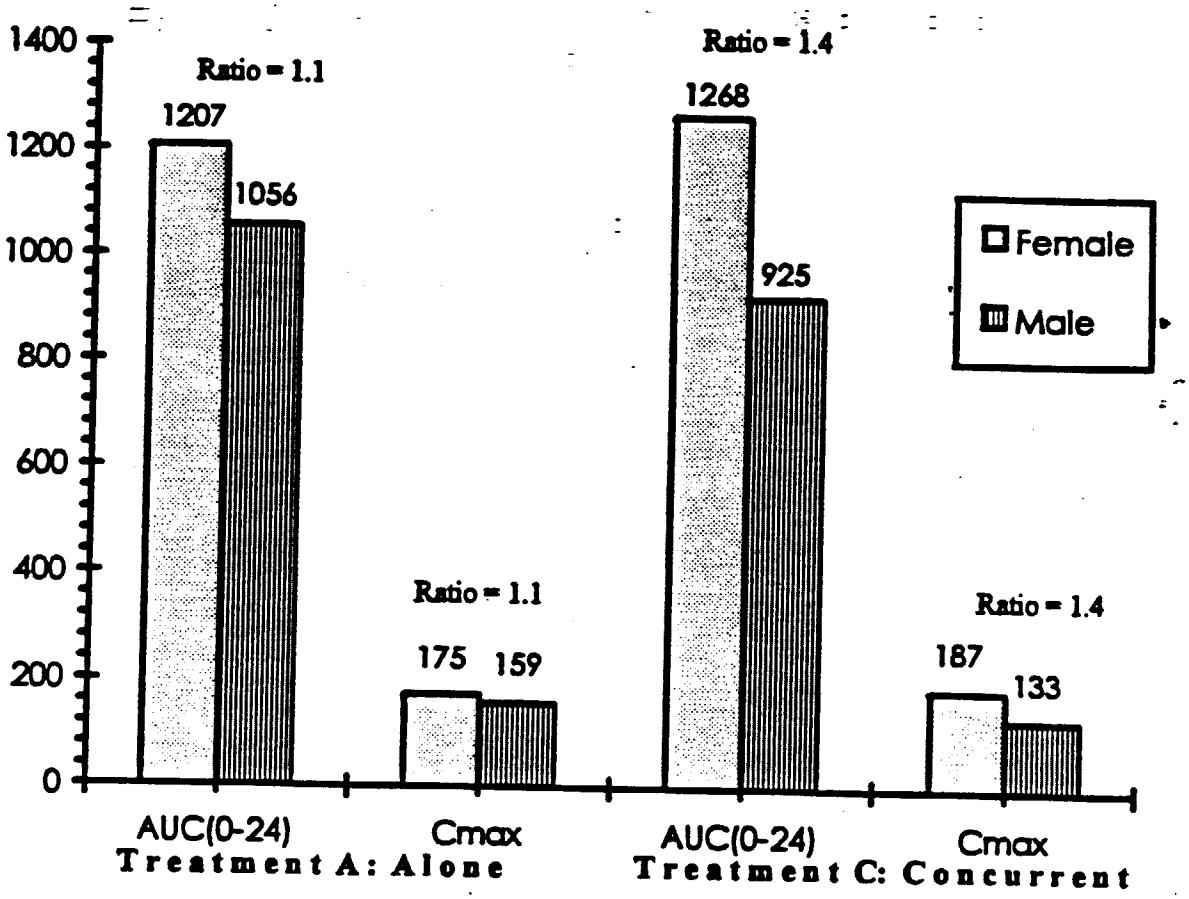
FIGURE 4. HCTZ Plasma AUC_{0-24} and C_{max} by Gender in Terms of Geometric Means



CONCLUSIONS: The data obtainned from the study showed that upon co-administration of telmisartan with HCTZ:

1. Bioequivalence of the two treatments was demonstrated for telmisartan with respect to AUC but not with Cmax.
2. Bioequivalence of the two treatments was demonstrated for HCTZ with respect to AUC, Cmax and amount of HCTZ excreted in urine.
3. 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.

TELMISARTAN-IBUPROFEN INTERACTION STUDY

STUDY 502.125 = VOLUMES: 1.104 - 1.105

INVESTIGATOR AND LOCATION:

STUDY DATE : May - July 1995.

OBJECTIVES: To investigate the influence of co-administered Telmisartan 120 mg daily on the pharmacokinetics of R-(-)-/S-(+)-Ibuprofen 400 mg t.i.d. over a administration period of 7 days.

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A1A, Batch no.: 31123
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE TA 030 2A1A, Batch no.: 31122
Ibuprofen tablets (400 mg), Ibuprofen 400 Heumann, Batch no.: 409509 = 502.125.

STUDY DESIGN: This was a two way crossover, randomized, open, multiple oral dose design with 12 healthy subjects (6 male, 6 female) and a wash out period of 13 days. Subjects received 400 mg Ibuprofen t.i.d. over 7 days (treatment 1, reference) and in the other trial period 400 mg Ibuprofen t.i.d. co-administered with 120 mg Telmisartan daily. (treatment 2, test), telmisartan dosing was simultaneously with the 400 mg Ibuprofen morning dose. Plasma levels of Telmisartan and/or Ibuprofen were determined at the following time points:*day 1*: before administration of the morning dose, *day 2 - day 6*: trough levels (before morning dose), *day 7*: before administration, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 23, 24, 36, 48, 72 and 96 hours after the morning administration of day 7.

ASSAYS:

DATA ANALYSIS: AUC, C_{max}, t_{max}, $t_{1/2}$, MRT_{ss}, R_A, $t_{max,ss}$, CL_{tot}/f, V_z/f of R(-)/S-(+)-Ibuprofen and telmisartan and ratio R/S-ibuprofen were determined. Analysis of variance (ANOVA) for crossover design was done, and 90% confidence intervals were calculated

RESULTS: Tables 1-7 and Figures 1-2 summarize the data obtained from the study.

TABLE 1. Descriptive statistics of AUC_{ss} values for R-(-)- and S-(+)- Ibuprofen after treatment 1 (reference, Ibuprofen) and treatment 2 (test, Ibuprofen + Telmisartan)

Parameter	Unit	Ibuprofen enantiomer	Treatment	N	Geom. Mean	Arithm. Mean	GCV (%)
AUC_{ss}	µg·h/ml]	R-(-)	1	12	128	134	29.3
			2	12	123	125	25.2
		S-(+)	1	12	179	186	30.5
			2	12	183	189	27.2

TABLE 2. Descriptive statistics of C_{maxss} values for R-(-)- and S-(+)- Ibuprofen after treatment 1 (reference, Ibuprofen) and treatment 2 (test, Ibuprofen + Telmisartan)

Parameter	Unit	Ibuprofen enantiomer	Treatment	N	Geom. Mean	Arithm. Mean	GCV (%)
$C_{max,ss}$	µg/ml]	R-(-)	1	12	17.3	17.8	26.2
			2	12	16.7	17.1	22.8
		S-(+)	1	12	19.4	19.7	19.4
			2	12	19.5	20.0	22.7

TABLE 3. 90% confidence limits and point estimators of the ratio of the parameters $C_{max,ss}$ and AUC_{ss} for R-(-)-Ibuprofen and S-(+)-Ibuprofen after treatment 1 (reference, Ibuprofen) and treatment 2 (test, Ibuprofen + Telmisartan).

TEST (Treatment 1 vs Treatment 2)	Ratio for parameter	Point estimator	Lower 90% confidence limit	Upper 90% confidence limit
R-(-)-Ibuprofen	AUC_{ss}	95.8	87.0	105.6
	$C_{max,ss}$	96.9	84.8	110.6
S-(+)-Ibuprofen	AUC_{ss}	102.3	93.8	111.5
	$C_{max,ss}$	100.7	92.7	109.4

TABLE 4. $t_{max,ss}$ values of R-(-)- and S-(+)-Ibuprofen after treatment 1 (reference) and treatment 2 (test).

Parameter	Unit	Ibuprofen enantiomer	Treatment	Adm. time	N	Median	Minimum	Maximum
$t_{max,ss}$	[h]	R-(-)	1	144	12	145.5	145	157
			2	144	12	145.5	144.5	157
		S-(+)	1	144	12	145.5	145	158
			2	144	12	151	145	158

TABLE 5. Further secondary parameters of R-(-)- and S-(+)-Ibuprofen after treatment 1 (reference) and treatment 2 (test).

Parameter	Unit	Ibuprofen enantiomer	Treatment	N	Geom. mean	Arith. mean	GCV%
MRT_{ss}	[h]	R-(-)	1	12	9.65	9.69	8.93
			2	12	9.92	10.0	13.1
		S-(+)	1	12	9.87	9.89	5.75
			2	12	10.2	10.2	6.67
$t_{1/2}$	[h]	R-(-)	1	12	2.70	2.92	40.6
			2	12	2.43	2.54	31.5
		S-(+)	1	12	2.44	2.54	27.8
			2	12	2.36	2.42	22.6
CL/f	[ml/min]	R-(-)	1	12	52.0	53.8	29.3
			2	12	54.3	55.4	22.6
		S-(+)	1	12	37.3	38.8	30.5
			2	12	36.4	37.6	27.2
V_z/f	[l]	R-(-)	1	12	12.2	12.9	37.0
			2	12	11.4	11.8	27.9
		S-(+)	1	12	7.88	8.48	39.8
			2	12	7.44	7.64	24.4

AGE / GENDER EFFECT STUDY

STUDY 502.124 = VOLUMES: 1.111 - 1.112

INVESTIGATOR AND LOCATION:

STUDY DATE : October 1994 - Febrary 1995.

OBJECTIVES: To investigate the pharmacokinetics and safety of single and repeated doses of telmisartan (20 and 120 mg) in elderly healthy subjects

FORMULATIONS:
Telmisartan Tablet (200 mg), Pharmaceutical code BIBR 277 SE TA 030 1A1A
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A1A
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE 030 2A1A

STUDY DESIGN: The study was a single-centre, open, randomised, two-way cross-over study with 12 healthy volunteers (6 male, 6 female, age 65 to 78 years) and a washout period of 14 days. Each subject was administered 20 or 120 mg (40 mg + 80 mg) telmisartan tablets daily for 7 days during each period of the study. Blood samples were collected before and 0.5, 1, 1.5, 2, 3, 6, 9 and 12 hours after dosing on Day 1, before and 0.5, 1 and 3 hours after dosing on Days 2 to 6 and before and 0.5, 1, 1.5, 2, 3, 6, 9, 12, 24, 48 and 72 hours after dosing on Day 7 (steady state). Plasma samples were stored at -20°C until assayed for telmisartan. A sample was taken at 0.5 hours on Day 7 of each period for determination of plasma protein binding.

ASSAYS:

DATA ANALYSIS: C_{max}, $C_{max,ss}$, AUC_{0-24}, AUC_{ss}, t_{max}, $t_{max,ss}$, $t_{1/2}$, MRT_{tot}, and R_A (the ratio of accumulation for C_{max} and AUC); plasma protein binding were calculated.

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

Table 1: Summary statistics of model free pharmacokinetic parameter after administration of 20 mg telmisartan

20 mg		arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	19.2	35.9	19.8	7.94	29.3	17.9	41.9
t_{max}	h	12	1.50	161	0.500	0.500	9.00		
AUC_{0-24h}	ng·h/ml	12	187	65.6	170	53.4	527	159	64.1
$C_{max,ss}$	ng/ml	12	34.0	72.8	25.8	10.7	98.6	28.3	66.0
$t_{max,ss}$	h	12	1.42	112	0.500	0.500	6.00	0.953	105
$C_{pre,ss}$	ng/ml	12	12.6	174	6.99	1.21	81.5	6.90	127
$t_{½}$	h	12	39.2	39.2	39.3	19.4	64.1	36.4	42.5
AUC_{ss}	ng·h/ml	12	402	123	268	97.6	1940	287	85.1
MRT_{tot}	h	12	43.9	35.4	42.8	21.9	67.8	41.3	38.5
Cl_{tot}/f	ml/min	12	1410	60.8	1260	172	3410	1160	85.0
V_z/f	l	12	4370	68.5	3570	887	12900	3660	70.0
$R_A(AUC)$		12			1.68	1.03	3.68	1.80	38.5
$R_A(C_{max})$		12			1.43	0.894	3.40	1.58	41.0

Table 2: Summary statistics of model free pharmacokinetic parameter after administration of 120 mg telmisartan

120 mg		arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	751	99.6	468	115	2850	533	102
t_{max}	h	12	0.875	55.2	0.750	0.500	2.00		
AUC_{0-24h}	ng·h/ml	12	1770	71.8	1570	356	4740	1420	79.5
$C_{max,ss}$	ng/ml	12	966	98.6	501	105	2700	592	147
$t_{max,ss}$	h	12	1.00	56.4	1.00	0.500	2.00	0.870	59.1
$C_{pre,ss}$	ng/ml	12	49.1	130	31.7	9.62	248	33.6	94.4
$t_{½}$	h	12	41.9	51.9	36.2	18.0	91.8	37.2	53.9
AUC_{ss}	ng·h/ml	12	2920	98.2	1990	545	11500	2200	86.3
MRT_{tot}	h	12	31.7	58.9	25.4	12.0	72.8	27.1	63.8
Cl_{tot}/f	ml/min	12	1150	77.8	1020	173	3670	909	86.5
V_z/f	l	12	4720	103	2120	572	16800	2930	140
$R_A(AUC)$		12			1.64	0.929	2.43	1.55	27.6
$R_A(C_{max})$		12			0.999	0.271	3.27	1.11	85.4

Table 3: Gender effects

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

Table 4: Percentage of telmisartan bound to plasma protein.

Subject	% bound, 20 mg dose	% bound, 120 mg dose
1	> 99.5	> 99.5
2	> 99.5	> 99.5
3	> 99.5	97.6
4	> 99.5	> 99.5
5	> 99.5	97.9
6	> 99.5	> 99.5
7	> 99.5	97.4
8	97.5	99.5
9	*	> 99.5
10	> 99.5	drop out
11	no sample	> 99.5
12	> 99.5	no sample
13	drop out	drop out
14	not done	not done

* value was out of acceptance range, no plasma left for reanalysis

FIGURE 1: Individual and Geometric Mean Plasma Concentration-time Profiles for 20 mg BIBR 277 SE on Day 1 and Day 7

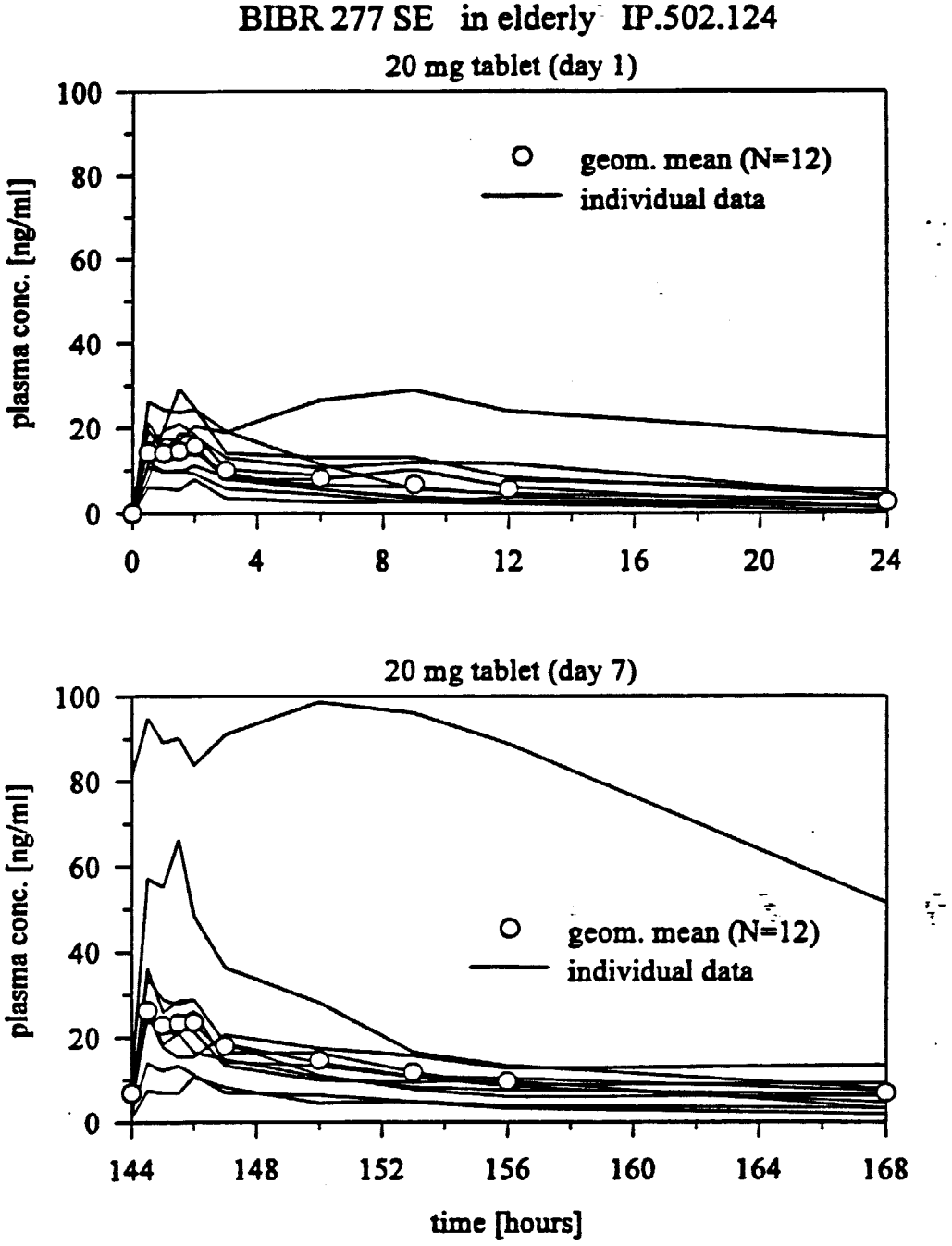


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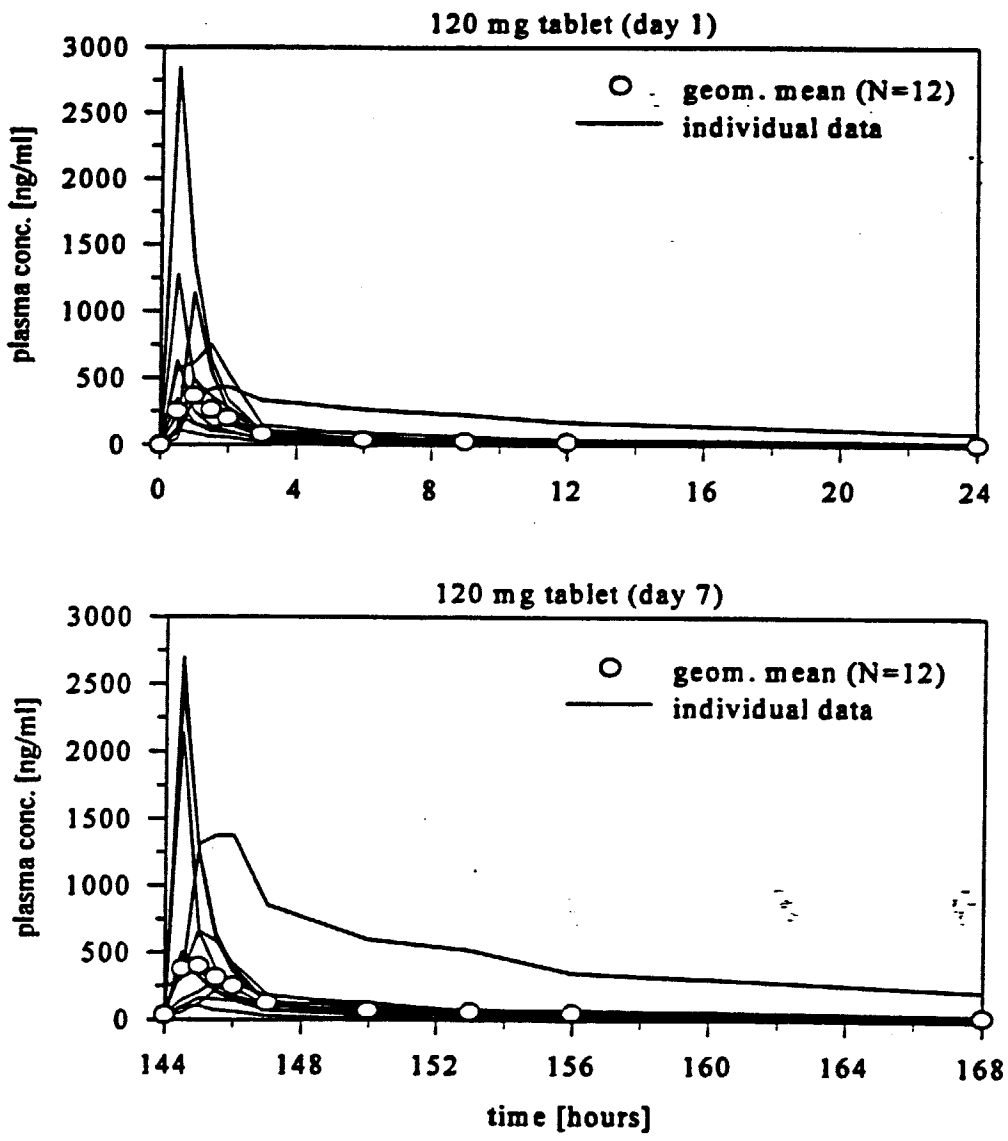
FIGURE 2: Individual and Geometric Mean Plasma Concentration-time Profiles for 120 mg BIBR 277 SE on Day 1 and Day 7



CONCLUSIONS: The results obtained from the study showed that

1. 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 - 1918 ng/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.
2. 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.
3. No decrease in protein binding of telmisartan was present in elderly subjects.

HEPATIC IMPAIRMENT STUDY

STUDY 502.123 **VOLUMES: 1.115 - 1.117**

INVESTIGATOR AND LOCATION:

STUDY DATE : October - December 1994.

OBJECTIVES: To investigate the pharmacokinetic variables after single oral dosing of telmisartan administered as 20 and 120 mg tablets to subjects with impaired liver function compared to healthy controls and, for the oral part of the study, to generate additional data on safety and tolerance. The subsequent administration of 60 and 120 mg BIBR 277 SE as intravenous infusion to subjects with impaired liver function should provide further information on the pharmacokinetic profile in the group of hepatically impaired subjects with regard to the significantly increased pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$.

FORMULATIONS:
Telmisartan Tablet (20 mg), Pharmaceutical code BIBR 277 SE TA 030 1A1A
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA 030 3A1A
Telmisartan Tablet (80 mg), BIBR 277 SE TA 030 2A1A

STUDY DESIGN: The study was an open label, two-period, group comparison (matched-pairs technique), single oral dose design with 12 hepatically impaired subjects (Child Pugh Score A or B) and 12 healthy controls and a washout period of 14 days. Each subject was administered single dose of 20 or 120 mg (40 mg + 80 mg) telmisartan tablets during each period of the study. Blood sampling time points for determination of telmisartan were as follows: pre dose and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0 h post dose. Additional blood samples were withdrawn for determination of telmisartan plasma protein binding at 0.5, 2.0 and 6.0 h post dose. Seven (7) male volunteers with impaired and compensated liver function out of the group of twelve (12) subjects who already received the 20 and 120 mg oral dose of telmisartan were included in the intravenous (30 minutes infusion 0f 120 mg) part of the study. Two out of seven subjects preceded the other participants as doseleaders for safety reasons and received only half of the intended dose (i.e. 60 mg telmisartan). Plasma levels of telmisartan were determined by a validated method at the following time points: at pre dose and at 5, 7.5, 10, 15, 20, 25, 29 minutes during infusion as well as at 31, 33, 36, 39, 45 minutes, and 1, 1.25, 1.5, 2.5, 3.5, 6.5, 8.5, 12.5, 24.5, 48.5, 72.5 h after start of infusion.

ASSAYS:

DATA ANALYSIS: AUC_{0-24h}, t_{max}, $t_{1/2}$, λ_z, MRT_{tot}, CL_{tot}/f, V_z/f after oral administration; $AUC_{0-24.5h}$, $t_{1/2}$, CL_{tot}, V_z, V_{ss}, MRT_{disp} after intravenous dosing.

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

TABLE 1: Summary statistics of model free pharmacokinetic parameter, 20 mg telmisartan administered to patients with hepatic impairment

20 mg patients		arithm.					Geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	105	84.5	80.4	10.5	265	68.7	141
t_{max}	h	12	1.25	94.2	0.500	0.500	4.00		
$t_{½}$	h	12	36.4	67.7	27.1	16.3	95.8	30.8	62.2
AUC_{0-24h}	ng·h/ml	12	492	49.5	466	112	836	425	67.2
$AUC_{tf-\infty}$	%	12	14.4	98.5	9.44	2.50	49.9	9.69	117
$AUC_{0-\infty}$	ng·h/ml	12	1290	93.7	1130	355	4930	996	81.2
MRT_{tot}	h	12	49.5	66.6	37.0	21.9	137	42.5	58.4
Cl_{tot}/f	ml/min	12	412	66.2	295	67.6	939	334	81.2
V_z/f	l	12	1130	85.2	889	386	3840	893	75.4

TABLE 2: Summary statistics of model free pharmacokinetic parameter, 20 mg telmisartan administered to healthy subjects.

20 mg healthy subj.		arithm.					Geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	16.2	35.2	15.3	7.73	26.7	15.3	37.2
t_{max}	h	12	2.50	57.8	3.00	0.500	4.00		
$t_{½}$	h	12	24.6	40.3	23.3	13.2	48.5	23.1	38.5
AUC_{0-24h}	ng·h/ml	12	208	41.6	194	105	409	194	40.4
$AUC_{tf-\infty}$	%	12	8.70	69.3	6.87	3.49	26.6	7.57	53.8
$AUC_{0-\infty}$	ng·h/ml	12	471	75.1	415	174	1530	401	58.6
MRT_{tot}	h	12	35.7	38.5	33.0	17.3	71.9	33.7	36.3
CL_{tot}/f	ml/min	12	934	46.7	804	217	1920	831	58.7
V_z/f	l	12	1780	42.4	1660	912	3830	1660	39.0

TABLE 3: Summary statistics of model free pharmacokinetic parameter, 120 mg telmisartan administered to patients with hepatic impairment.

120 mg patients		arithm.					geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	1520	54.9	1330	514	3280	1340	57.2
t_{max}	h	12	0.917	51.1	1.00	0.500	2.00		
$t_{½}$	h	12	31.8	88.7	24.5	12.6	119	26.3	60.1
AUC_{0-24h}	ng·h/ml	12	5420	53.1	5130	1470	11300	4700	63.6
$AUC_{tf-\infty}$	%	12	9.19	155	5.54	0.460	53.3	4.63	188
$AUC_{0-\infty}$	ng·h/ml	12	11300	107	7800	2760	48400	8490	80.4
MRT_{tot}	h	12	37.6	104	26.5	14.4	159	29.3	70.2
CL_{tot}/f	ml/min	12	285	61.3	257	41.3	724	236	80.4
V_z/f	l	12	599	43.3	612	188	1010	537	56.4

TABLE 4: Summary statistics of model free pharmacokinetic parameter, 120 mg telmisartan administered to healthy subjects.

120 mg healthy subj.		arithm.					geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
C_{max}	ng/ml	12	475	37.1	486	167	760	438	47.5
t_{max}	h	12	1.00	42.6	1.00	0.500	2.00		
$t_{½}$	h	12	27.1	32.4	25.4	18.5	46.4	25.9	30.6
AUC_{0-24h}	ng·h/ml	12	2170	50.3	1990	758	4790	1940	53.1
$AUC_{tf-\infty}$	%	12	6.52	81.9	4.20	1.65	16.8	4.94	88.2
$AUC_{0-\infty}$	ng·h/ml	12	3670	68.7	3230	1490	11100	3190	55.0
MRT_{tot}	h	12	28.8	39.1	25.0	14.4	47.8	26.9	39.1
CL_{tot}/f	ml/min	12	697	43.8	622	180	1340	627	55.0
V_z/f	l	12	1690	75.5	1420	590	5400	1410	64.9

TABLE 5: Summary statistics on model free pharmacokinetic after 30 minute infusion of 120 mg BIBR 277 SE to liver insufficient subjects.

120 mg infusion			arithm.					geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
$C_{29'}$	ng/ml	5	2680	29.3	2720	1740	3710	2590	31.0
$t_{½}$	h	5	30.3	41.9	28.5	17.7	49.7	28.3	42.8
$AUC_{0-24.5h}$	ng·h/ml	5	5540	27.5	5670	3850	7580	5370	28.5
$AUC_{0-\infty}$	ng·h/ml	5	8870	37.3	10500	4900	12200	8320	43.5
$AUC_{t_f-\infty}$	%	5	11.6	70.7	8.10	3.22	21.7	9.17	94.4
MRT_{tot}	h	5	28.5	49.2	20.2	14.8	44.1	25.8	52.8
MRT_{disp}	h	5	28.2	49.6	20.0	14.5	43.8	25.5	53.4
CL_{tot}	ml/min	5	258	43.3	190	164	408	240	43.6
V_z	l	5	620	33.6	625	344	857	589	38.1
V_{ss}	l	5	379	25.1	415	227	476	368	29.5

Assessment of telmisartan protein binding

Independent of the time of blood sampling, telmisartan is bound to plasma proteins to an extent of > 99%. The group of 12 healthy controls presents an extent of telmisartan protein binding of 99.2 - 99.6% for the treatment with 20 mg and a mean of 99.5% (arithm. mean) for the treatment with 120 mg telmisartan. In the group of subjects with hepatic impairment the extent of protein binding was > 99.5% after administration of 20 mg. The mean percentage binding at 120 mg was 99.5%. This indicates that there is no change in protein binding of telmisartan in subjects with hepatic impairment

FIGURE 1: Plasma concentration-time plots of telmisartan after oral administration of 20 and 120 mg

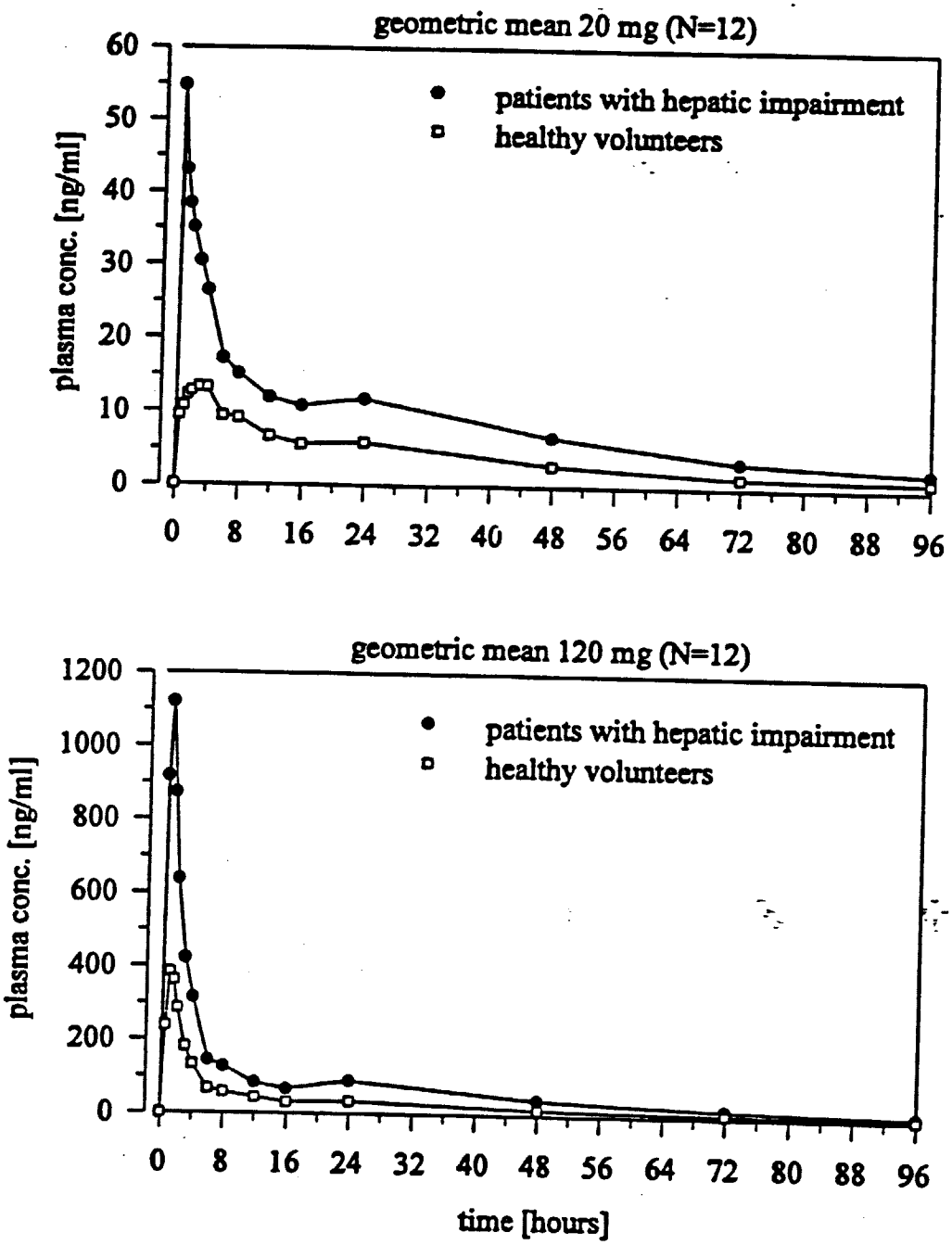


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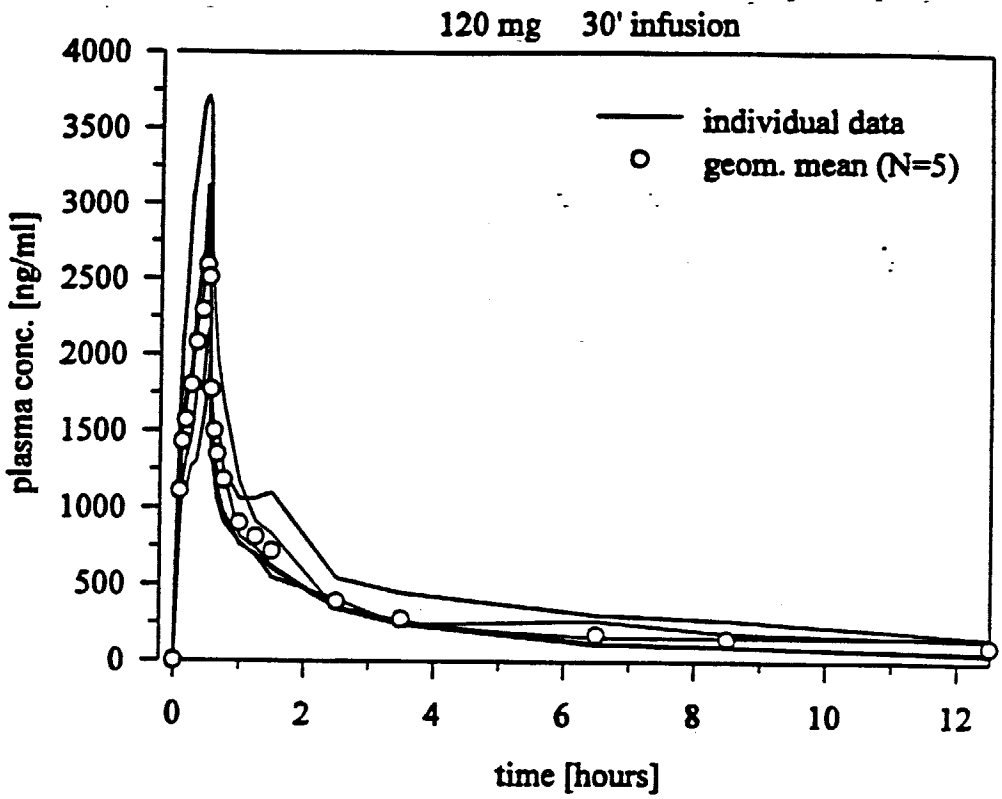
FIGURE 2: Individual plasma concentration-time plots of telmisartan after intravenous infusion of 120 mg



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CONCLUSIONS: The data obtainned from the study showed that:

1. 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.
2. At the 120 mg dose level, there was aapproximately 3 fold increase in C_{max} and $AUC_{0-\infty}$ and about 60% decrease in oral clearance 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.
3. The absolute bioavailability of telmisartan in hepatically impaired subjects was close to 100 %, whereas in healthy subjects absolute bioavailability was approximately 50 %.
4. As increase in bioavailability and decrease in hepatic clearance implicate a multiplicative effect on the $AUC_{0-\infty}$, a dose reduction of telmisartan should be considered when administered orally to patients with liver disease
5. Telmisartan is bound to plasma proteins to an extent of > 99% in the subjects with hepatic impairment as well as in the healthy controls.

TABLE 6. Summary statistics of pharmacokinetic parameters. Treatment 2, (Ibuprofen+BIBR 277 SE) **male** (upper) and **female** (lower).

male

Ibuprofen+ BIBR 277 SE			arithm.					geom.	
Parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
$C_{max,ss}$	ng/ml	6	376	98.8	215	59.2	907	231	162
$t_{max,ss}$	h	6	1.08	34.7	1.00	0.500	1.50		
AUC_{ss}	ng·h/ml	6	1610	90.3	1130	201	3800	1030	160
$t_{½}$	h	5	28.3	40.7	27.4	15.5	43.6	26.4	44.4
MRT_{tot}	h	5	24.5	22.4	26.9	15.0	28.3	23.9	27.1
CL_{tot}/f	ml/min	6	3250	111	1790	527	9940	1940	160
V_z/f	l	5	7310	129	2670	707	23600	3700	222

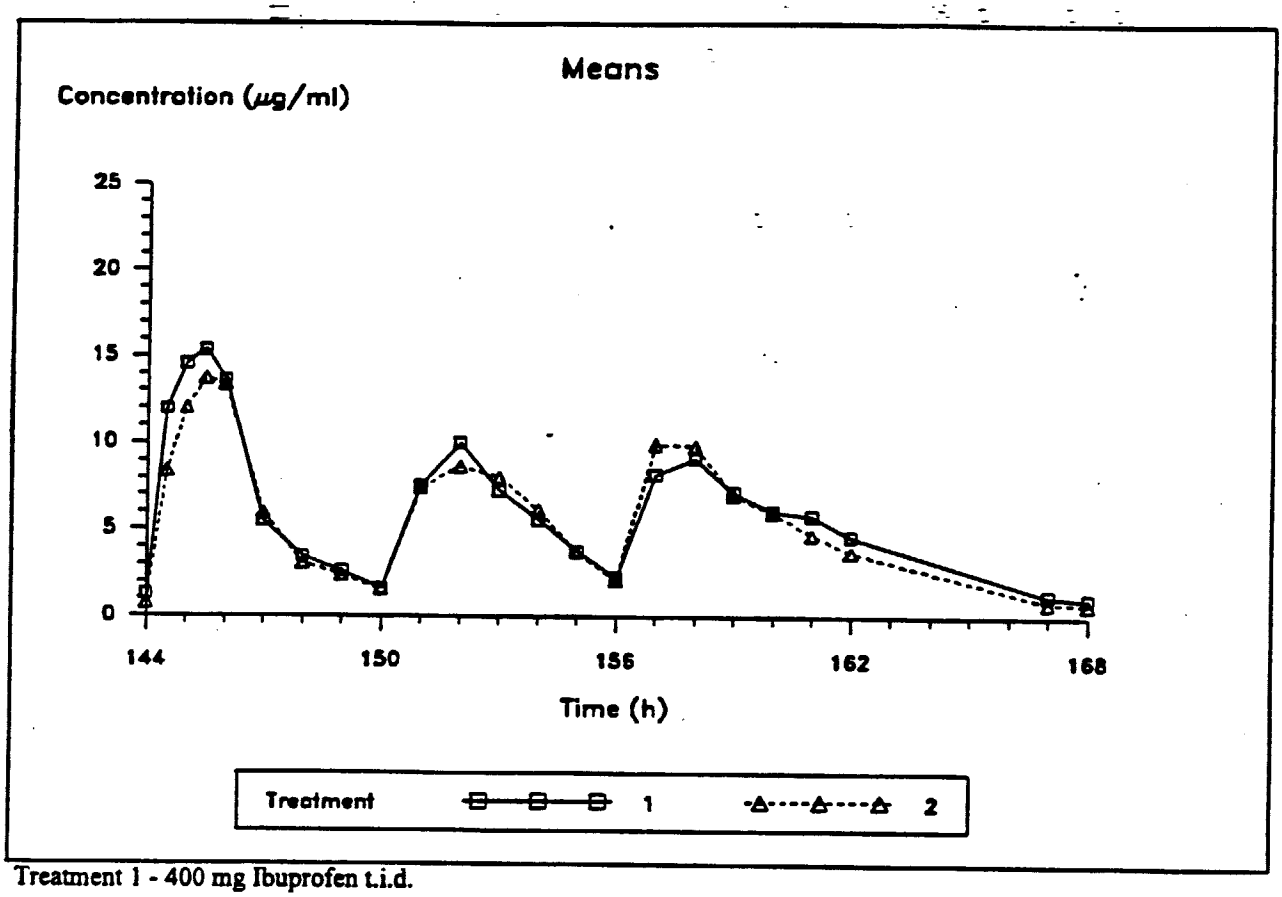
female

Ibuprofen+ BIBR 277 SE			arithm.					geom.	
parameter	unit	N	mean	CV (%)	median	min	max	mean	gCV (%)
$C_{max,ss}$	ng/ml	6	511	69.8	412	149	1100	413	84.5
$t_{max,ss}$	h	6	1.17	51.9	1.25	0.500	2.00		
AUC_{ss}	ng·h/ml	6	1530	68.9	1080	593	3160	1270	75.4
$t_{½}$	h	6	51.0	99.8	24.4	20.3	149	37.2	94.8
MRT_{tot}	h	6	34.9	70.7	26.3	16.6	82.4	29.7	64.8
CL_{tot}/f	ml/min	6	1870	57.0	1900	632	3370	1580	75.4
V_z/f	l	6	9520	128	5850	1110	33600	5090	192

TABLE 7 Comparison of geometric Means of $C_{max,ss}$ and AUC_{ss} of BIBR 277 SE, Trials 502.119, 502.120, 502.122, 502.124, 502.126 and 502.125

N	dose [mg]	sex []	trial	$C_{max,ss}$ [ng/ml]	CV%	AUC_{ss} [ng·h/ml]	CV%
12	120	m	502.119	574	90	1462	83
12	120	m	502.120	371	58	1230	72
12	120	m	502.122	355	112	1650	76
5	120	m	502.124	247	113	1440	127
12	120	m	502.126	494	116	1590	109
6	**120**	**m**	**502.125**	**231**	**162**	**1030**	**160**
6	**120**	**f**	**502.125**	**413**	**85**	**1270**	**75**

FIGURE 1: **Arithmetic mean plasma concentrations of R-(-)-Ibuprofen on day 7 after multiple oral administration of 400 mg Ibuprofen t.i.d over 7 days.**



Treatment 1 - 400 mg Ibuprofen t.i.d.
Treatment 2 - 400 mg Ibuprofen t.i.d./120 mg Telmisartan o.d.

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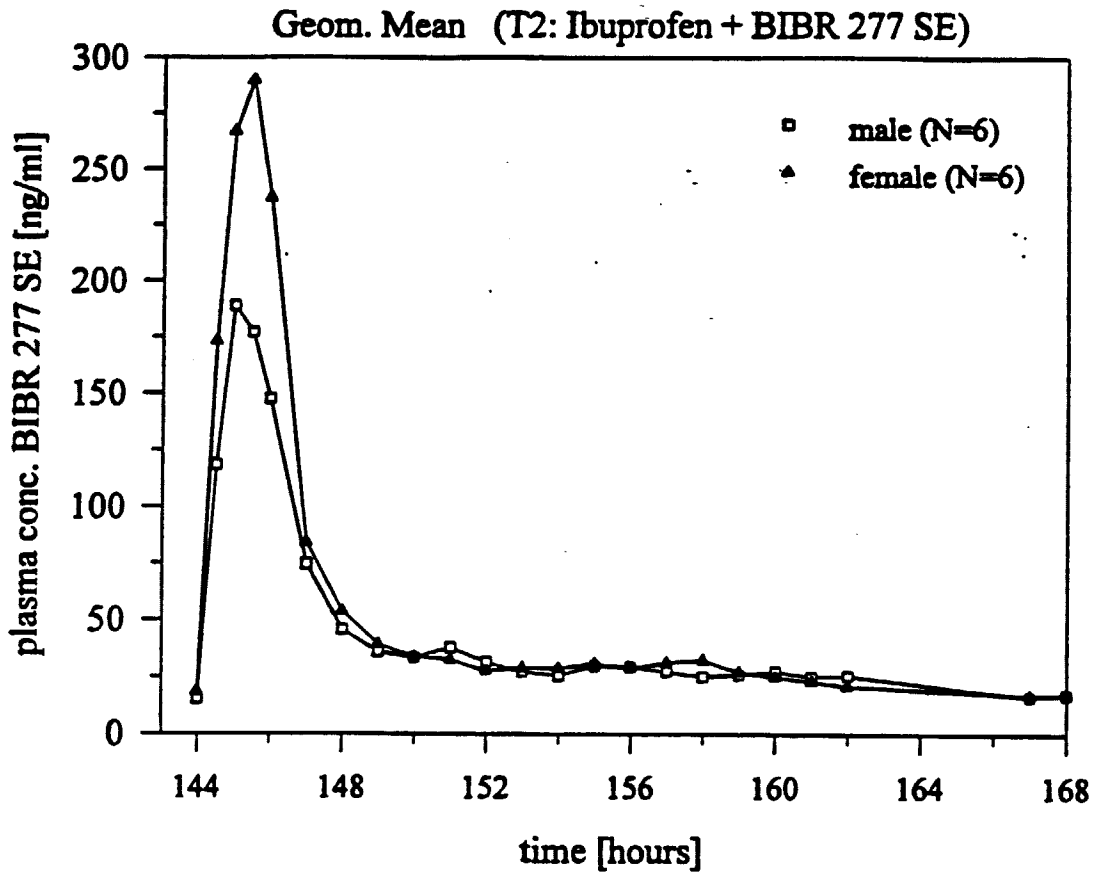
FIGURE 2: Geometric mean plasma concentration-time plots of telmisartan for male and female subjects.



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CONCLUSIONS: The data obtainned from the study showed that upon co-administration of telmisartan with ibuprofen:

1. Bioequivalence of the two treatments was demonstrated for the Ibuprofen enantiomers after both treatment regimens thus showing that that concomitant administration of telmisartan had no influence on the pharmacokinetics of Ibuprofen.
2. 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.
3. There is a trend toward higher C_{max} and lower oral clearance for telmisartan in female subjects.

TELMISARTAN-AMLODIPE INTERACTION STUDY

STUDY 502.126 **VOLUMES: 1.109 - 1.110**

INVESTIGATOR AND LOCATION:

STUDY DATE : May - July 1995.

OBJECTIVES: To assess the safety and pharmacokinetic interactions between amlodipine and telmisartan.

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code BIBR 277 SE TA TA 030 3A1A
Telmisartan Tablet (80 mg), Pharmaceutical code BIBR 277 SE TA TA 030 2A1A
Amlodipine, Norvasc® 5 mg tablets

STUDY DESIGN: This was a two way crossover, randomized, open, multiple oral dose design with 12 healthy male subjects and a wash out period of 15 days. Subjects received received nine days of oral medication of amlodipine 10 mg/day or amlodipine 10 mg/day plus telmisartan 120 mg/day. Plasma levels of telmisartan and/or amlodipine were determined at the following time points during both medication periods: day 1: before administration, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 h post dose; day 2 through day 8: morning trough levels; day 9: before administration, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 48, 72 and 96 h after last administration.

ASSAYS:

DATA ANALYSIS: AUC_{SS}, AUC_{day1}, C_{max}, $C_{max,ss}$, t_{max}, $t_{max,ss}$, $t_{1/2}$, MRT_{ss}, Cl_{tot}/f, V_Z/f, R_A, Ae, CL_{ren}, amlodipine. Analysis of variance (ANOVA) for crossover design was done, and 90% confidence intervals were calculated

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

TABLE 1. Comparison of Pharmacokinetic Variables of Amlodipine and Amlodipine/Telmisartan

			Treatment 1 Amlodipine		**Treatment 2 Amlodipine+BIBR 277 SE**	
Parameter	Unit	N	Geom. Mean	gCV (%)	Geom. Mean	gCV (%)
C_{max}	ng/ml	12	5.40	27.0	5.55	31.8
t_{max}	h	12	7.00*		8.00*	
$C_{max,ss}$	ng/ml	12	17.7	29.6	18.7	29.6
$t_{max,ss}$	h	12	6.00*		6.00*	
$C_{pre(192h)}$	ng/ml	12	10.2	39.5	11.5	33.5
AUC_{0-24h}	ngh/ml	12	90.5	22.9	95.8	27.0
AUC_{ss}	ngh/ml	12	331	32.1	352	30.9
$t_{½}$	h	12	55.9	39.2	52.0	33.0
MRT_{tot}	h	12	77.7	34.5	70.4	27.8
CL_{tot}/f	ml/min	12	504	32.1	474	31.0
V_Z/f	l	12	2440	38.4	2130	32.0
R_A (AUC)		12	3.66	22.8	3.67	18.4
R_A (C_{max})		12	3.28	27.0	3.38	18.6

* median, R_A= Accumulation Index

TABLE 2 Urinary Excretion and Renal Clearance of 10 mg Amlodipine

Parameter	Unit	N	Treatment 1 Amlodipine Geom. Mean	gCV (%)	Treatment 2 Amlodipine+BIBR 277 SE Geom. Mean	gCV (%)
$A_{e,ss}$	% dose	12	7.98	51.6	9.36	33.2
CL_{ren}	ml/min	12	39.5	51.0	43.0	37.8

TABLE 3. Analysis of Variance, 90 % Confidence Interval Limits

Parameter	Lower Limit	Point Estimator	Upper Limit
C_{max}	0.85	1.03	1.24
$C_{max,ss}$	0.97	1.06	1.14
AUC_{0-24h}	0.91	1.06	1.23
AUC_{ss}	0.98	1.06	1.16
$t_{½}$	0.76	0.93	1.14
MRT_{tot}	0.78	0.91	1.05
CL_{tot}/f	0.86	0.94	1.03
CL_{ren}	0.79	1.09	1.50
V_z/f	0.70	0.88	1.10
A_e	0.86	1.17	1.61
$C_{max,ss}/AUC_{ss}$	0.95	0.99	1.04

TABLE 4: Comparison of geometric Means of C_{max}, $C_{max,ss}$ AUC_{0-24h} and AUC_{ss} of BIBR 277 SE, Trials 502.119, 502.120, 502.124 and 502.126

N	dose [mg]	sex []	trial	C_{max} [ng/ml]	$C_{max,ss}$ [ng/ml]	AUC_{0-24h} [ng·h/ml]	AUC_{ss} [ng·h/ml]
6	120	m	502.124	284	329	1140	2040
5*	120	m	502.124	260	247	856	1440
12	120	m	502.126	311	494	1000	1590
12	120	m	502.120	433	371	1130	1230
12	120	m	502.119	—	574	—	1462

* one subject excluded from calculation of means (changed elimination kinetics)

FIGURE 1: Comparison of median, arithmetic and geometric mean plasma concentration-time profiles of telmisartan observed at day 1 and day 9 after once daily administration of 120 mg telmisartan and 10 mg amlodipine. (Treatment 2)

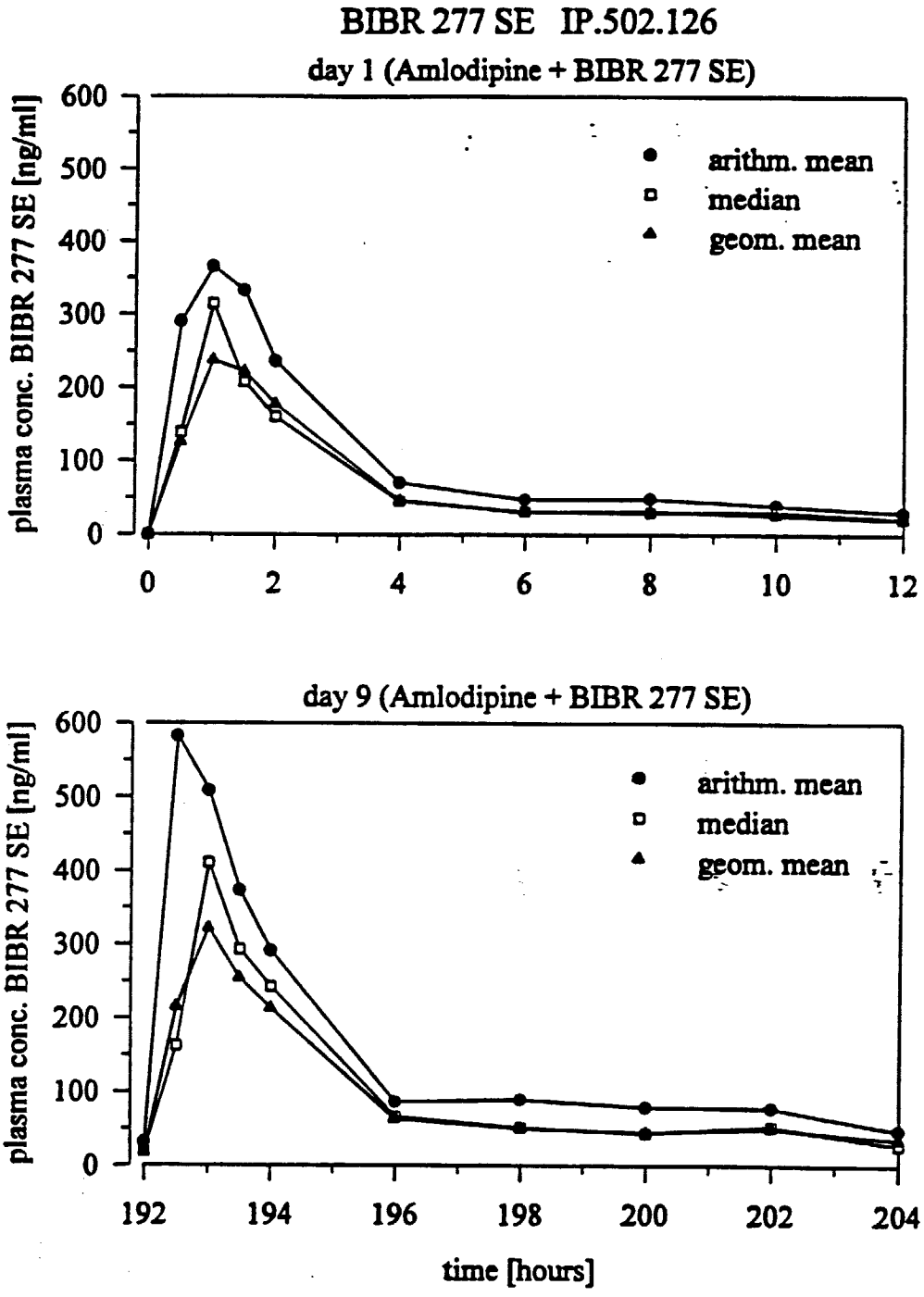
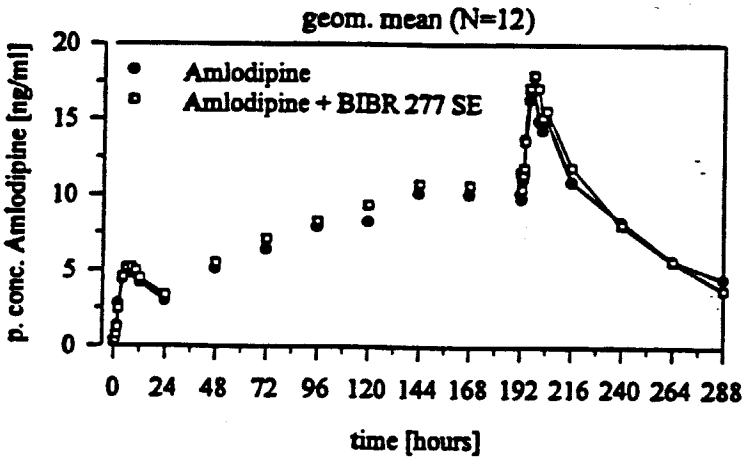


FIGURE 2: Mean amlodipine plasma concentration-time profiles alone and with concurrent administration of telmisartan



CONCLUSIONS: The data obtainned from the study showed that upon co-administration of telmisartan with amlodipine:

1. 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%.
2. 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.

TELMISARTAN - GLIBENCLAMIDE INTERACTION STUDY

STUDY 502.122 **VOLUMES: 1.107 - 1.108**

INVESTIGATOR AND LOCATION:

STUDY DATE : May - June 1995.

OBJECTIVES: To assess the safety and pharmacokinetic interactions between glibenclamide and telmisartan.

FORMULATIONS:
Telmisartan Tablet (40 mg), Pharmaceutical code: BIBR 277 SE TA 30 3A1A, Batch No. 31123
Telmisartan Tablet (80 mg), Batch No. 31122
1.75 mg glibenclamide, tablet, Semi-Euglucon® N, Batch No. 01Do34

STUDY DESIGN: The study was performed in a single period, open, uncontrolled, multiple dosing design with 12 healthy volunteers in one centre. Volunteers received 1.75 mg glibenclamide daily for six days and afterwards 1.75 mg glibenclamide daily and 120 mg telmisartan daily for seven further days. Blood samples for determination of glibenclamide serum concentrations were taken predose on days 1 to 13, during twelve hours on days 6 and 7 (before administration, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 h after drug administration) and up to 96 hours after dosage on day 13. Blood samples for determination of telmisartan were taken predose on days 7 to 13, during 12 hours on day 7 and up to 96 hours after drug administration on day 13 (before administration, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96 h after drug administration).

ASSAYS:

DATA ANALYSIS: $C_{max,ss}$, AUC_{ss}, $t_{max,ss}$, λ_z, $t_{½ss}$, MRT_{ss}, CL/f, V_z/f (days 6, 7 and 13) of glibenclamide, C_{max}, t_{max}, $C_{max,ss}$, $C_{pre,ss}$, $t_{max,ss}$, $t_{1/2}$, AUC_{day1}, AUC_{ss}, MRT_{tot}, CL_{tot}/f, V_z/f, $C_{max,ss}/AUC_{ss}$, $R_A(AUC)$, $R_A(C_{max})$ of telmisartan. Analysis of variance (ANOVA) for crossover design was done, and 90% confidence intervals were calculated.

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

TABLE 1: Summary Statistics of Telmisartan Pharmacokinetic Parameters

BIBR 277 SE + Glibenclamide					geom.	
Parameter	unit	N	min	max	mean	gCV(%)
C_{max}	ng/ml	12	76.5	921	230	94.2
t_{max}	h	12	0.500	4.00	1.00*	
$C_{max,ss}$	ng/ml	12	68.8	1060	355	112
$t_{max,ss}$	h	12	0.500	2.00	1.00*	
$C_{pre,ss}$	ng/ml	12	4.08	51.5	19.5	93.5
$t_{½}$	h	12	11.1	23.2	16.7	21.4
AUC_{0-24h}	ng*h/ml	12	256	2400	1030	75.1
AUC_{ss}	ng*h/ml	12	603	4090	1650	75.5
MRT_{tot}	h	12	12.9	24.4	16.1	19.2
CL_{tot}/f	ml/min	12	489	3320	1210	75.6
V_z/f	l	12	876	5200	1750	62.0
$C_{max,ss}/AUC_{ss}$	1/h	12	0.114	0.456	0.215	47.5
R_A (AUC)		12	1.08	2.53	1.60	25.6
R_A (C_{max})		12	0.597	7.74	1.54	88.4

* = median

TABLE 2: Comparison of geometric means of $C_{max,ss}$ and AUC_{ss} of telmisartan, Trials 502.119, 502.120, 502.124, 502.125, 502.126 and 502.122.

N	dose [mg]	sex []	trial	$C_{max,ss}$ [ng/ml]	CV%	AUC_{ss} [ng·h/ml]	CV%
5	120	m	502.124	247	113	1440	127
12	120	m	502.126	494	116	1590	109
12	120	m	502.120	371	58	1230	72
12	120	m	502.119	574	90	1462	83
12	**120**	**m**	**502.122**	**355**	**112**	**1650**	**76**

TABLE 3: Overview of Geometric Means (Arithmetic Means for $t_{max,ss}$) and of Geometric Coefficients of Variation, n=12 for glibenclamide

		day 6 gmean	day 6 gCV(%)	day 7 gmean	day 7 gCV(%)	day 13 gmean	day 13 gCV(%)
AUC_{ss}	[h*ng/ml]	277.0	24.9	286.9*	26.2*	272.8	21.2
$C_{max,ss}$	[ng/ml]	77.12	23.9	67.83	42.7	63.99	35.4
$t_{max,ss}$	[h]	1.29		1.21		1.50	
$t_{½ss}$	[h]	1.72	24.2	2.40*	26.6*	2.49	41.9
MRT_{ss}	[h]	3.21	19.0	4.02*	24.2*	4.43	36.3
CL/f	[ml/min]	105.30	24.9	101.67*	26.2*	106.92	21.2
V_z/f	[l]	15.67	21.3	21.15*	30.3*	23.02	45.0

* n = 11

TABLE 4. Analysis of Variance, 90 % Confidence Interval Limits for glibenclamide

TEST (Treatment Day)	Ratio for parameter	Point estimator	Lower 90% confidence limit	Upper 90% confidence limit
Day 7 /Day 6	AUC_{ss}	102.8	96.0	110.1
	$C_{max,ss}$	88.0	73.5	105.3
Day 13 /Day 6	AUC_{ss}	98.5	92.2	105.2
	$C_{max,ss}$	83.0	69.3	99.3

Precision: Satisfactory. %CV - 4.4% at 10 ng/ml, 2.7% at 100 ng/ml and 0.8% at 200 ng/ml
Sensitivity: LOQ - 5 ng/ml.
Selectivity: Satisfactory. Chromatograms submitted.
The assay has been validated over the range of amlodipine plasma and urine concentrations observed in the study.
DATA ANALYSIS: $C_{max,ss}$, AUC_{ss}, $t_{max,ss}$, λ_z, $t_{½ss}$, MRT_{ss}, CL/f, V_z/f (days 6, 7 and 13) of glibenclamide, C_{max}, t_{max}, $C_{max,ss}$, $C_{pre,ss}$, $t_{max,ss}$, $t_{1/2}$, AUC_{day1}, AUC_{ss}, MRT_{tot}, CL_{tot}/f, V_z/f, $C_{max,ss}/AUC_{ss}$, $R_A(AUC)$, $R_A(C_{max})$ of telmisartan. Analysis of variance (ANOVA) for crossover design was done, and 90% confidence intervals were calculated.

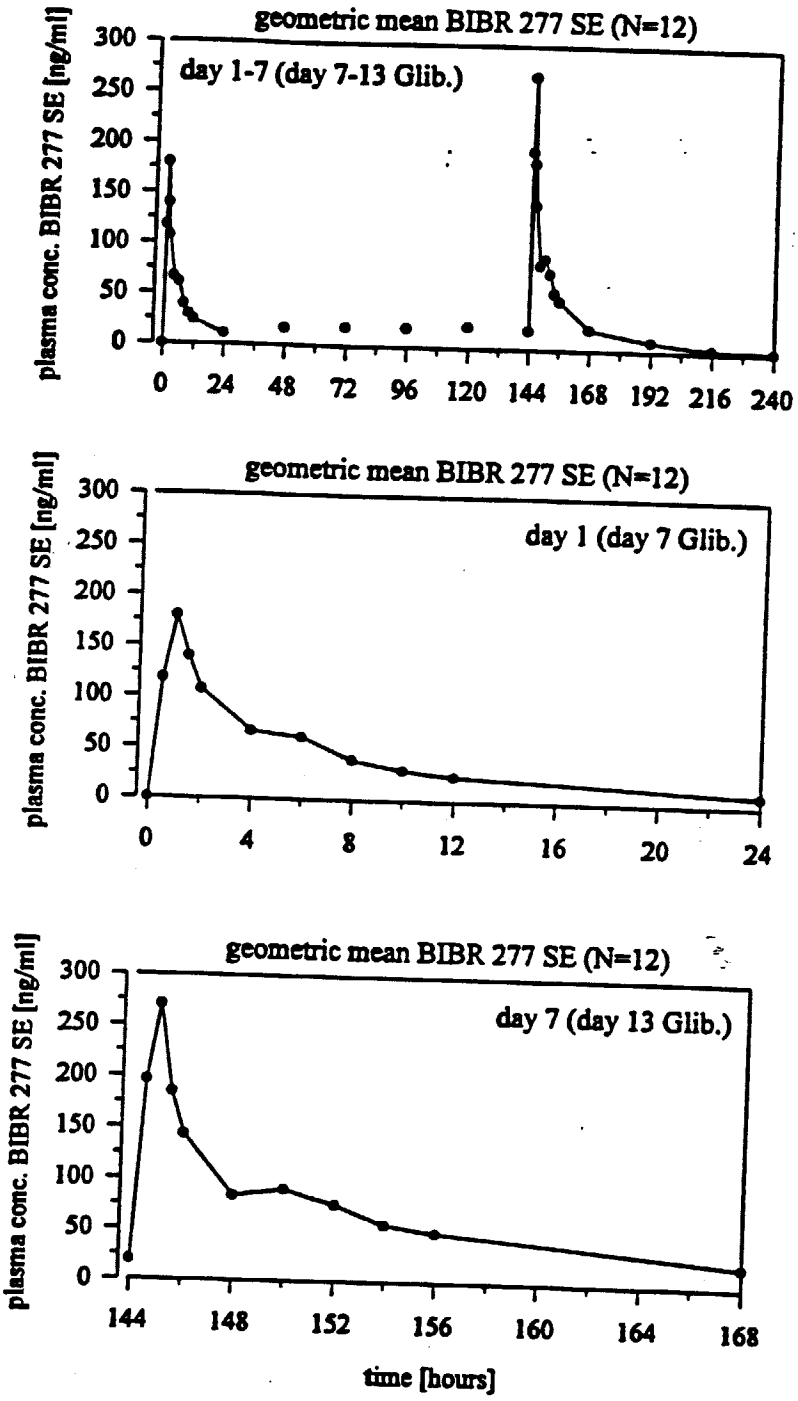
RESULTS: Tables 1-4 and Figure 1 summarize the data obtained from the study.

TABLE 1: Summary Statistics of Telmisartan Pharmacokinetic Parameters

BIBR 277 SE + Glibenclamide					geom.	
Parameter	unit	N	min	max	mean	gCV(%)
C_{max}	ng/ml	12			230	94.2
t_{max}	h	12			1.00*	
$C_{max,ss}$	ng/ml	12			355	112
$t_{max,ss}$	h	12			1.00*	
$C_{pre,ss}$	ng/ml	12			19.5	93.5
$t_{½}$	h	12			16.7	21.4
AUC_{0-24h}	ng*h/ml	12			1030	75.1
AUC_{ss}	ng*h/ml	12			1650	75.5
MRT_{tot}	h	12			16.1	19.2
CL_{tot}/f	ml/min	12			1210	75.6
V_z/f	l	12			1750	62.0
$C_{max,ss}/AUC_{ss}$	1/h	12			0.215	47.5
R_A (AUC)		12			1.60	25.6
R_A (C_{max})		12			1.54	88.4

* = median

Figure 1. Mean (geom. mean) plasma concentration-time plots of telmisartan at day 1, day 7 and for the 7 days treatment period. Day 1 of treatment with telmisartan corresponds to day 7 of treatment with glibenclamide.



CONCLUSIONS: The data obtainned from the study showed that upon co-administration of telmisartan with glibenclamide:

1. 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%.
2. 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.

IN VITRO METABOLIC STUDIES

PROTOCOL NUMBER: B 782

INVESTIGATOR AND LOCATION:

STUDY DATES: September 1996 to May 1997

OBJECTIVE: To obtain further information on the affinity of telmisartan to human cytochrome P450 enzymes and to evaluate the potential of telmisartan for metabolic drug-drug interactions.

PROCEDURES:

Assays for phenacetin O-dealkylation (CYP1A1 and CYP1A2), tolbutamide hydroxylation (CYP2C9), S-mephenytoin N-dealkylation (CYP2B6), S-mephenytoin 4'-hydroxylation (CYP2C19), bufuralol 1'-hydroxylation (CYP2D6), nifedipine oxidation (CYP3A), and testosterone 6β-hydroxylation (CYP3A) were performed by incubations with pooled microsomes from seven donors using telmisartan concentrations of 0.1 μM, 1 μM and 10 μM.

RESULTS: Tables 1 and 2 summarise the results obtained from the study.

TABLE 1. Effects of telmisartan on Cytochrome P450 catalyzed test reactions

Phenacetin CYP 1A2		product formation paracetamol		
	BIBR 277 SE concentration	amount [nmol]	rate [pmol/min/mg]	(%) of control
	control	2.283	746.0	100.0
	0.1 μM	2.465	821.7	110.1
	1 μM	2.350	783.3	105.0
	10 μM	2.317	772.3	103.5

mephenytoin CYP 2C19		product formation 4-OH-mephenytoin		
	BIBR 277 SE concentration	amount [nmol]	rate [pmol/min/mg]	(%) of control
	control	0.2500	125.00	100.0
	0.1 μM	0.1625	81.25	65.0
	1 μM	0.1535	76.75	61.4
	10 μM	0.1470	73.50	58.8

TABLE 2: Effects of telmisartan on Cytochrome P450 catalyzed test reactions.

mephenytoin CYP 2B6		product formation nirvanol		
	BIBR 277 SE concentration	amount [nmol]	rate [pmol/min/mg]	(%) of control
	control	0.0820	41.00	100.0
	0.1 µM	0.0815	40.75	99.4
	1 µM	0.0740	37.00	90.2
	10 µM	0.0690	34.50	84.2

bufuralol CYP 2D6		product formation 1'-OH-bufuralol		
	BIBR 277 SE concentration	amount [nmol]	rate [pmol/min/mg]	(%) of control
	control	1.803	240.4	100.0
	0.1 µM	1.701	226.7	94.3
	1 µM	1.598	213.1	88.6
	10 µM	1.475	196.7	81.8

testosterone CYP 3A4		product formation 6β-OH-testosterone		
	BIBR 277 SE concentration	amount [nmol]	rate [pmol/min/mg]	(%) of control
	control	4.053	2026.7	100.0
	0.1 µM	4.243	2121.6	106.1
	1 µM	3.819	1909.4	95.5
	10 µM	4.074	2036.7	101.8

nifedipine CYP 3A4		product formation oxidized nifidipine		
	BIBR 277 SE concentration	amount [nmol]	rate [pmol/min/mg]	(%) of control
	control	4.152	4152.1	100.0
	0.1 µM	4.319	4318.9	104.0
	1 µM	4.135	4135.1	99.6
	10 µM	3.791	3791.2	91.3

tolbutamide CYP 2C9		product formation hydroxy-tolbutamide		
	BIBR 277 SE concentration	amount [nmol]	rate [pmol/min/mg]	(%) of control
	control	2.290	508.2	100.0
	0.1 µM	2.230	496.2	97.6
	1 µM	2.105	468.3	92.2
	10 µM	1.530	340.4	67.0

CONCLUSIONS: The results obtained from the study showed that:

1. 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 (CYP2B6).
2. An inhibition was observed for CYP2C19 catalyzed S-mephenytoin 4'- hydroxylation that was independent of telmisatan concentration (and therefore may not be related a potential inhibition of the CYP2C19 molecule but rather due to the effect on the membrane integrity of the microsomal membrane-bound CYP2C19).
3. 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 therfore not considered therapeutically relevant).
4. 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.

IN VITRO PROTEIN BINDING

PROTOCOL NUMBERS: U93-0386, U97-2047, U97-2046, M97-0034

INVESTIGATOR AND LOCATION:

PROCEDURES:

Protein Binding: Experiments were carried out using ^{14}C-telmisartan which was added to plasma at concentrations ranging from 100 to 5000 ng/ml, incubated in glass tubes on a thermostated water bath at 37°C and agitated for 2 hours. After incubation, ultrafiltration or ultracentrifugation was performed. Radioactivity was determined using a scintillation counter.

Experiments were carried out using ^{14}C-telmisartan to assess the role of the proteins human serum albumin (HSA), α1-acid glycoprotein (AAG), γ-globulin (GG), lipoprotein (high, low and very low density, HDL, LDL, VLDL), and erythrocytes in the binding of telmisartan. ^{14}C-telmisartan was incubated in serum at 37°C for 5 hours and the binding was measured at intervals by equilibrium dialysis.

RESULTS: Tables 1-3 summarize the results obtained from the study.

TABLE 1: Protein binding of [^{14}C]BIBR 277 SE in human plasma expressed as % of added radioactivity. mean values are given for N = 2, and mean ±SD otherwise. individual values are given in the appendix.

plasma concentration [ng/ml]	ultrafiltration (UF)		ultracentrifugation (UC)		UF and UC combined	
	binding (%)	N	binding (%)	N	binding (%)	N
500	99.58	2	99.57 ±0.02	4	99.57 ±0.01	6
100	99.57 ±0.11	3	99.60 ±0.08	4	99.58 ±0.08	7
				100 and 500 combined	99.58 ±0.06	13

TABLE 2: Mean values (±SD) of protein binding of [^{14}C]BIBR 277 SE in human plasma expressed as % of added radioactivity obtained by ultrafiltration and ultracentrifugation (N = number of samples/concentration)

plasma concentration [ng/ml]	ultrafiltration (UF)		ultracentrifugation (UC)		UF and UC combined	
	binding (%)	N	binding (%)	N	binding (%)	N
5000	99.54 ±0.03	3	99.64 ±0.01	4	99.60 ±0.06	7
500	99.61 ±0.02	3	99.68 ±0.03	4	99.65 ±0.04	7
				5000 and 500 combined	99.63 ±0.06	14

TABLE 3 Summary of protein binding data at different telmisartan concentrations

proteins	binding percentages ±SD			
	0.5 [µg/ml]	2 [µg/ml]	5 [µg/ml]	mean
serum	99.76 ±0.09%	99.63 ±0.07%	99.59 ±0.05%	99.66 ±0.09%
HSA	99.92 ±0.01%	99.86 ±0.04%	99.81 ±0.06%	99.86 ±0.06%
AAG	77.83 ±4.03%	67.75 ±3.16%	54.34 ±4.37%	
GG	55.99 ±3.11	54.01 ±2.40	53.69 ±1.26	54.56 ±1.25%
HDL	93.48 ±0.58	93.09 ±0.91	91.78 ±0.47	92.78 ±0.89%
LDL	68.76 ±4.69	66.02 ±3.26	63.02 ±0.29	65.93 ±2.87%
VLDL	26.84 ±3.77%	21.22 ±4.79%	18.40 ±0.11%	
erythrocytes				
in buffer	95.60 ±0.47%	89.78 ±0.91%	82.81 ±0.97%	
in serum	7.94 ±1.31	10.53 ±0.76	9.00 ±0.71	9.61 ±1.30%

CONCLUSIONS: The data obtained from the study show that;

(i) 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).

(ii) 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.

(iii) The erythrocyte uptake of telmisartan is significant but very low in the presence of serum indicating a very high binding capacity of serum (albumin).

DRUG PRODUCT DISSOLUTION TESTING

The following dissolution data were submitted to the NDA:

BIBR 277 SE Tablets 40/240 mg
B.:40813
Clinical Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	53.9	7.5	7.9	46.0	61.8
	85.5	7.5	7.9	77.6	93.3
	99.7	1.6	1.7	98.0	101.4
	101.4	1.0	1.1	100.3	102.5

BIBR 277 SE Tablets 40/240 mg
B.:50212
Clinical Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	81.6	10.4	11.0	70.6	92.5
	96.6	1.9	2.0	94.6	98.6
	97.9	3.0	3.1	94.8	101.0
	98.3	3.0	3.2	95.1	101.4

BIBR 277 SE Tablets 40/240 mg
B.:41209
Clinical Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	77.4	9.2	9.6	67.8	87.0
	95.2	1.4	1.4	93.8	96.6
	96.4	1.2	1.2	95.2	97.7
	96.4	1.1	1.1	95.3	97.5

BIBR 277 SE Tablets 40/240 mg
B.:901810
Clinical Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	57.3	4.0	4.2	53.1	61.6
	93.0	5.6	5.8	87.1	98.8
	100.5	3.5	3.7	96.8	104.2
	101.8	1.7	1.8	100.0	103.5

BIBR 277 SE Tablets 40/240 mg
B.:901811
NDA-Bulk

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	53.7	6.9	7.2	46.5	60.9
	92.7	5.5	5.8	86.9	98.5
	101.2	1.9	2.0	99.2	103.2
	101.9	1.2	1.3	100.6	103.2

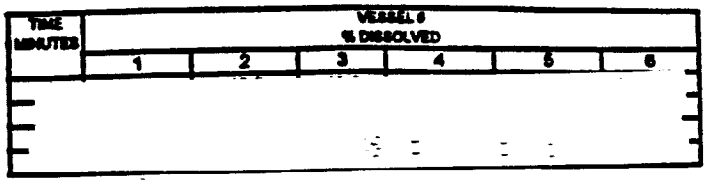
BIBR 277 SE Tablets 40/240 mg
B.:901812
NDA-Bulk

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	64.1	10.5	11.0	53.1	75.1
	94.9	4.0	4.2	90.7	99.1
	99.3	1.2	1.3	98.0	100.6
	100.5	2.9	3.1	97.4	103.5

SIBR 277 SE Tablets 80/480 mg
B.:40824
Clinical Batch

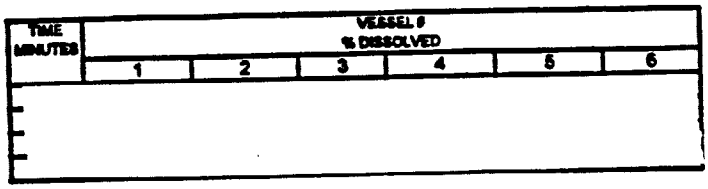
TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6



TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- a = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	47.3	4.0	4.2	43.1	51.6
	74.6	4.8	5.0	69.5	79.6
	93.7	6.2	6.5	87.2	100.3
	100.8	4.1	4.3	96.5	105.0

SIBR 277 SE Tablets 80/480 mg
B.:50211
Clinical Batch

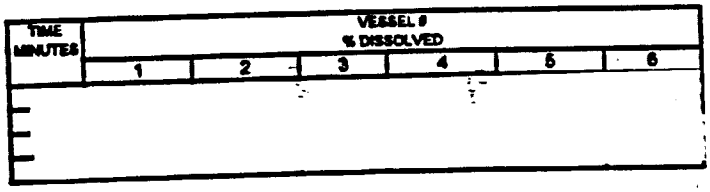
TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6



TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- a = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	74.6	8.1	8.5	66.1	83.1
	95.5	2.2	2.3	93.2	97.8
	95.8	1.6	1.7	94.1	97.5
	95.8	2.9	3.1	92.7	98.9

SIBR 277 SE Tablets 80/480 mg
B.:41225
Clinical Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6



TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- a = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	77.0	5.6	5.9	71.1	82.9
	98.9	1.5	1.6	97.3	100.5
	99.1	1.6	1.7	97.4	100.8
	99.1	1.5	1.6	97.6	100.7

BIBR 277 SE Tablets 80/480 mg
B.:901817
NDA-Bulk

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	69.5	10.3	10.8	58.8	80.3
	94.6	7.3	7.6	86.9	102.2
	102.2	1.7	1.8	100.4	104.0
	102.7	2.6	2.8	99.9	105.4

BIBR 277 SE Tablets 80/480 mg
B.:901818
NDA-Bulk

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	70.3	7.8	8.2	82.1	78.4
	97.3	3.4	3.6	93.7	100.9
	102.7	1.1	1.2	101.5	103.8
	103.2	0.8	0.8	102.4	104.0

BIBR 277 SE Tablets 80/480 mg
B.:B951110
Clinical-Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	90.5	7.7	8.1	82.4	98.6
	103.4	1.7	1.8	101.6	105.1
	103.2	1.8	1.9	101.3	105.0
	104.1	1.7	1.8	102.3	105.9

BIBR 277 SE Tablets 40/240 mg
B.:9951113
Clinical-Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	78.7	8.0	8.4	70.2	87.1
	96.1	1.8	1.8	94.2	97.9
	96.0	1.9	1.9	94.1	98.0
	96.0	1.9	1.9	94.1	97.9

BIBR 277 SE Tablets 80/480 mg
B.:9951207
Clinical-Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	61.4	3.9	4.1	57.3	65.5
	90.3	3.6	3.8	86.5	94.1
	92.8	1.6	1.6	91.2	94.4
	92.7	1.5	1.6	91.1	94.2

BIBR 277 SE Tablets 40/240 mg
B.:50712
Clinical-Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- S = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	75.5	5.8	6.1	69.4	81.6
	95.3	0.7	0.7	94.6	96.0
	95.6	1.2	1.2	94.3	96.8
	95.9	1.3	1.4	94.5	97.2

BIBR 277 BE Tablets 80/480 mg
B.S1002
Clinical-Batch

TIME MINUTES	VESSEL # % DISSOLVED					
	1	2	3	4	5	6

TIME MINUTES	MEAN %DISSOLVED	SDV %DISSOLVED	ERROR OF THE MEAN +/- 0 = 95%	CONFIDENCE INTERVAL LOW VALUE	CONFIDENCE INTERVAL HIGH VALUE
	64.9	3.7	3.9	61.0	68.8
	88.8	2.8	3.0	85.8	91.8
	92.1	2.0	2.1	90.0	94.2
	92.4	2.5	2.6	89.8	95.0

Analytical Results* for Telmisartan Tablet Batches Used in Clinical and Stability Studies

Tablet Strength	Lot No.	Mnf **	Mfg Date	Batch Size (kg)	Assay (%)	% Dissolved in 30 min., Individual Values	% Dissolved in 30 min. (mean ± SD)
40 mg	80212		2/95	35			86.8 ± 1.83
	80712		8/95	42.8			85.3 ± 0.68
	8951113		11/95	16.2			86.1 ± 1.74
	801810		2/96	66			83.0 ± 5.57
	801811		2/96	66			82.7 ± 5.66
	801812		2/96	66			84.9 ± 4.01
	9960335		10/96	79.2			86.1 ± 1.71
	9960336		10/96	79.2			87.9 ± 1.81
80 mg	80211		2/95	120			86.5 ± 2.22
	80714		8/95	49.9			82.2 ± 3.01
	801816		2/96	136			91.1 ± 6.10
	801817		2/96	136			94.8 ± 7.27
	801818		2/96	136			97.3 ± 3.44
	9960325		10/96	168.4			97.7 ± 7.11
	81002		8/95	57.6			88.8 ± 2.85
	8951110		11/95	32.4			103.3 ± 1.70
	8951207		8/96	66.9			90.3 ± 3.89
	9960326		10/96	168.4			92.7 ± 8.61

*At time of release (pH 7.5 phosphate buffer, paddle speed 75 rpm)
**TH = site of granulate production and tablet compression is
= site of granulate production is Thomae, site of tablet compression is

Based on the above results the sponsor is proposing the following method and specifications:

Dosage Form, Strength: Uncoated tablets, 40 and 80 mg

Dissolution Apparatus: USP, Apparatus II (paddle)

Speed of Rotation: 75 rpm

Dissolution Medium: Phosphate buffer, pH 7.5 (at 37° ±0.5°C)

Volume: 900 ml

Sampling Time: 30 minutes

Procedure: Determine the amount of telmisartan dissolved using [redacted] method.

Recommended Specification: Q [redacted] % at [redacted] minutes

COMMENTS: Telmisartan is a low-solubility, high-permeability drug (Case 2 of the Biopharmaceutics Classification System) and based on the in vitro dissolution data on the clinical lot 50211 and the commercial lot 601816 (80 mg tablets used for the pivotal bioequivalence study), as well as the mean data at 30 minutes for the tablet batches used for clinical and stability studies the dissolution specification should be changed to Q [redacted] % at [redacted] minutes.

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POPULATION PHARMACOKINETIC ANALYSIS

OBJECTIVE

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).

DATA:

TABLE 1: Demographics

Study No.	Gender		Race			
	Male	Female	White	Black	Hispanic	Other
502.202	71	46	81	10	24	2
502.203	154	66	172	31	15	2
502.206	180	98	195	43	36	4
502.214	240	118	266	66	21	5
502.114	7	5	8	4	0	0
502.210	38	56	94	0	0	0
502.211	7	2	9	0	0	0
502.218	91	15	105	0	0	1
Total	788	406	930	154	96	14
%	66	34	78	13	8	1

Study Number	N	White		Black		Hispanic		Other	
		Female	Male	Female	Male	Female	Male	Female	Male
502.202	117	27	54	5	5	12	12	2	0
502.203	220	45	127	17	14	4	11	0	2
502.206	278	58	137	22	21	15	21	3	1
502.214	358	89	177	21	45	8	13	0	5
502.114	12	3	5	2	2	0	0	0	0
502.210	94	56	38	0	0	0	0	0	0
502.211	9	2	7	0	0	0	0	0	0
502.218	106	15	90	0	0	0	0	0	1
Total	1194	295	635	67	87	39	57	5	9
%	–	24.7	53.2	5.6	7.3	3.3	4.8	0.4	0.8

Study No.	N	Age (yr)		Body Weight (kg)		Creatinine Clearance (mL/min)	
		Range	Mean	Range	Mean	Range	Mean
502.202	117	30-67	52	52.73-128.18	82.14	40.27-136.08	71.6
502.203	220	28-72	53	38.64-137.27	86.1	43.71-151.33	87.21
502.206	278	23-83	54	44.09-159.09	91	35-75-195	86.17
502.214	358	24-80	54	49.09-159.09	91.15	37.8-180.9	85.89
502.114	12	19-44	31	54.55-97.27	74.47	75-118.2	98.14
502.210	94	65-86	71	52.8-102.6	76.1	24.73-105.85	55.57
502.211	9	36-70	53	52-94	76.33	20.6-75.6	44.98
502.218	106	40-79	67	52.9-100.8	76.07	23.87-90.84	51.91
Total	1194	19-86		38-159		20-195	

Study No.	N	Smoking History		
		Non-Smoker	Smoker	Ex-Smoker
502.202	117	71	24	22
502.203	220	120	62	38
502.206	278	124	92	62
502.214	358	175	121	62
502.114	12	8	4	0
502.210	94	60	25	9
502.211	9	4	4	1
502.218	106	12	63	31

Study No.	N	Alcohol Consumption		
		Non-Drinker	Average Drinker	Excessive Drinker
502.202	117	62	55	0
502.203	220	104	116	0
502.206	278	134	140	4
502.214	358	146	210	2
502.114	12	7	5	0
502.210	94	30	64	0
502.211	9	3	6	0
502.218	106	37	69	0

Study No.	N	HCTZ Co-adimistration	
		No	Yes
502.202	117	117	0
502.203	220	220	0
502.206	278	278	0
502.214	358	630*	151*
502.114	12	12	12
502.210	94	58	36
502.211	9	14*	0*
502.218	106	96	10

*Number based on an individual occurrence.

Plasma Concentrations

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.

METHODS:

Model Building:

Pharmacokinetic model: A two-compartment open model with first order absorption was evaluated as to the appropriateness as a base model. Individual subject pharmacokinetic parameters were described by the following equations:

$$CL = \theta_{CL} \cdot e^{\eta_{CL}} \quad [1]$$

$$V_2 = \theta_{V_2} \cdot e^{\eta_{V_2}} \quad [2]$$

$$Q = \theta_Q \cdot e^{\eta_Q} \quad [3]$$

$$V_3 = \theta_{V_3} \cdot e^{\eta_{V_3}} \quad [4]$$

$$K_a = \theta_{K_a} \cdot e^{\eta_{K_a}} \quad [5]$$

where CL is the apparent oral clearance, V_2 is the apparent volume of distribution of the central compartment, Q is the apparent intercompartmental clearance, V_3 is the apparent volume of distribution of the peripheral compartment, K_a is the first order absorption rate constant, θ is the population mean estimate (or typical value) of the corresponding pharmacokinetic parameter, and η is the associated interindividual variability. The η values are independent, identically distributed random errors with mean of zero and a variance equal to ω^2 . Interindividual variability was described as an exponential error model. The model was parameterized in terms of those described by equations 1 to 5 using library subroutines ADVAN4 and TRANS4.

The intraindividual residual variability of telmisartan plasma concentration was estimated using a combined additive and proportional error model by the following equation:

$$C_{pij} = \tilde{C}_{pij} \cdot (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \quad [6]$$

where C_{pij} is the observed value of the j^{th} plasma concentration of individual i; $\tilde{C}_{pij}$ is the predicted j^{th} plasma concentration of individual i; and e_{1ij} and e_{2ij} are random variables which represent the discrepancy between the observed and predicted j^{th} concentration. The e_{1ij} and e_{2ij}

are independent, identically distributed errors with means of zero and variances equal to σ_1^2 and σ_2^2, respectively.

RESULTS:

Summary of NONMEM Posthoc Pharmacokinetic Parameters

TABLE 2: 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

Source Data: NONMEM final model Posthoc result file

TABLE 3: Summary of Posthoc Individual Telmisartan CL and Ka by Dose

Dose (mg q.d.)	10	20	40	80	120	160
CL (L/hr)						
N	25	90	528	258	151	142
Mean	41.02	30.97	27.48	23.06	23.06	22.35
SD	12.4	13.12	10.28	9.7	9.63	9.6
CV	30.23	42.37	37.42	42.07	41.74	42.95
Median	44.5	32.92	27.46	23.01	22.72	21.7
Ka (hr^{-1})						
N	25	90	528	258	151	142
Mean	0.021	0.065	0.182	0.602	1.02	1.48
SD	0.001	0.0163	0.094	0.449	0.638	0.405
CV	4.47	25.03	51.53	74.66	62.63	27.31
Median	0.021	0.069	0.186	0.488	0.848	1.5

Source Data: NONMEM final model Posthoc result file

TABLE 4: Summary of Posthoc Individual Telmisartan CL by Smoking History

	Never	Ex-Smoker	Smoker
N	574	395	225
Mean	23.2	29.2	26.9
SD	9.82	11.4	10.5
CV	42.3	39.1	39.2
Median	22.2	29.2	27.3

TABLE 5: Summary of Posthoc Individual Telmisartan CL by Alcohol Consumption

	Non-drinker	Average Drinker	Excessive Drinker
N	523	665	6
Mean	23.4	27.9	28.2
SD	10.2	11.0	11.4
CV	43.5	39.4	40.5
Median	22.3	27.9	31.3

Source Data: NONMEM final model Posthoc result file

TABLE 6: Summary of Posthoc Individual Telmisartan CL by HCTZ Co-Administration

	HCTZ	No HCTZ	Ratio (%) HCTZ/No HCTZ
N	209	1425	15%
Mean	20.77	25.58	81%
SD	9.15	10.41	88%
CV	44.08	40.69	108%
Median	19.11	24.82	77%

TABLE 7: Summary of Posthoc Individual Telmisartan AUC_{0-24}, Half life, C_{max}, t_{max}, and $V_{d\beta}$ by Dose

AUC_{0-24} (hr x ng/mL)

Dose (mg)	10	20	40	80	120	160
N	25	90	528	258	151	142
Mean	309.56	916.51	1770.32	4653.9	6728.2	8962.28
SD	300.07	831.62	1071.66	4383.26	4770.81	5841.98
CV	96.93	90.74	60.53	94.18	70.91	65.18
Median	224.75	607.67	1456.86	3477.11	5281.92	7374.11

Half life (hr)

Dose (mg)	10	20	40	80	120	160
Mean	19.96	33.67	25.25	32.7	28.82	29.54
SD	11.68	46.74	21.76	43.21	21.5	22.29
CV	58.52	138.8	86.19	132.12	74.6	75.44
Median	16.34	19.58	21.04	23.4	22.08	24.62

C_{max} (ng/mL)

Dose (mg)	10	20	40	80	120	160
Mean	13.88	46.43	127.6	568.7	1131	1840
SD	12.76	36.95	71.80	476.3	653.7	857.7
CV	91.9	79.6	56.3	83.8	57.8	46.6
Median	10.27	32.26	109.9	573.8	873.7	1529.6

t_{max} (hr)

Dose (mg)	10	20	40	80	120	160
Mean	1.8	1.8	1.5	1.0	0.82	0.67
SD	0.37	0.54	0.44	0.34	0.30	0.19
CV	20.6	30.3	30.1	33.5	36.6	28.1
Median	1.8	1.9	1.75	1.1	0.8	0.7

$V_{d\beta}$ (L)

Dose (mg)	10	20	40	80	120	160
Mean	1029	1003	835.0	828.1	774.9	798.4
SD	139.3	354.8	148.0	381.5	222.0	261.0
CV	13.5	35.4	17.7	46.1	28.6	32.7
Median	1059	960.0	830.8	786.8	758.1	760.1

TABLE 8: Comparison of Pharmaokinetic Parameters in Study 502.202 Obtained by NONMEM Posthoc and by the Standard Two-stage Methods

Dose (mg q.d.)	40		80		120	
Method	Posthoc N=39	2-Stage N=39	Posthoc N=38	2-Stage N=37	Posthoc N=40	2-Stage N=38
$AUC_{0\text{-}24}$ (hr • ng/mL)						
Mean	1810	3646	3947	6663	6427	9270
%CV	57.1	88.3	61.8	106	58.5	87.5
Median	1497	2787	2956	3477	5603	5902
C_{max} (ng/mL)						
Mean	143.9	158.7	495.7	693.5	1223	1635
%CV	63.6	65.7	71.8	87.4	62.4	86
Median	108.8	132.5	344.7	480.4	989.3	1119
t_{max} (hr)						
Mean	1.3	1.6	1.0	1.3	0.8	1.4
%CV	35.6	65.0	31.8	97.2	30.9	103
Median	1.5	1.0	1.1	1.0	0.9	1.0
Half life (hr)						
Mean	26.1	25.2	22.5	21.6	28.3	21.8
%CV	50.4	44.8	43.3	51.5	55.4	59.8
Median	22.9	23.0	19.9	19.8	23.1	19.4

TABLE 9: Magnitude of Interindividual Variability

No.	ω^2 =	Final Estimate,η (%CV)	%RSE
1	ω^2_{CL}	66.0	14.0
2	$\omega^2_{V_1}$	Fixed to 0	n/a
3	ω^2_{Q}	94.9	51.2
4	$\omega^2_{V_2}$	108	89.7
5	ω^2_{Ke}	91.7	34.9

Source Data: NONMEM final model output, Appendix 10.4

TABLE 10: Magnitude of Residual Variability

No.	σ^2	Final Estimate, ε	%RSE
1	σ^2_1	71.6 (%CV)	12.7
2	σ^2_2	20.5 (ng/mL)	43.4

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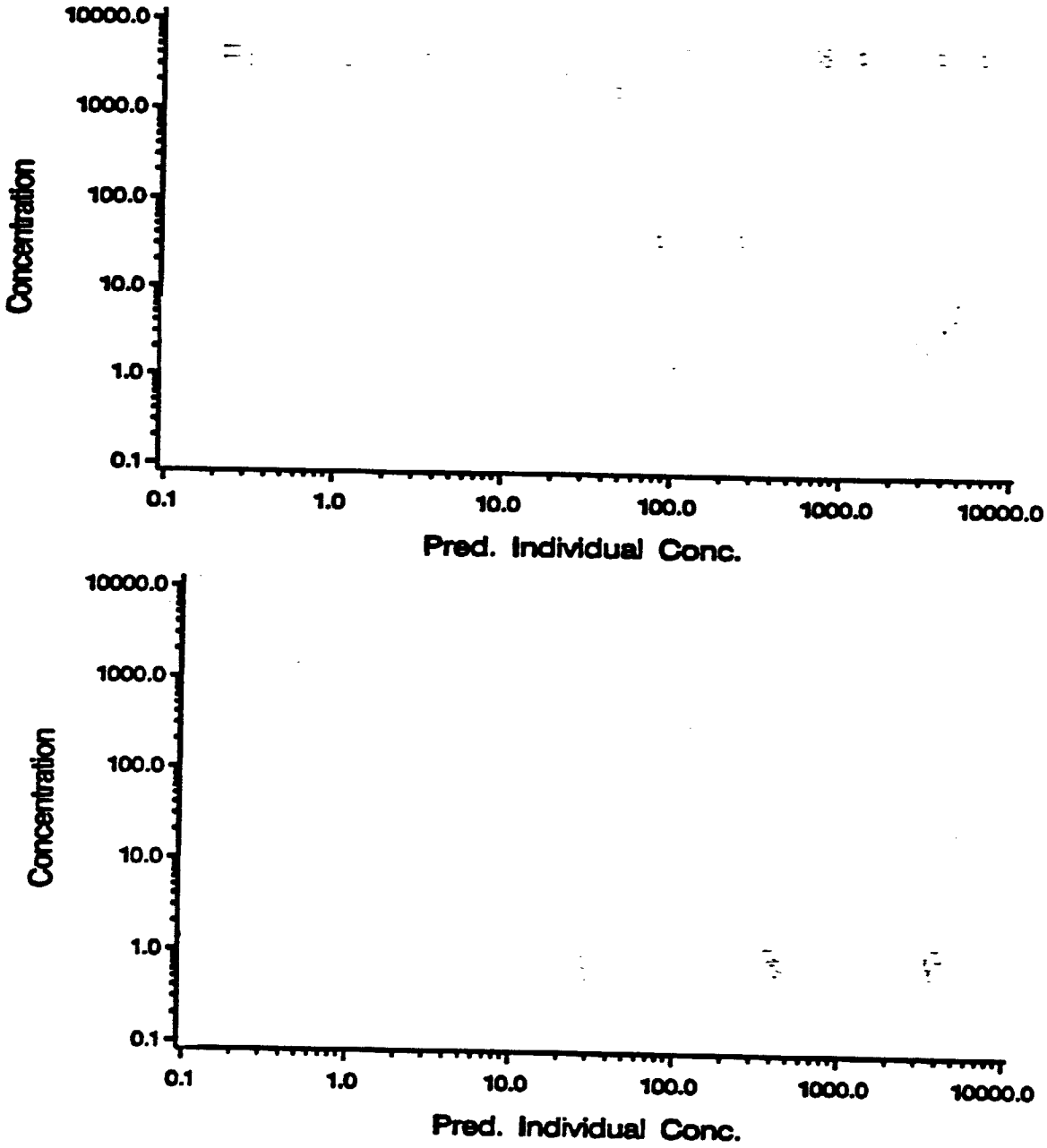
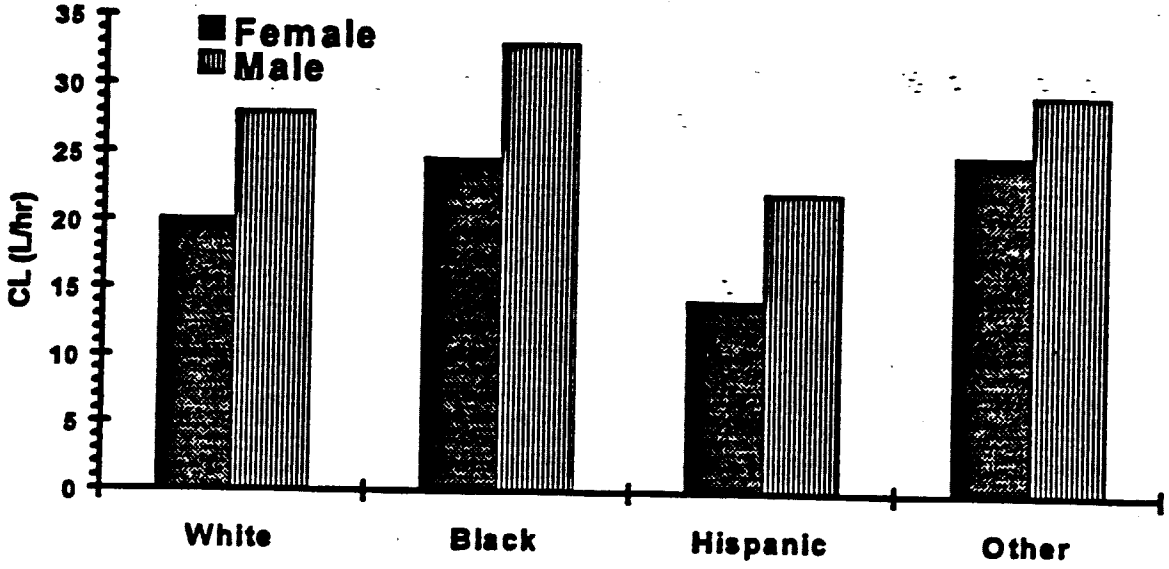
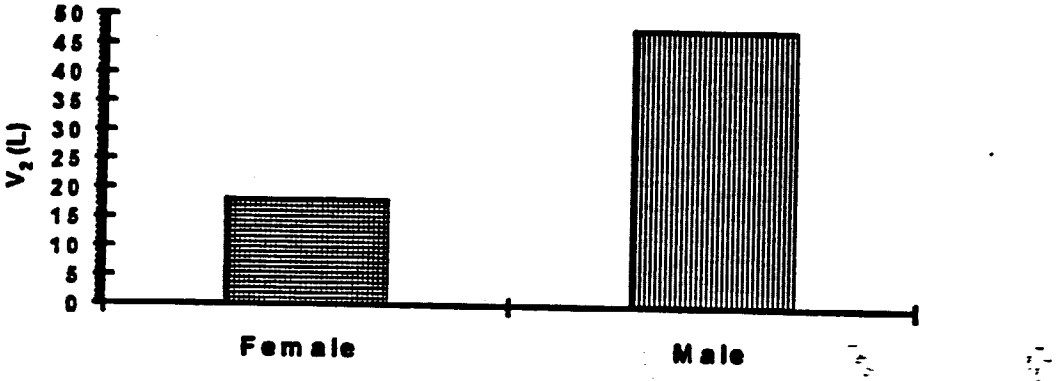


FIGURE 1: Observed Concentration vs. Predicted Individual Concentration from the Two-Compartment Base Model (upper panel), and from the One-Compartment Base Model (lower panel). The dashed line represents the line of identity.



FIGURES 2: Comparison of Posterior Estimate of Individual CL by Gender and Race

Source Data: NONMEM final model POSTHOC result file



FIGURES 3: Comparison of Posterior Estimate of Individual V_2 by Gender

SUMMARY: 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. The final population model can be best expressed by the following equations:

$$\hat{CL}\,(L/hr) = \left[\theta_{CL}^{Race} \cdot Dose(mg)^{-0.483} + 3.29(Alcohol\ drinker) + 2.51(No\ HCTZ) + 4.83(Male)\right] \cdot \theta_{CL}^{Smoking}$$

For race white, $\theta_{CL}^{White} = 90.1$; black, $\theta_{CL}^{Black} = 128$; Hispanic, $\theta_{CL}^{Hispanic} = 64.5$;
and other, $\theta_{CL}^{Other\ race} = 124$, and
for non-smoker, $\theta_{CL}^{Non-smoker} = 1$; ex-smoker, $\theta_{CL}^{Ex-smoker} = 1.33$; smoker, $\theta_{CL}^{Smoker} = 1.07$.

$$\hat{V}_2\ (L) = 18.1 + 29.7 \cdot Gender$$

$$\hat{Q}\ (L/hr) = 45.0$$

$$\hat{V}_3\ (L) = 526$$

$$\hat{K}_a\ (hr^{-1}) = 6.01x10^{-4} \cdot Dose(mg)^{1.54}$$

where $\hat{CL}$, $\hat{V}_2$, $\hat{Q}$, $\hat{V}_3$, and $\hat{K}_a$ are typical values for the population mean parameters.

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.

Interindividual random effect can be best described by an exponential error model. 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.

CONCLUSION:

The present findings illustrate 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.

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