

10.3. Pharmacokinetic evaluation

The following pharmacokinetic parameters for CV-11974 will be determined from individual plasma concentration-time courses by non-compartmental analysis using Topfit 2.0:

C_{max} , t_{max} , AUC_{0-t} , $AUC_{t-\infty}$, $AUC_{0-\infty}$, AUC_t , $t_{1/2}$, MRT_{0-t} , $MRT_{0-\infty}$, MRT_t , C_{av} , PTS, PTF, R, f_u .

C_{max} and t_{max} are observed values. $AUC_{0 \rightarrow t}$ will be calculated by trapezoidal rule. $AUC_{0 \rightarrow \infty}$ is calculated after extrapolation from zero to infinity. $AUC_{t-\infty}$ will be calculated after extrapolation from the time point of the last measured concentration to infinity. $t_{1/2}$ will be calculated by least square regression analysis.

MRT will be calculated according to the following equation:

$$MRT = \frac{AUMC}{AUC}$$

The peak trough fluctuation (PTF) and Swing (PTS) will be calculated according to the following equations:

$$PTF = \frac{C_{max} - C_{min}}{C_{av}}$$

page 26 of 45

Item 6: Human Pharmacokinetics & Bioavailability

TAKEDA EURO R&D CENTRE CANDESARTAN CILEXITIL (TCV-116/EC041) Final version: February 14, 1995

where C_{min} is the trough concentration measured and $C_{AV} = AUC/\text{dose interval}$

$$PTS = \frac{C_{max} - C_{min}}{C_{min}}$$

R is the accumulation factor and will be calculated according to:

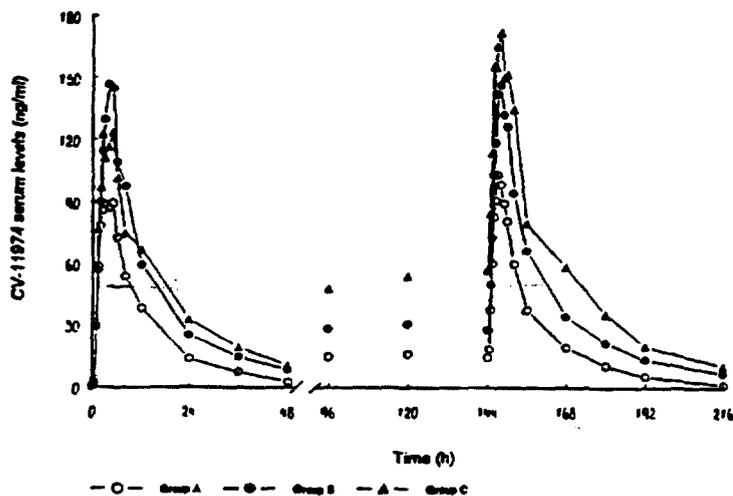
$$R = \frac{AUC_t}{AUC_{0-\infty}}$$

f_u = is the fraction of CV-11974 not bound to plasma proteins (free fraction) and will be calculated according to:

$$f_u = C_f/C_t$$

where C_f is the concentration of free (unbound) and C_t the total plasma concentration of CV-11974. The plasma protein binding will be determined in a sub-set of plasma samples obtained for pharmacokinetics by using HPLC with membrane dialysis (SOP Pharma Bio-Research Laboratories B.V.)

T-Figure 2: Mean candesartan serum concentration - time courses following dosing on study days 1 - 7 of patients with normal renal function (group A, n=8), patients with mild renal dysfunction (group B, n=9) and patients with severe renal dysfunction (group C, n=7). Linear scale.



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candesartan cilexetil once daily in a 21-day repeated, cross-over, study in 12 healthy female subjects. The pharmacokinetics of candesartan were similar on days 14 and 21, indicating that this typical oral contraceptive does not influence the disposition of candesartan. The levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), measured on days 7, 14 and 21, were consistently low throughout both investigational periods, indicating that ovulation did not occur during the study.

In conclusion, Candesartan is not likely to influence the metabolism of other drugs, or be influenced by other drugs, as candesartan is metabolized only to a minor extent, with enzyme kinetics characterized by high K_m and V_{max} values.

General Comments:

1. The pharmacokinetic results of the renal dysfunction study showed higher C_{max} , greater AUC and longer elimination half-lives of candesartan in patients with severe renal dysfunction, as compared to patients with normal renal function. The relevance of these kinetic changes for the clinical use of candesartan cilexetil in patients with severe renal impairment could be evaluated further, based on general risk/benefit considerations, and a validated PK/PD relationship.
2. The mechanism of interaction of candesartan and HCTZ was not investigated and still hard to understand. The increase of candesartan bioavailability by about 20% may be insignificant for healthy young population but may result in compounded increase in candesartan concentration in older or renally impaired patients.
3. Although the population analysis found no covariates that significantly affect the clearance of candesartan, it was apparent that age has an effect on CL. Non-linear relationship between age, weight and CL will be investigated in the near future by the reviewer. The use of invalidated version of NONMEM is not usually encouraged.

Labeling Comments:

The firm suggests that no initial dosage adjustment is necessary for elderly patients, for patients with impaired renal function, or for patients with impaired hepatic function. We think for patients with impaired renal function the dose should be initially lower. The same should apply to the elderly specially if treated with diuretics. This issue will be discussed in detail with the medical reviewer as it relates to the safety and tolerability of this drug.

“Relative bioavailability of candesartan tablet compared with oral solution is estimated to be 33.5%” should be added to the label at the second paragraph/second sentence of Pharmacokinetics General.

7.3 PROTEIN BINDING OF CANDESARTAN (CV-11974) IN SERUM

Individual data of the free fraction (unbound to serum proteins) of CV-11974 are compiled in Table E-4 and summarized in T-Table 5. Results of the statistical evaluation are summarized in T-Table 6 and T-Table 7.

T-Table 5: Free fraction of CV-11974 in % of total serum concentration of CV-11974 Geometric means

Group A		Group B		Group C	
Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
0.562	0.542	0.703	0.705	0.783	0.754
0.55*		0.70*		0.77*	

* = Arithmetic mean (pooled results)

T-Table 6: Geometric means, and 2-sided 90% confidence intervals (CI), of fractional changes between day 1 (baseline) and day 7 of CV-11974 serum concentrations unbound to serum proteins. Within-group evaluation.

	mean	90% CI		signific.
group A (day 7) / group A (day 1)	0.96	0.91	- 1.02	N
group B (day 7) / group B (day 1)	1.00	0.95	- 1.06	N
group C (day 7) / group C (day 1)	0.96	0.90	- 1.02	N
groups (A+B+C) (day 7) / groups (A+B+C) (day 1)	0.98	0.95	- 1.01	N

T-Table 7: Geometric means of the ratios, and 2-sided 90% confidence intervals (CI), of CV-11974 serum concentrations unbound to serum. Between-group evaluation.

	day 1			day 7				
	mean	90% CI		signific.	mean	90% CI		signific.
group B / group A	1.25	0.94	- 1.67	N	1.30	1.00	- 1.70	N
group C / group A	1.39	1.03	- 1.89	Y	1.39	1.05	- 1.85	Y
group C / group B	1.12	0.83	- 1.50	N	1.07	0.81	- 1.41	N

signific.: Y = significant difference from unity, N = non-significant difference

After pooling results of day 1 and day 7 the geometric means of the free fraction (% of total serum concentration) were 0.55, 0.70 and 0.77 in group A, group B and group C, respectively, indicating an increase of free fraction in patients with mild to moderate and severe renal dysfunction as compared to patients with normal renal function. There was no change between day 1 and day 7 in free fraction of CV-11974 in either group.

9.3. SERUM PROTEIN BINDING OF CANDESARTAN (CV-11974)

TABLE E-4: CONCENTRATION OF UNBOUND CV-11974 IN SERUM IN % OF TOTAL CONCENTRATION OF CV-11974. DESCRIPTIVE STATISTICS.

Group A			Group B			Group C		
Patient	Day 1	Day 7	Patient	Day 1	Day 7	Patient	Day 1	Day 7
01	0.614	0.751	05	0.691	0.547	02	0.541	0.604
04	0.703	0.815	08	0.646	0.807	17	0.680	0.706
			12	0.544	0.565			
			15	0.770	0.893			
27	0.523	0.462	32	0.521	0.537	25	0.618	0.618
28	0.590	0.510	33	0.672	0.669	26	0.897	0.800
30	0.500	0.514	36	2.48	2.21	29	0.719	0.620
31	0.369	0.453	44	0.641	0.634	34	1.08	1.09
41	0.676	0.535	46	0.633	0.729	35	0.801	0.821
42	0.662	0.600	48	0.560	0.539	47	0.651	0.559
43	0.858	0.788	49	0.557	0.554	50	0.808	0.902
45	0.533	0.533	51	0.611	0.655			
			52	0.622	0.605			
Mean	0.562	0.542		0.703	0.705		0.783	0.754
SD	0.034	0.099		0.36	0.33		0.15	0.16
Median	0.56	0.53		0.62	0.63		0.80	0.80

Legend: - Mean and SD based on log-transformed data (geometric mean).
 - Patients 01 to 17 not considered for statistics

9.4. PHARMACODYNAMIC DATA

TABLE E-5: INDIVIDUAL CLEARANCES OF CREATININE, INULIN AND PAH AND DESCRIPTIVE STATISTICS.

GROUP A: PATIENTS WITH NORMAL RENAL FUNCTION

Patient No.	Creatinine clearance	Inulin clearance (ml/min/1.73 m ² BS)						PAH clearance (ml/min/1.73 m ² BS)					
		Day -1			Day 7			Day -1			Day 7		
		0-1 h	1-2 h	2-3 h	0-1 h	1-2 h	2-3 h	0-1 h	1-2 h	2-3 h	0-1 h	1-2 h	2-3 h
27	155	63.5	65.9	64.9	77.7	63.3	82.7	219	229	227	335	356	366
28	99.0	49.5	52.0	52.1	66.7	57.3	76.8	122	120	132	207	210	220
30	153	119	101	87.2	88.9	91.7	106	472	402	349	401	417	484
31	182	107	94.2	87.6	114	97.9	105	510	448	417	543	466	498
41	83.4	56.0	55.7	57.7	55.9	55.9	66.4	198	203	207	200	205	237
42	84.3	48.4	61.7	60.3	48.6	67.6	55.8	228	230	212	200	239	237
43	65.1	60.8	55.0	64.2	67.3	62.8	64.7	298	274	246	347	344	339
45	64.1	55.2	57.9	51.2	46.3	50.5	50.7	208	220	191	215	222	214
Mean	103	66.1	65.9	64.4	67.8	66.7	73.6	255	247	234	286	293	307
SD	44	23	17	13	21	16	20	128	106	86	114	99	111
Median	92	58	60	62	67	63	72	224	230	220	275	292	288

Legend: - Creatinine clearance (ml/min/1.73 m² BS) determined from 24-hour urine
 - Mean and SD based on log-transformed data (geometric mean)
 - BS = body surface

A Phase I, Open Label, Randomized, Single Dose, Two-Way Crossover Study in Healthy Male Volunteers, to Investigate the Effect of Food on the Pharmacokinetics of a New Antihypertensive Agent; Candesartan Cilexetil (TCV-116)

Investigator:
Study Center:

Objectives: To evaluate the effect of food on the pharmacokinetics of candesartan cilexetil and two of its metabolites, CV-11974 and CV-15959

Methodology: Open label, randomized, single dose, two period crossover study

Number of Subjects (planned and analyzed): Eighteen (18) subjects were enrolled in the study. All subjects successfully completed all treatments and were included in the evaluation.

Diagnosis and main criteria for inclusion: Healthy male volunteers aged 18-50; body weight within $\pm 15\%$ of normal body weight range; having given written informed consent.

Test Product, dose and mode of administration, batch number, lot number: candesartan cilexetil; 8.0 mg tablet; batch number E1160271; lot number Z5429021

Duration of treatment: Single oral dose; 2 dosing periods; 2 possible treatments (following a high fat breakfast, or in the fasting state, 10 hours after a standard snack and 4 hours before a standard meal); subjects in Sequence 1 received the dose after food the Period 1 and in the fasted state in Period 2; subjects in Sequence 2 received the dose in the fasted state in Period 1 and after food in Period 2

Name of Active Ingredient: Candesartan cilexetil (TCV-116), absorbed as the metabolite CV-11974 (active)

Criteria for evaluation:

Pharmacokinetics: Urine samples for analysis of CV-11974 and CV-15959. Blood samples for analysis of candesartan cilexetil, CV-11974, and CV-15959.

Statistical methods: Analysis of variance and regression methods were used to analyze pharmacokinetic variables.

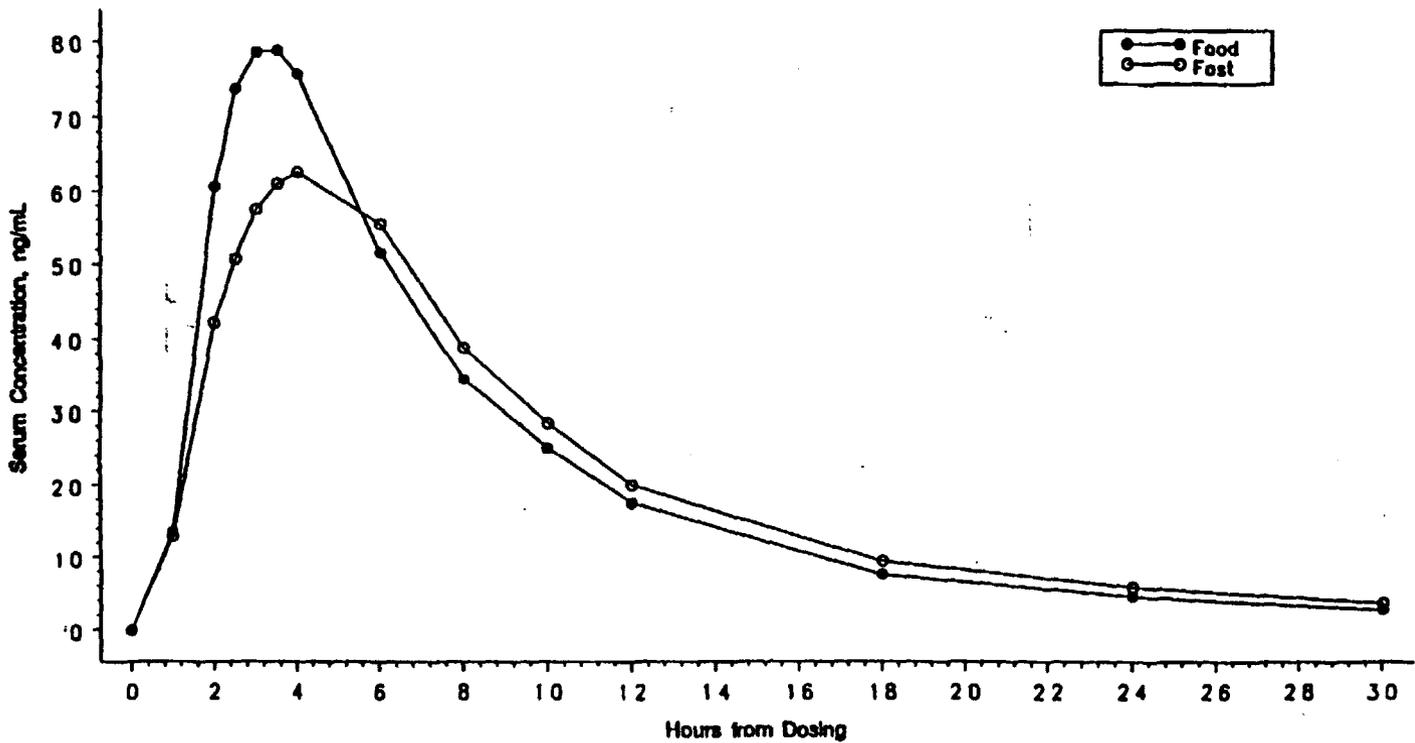
PHARMACOKINETIC RESULTS: The mean serum CV-11974 C_{max} values were 86.8 (fed) and 68.7 (fasted) ng/mL, and the mean T_{max} values were 3.3 (fed) and 4.4 (fasted) hours. These values suggest that the high-fat meal increased the rate of CV-11974 appearance in the serum. The mean AUC values were 642 (fed) and 636 (fasted) ng*hr/mL, and these values suggest that food did not change the extent of CV-11974 appearance in serum. The mean elimination half-life was 9.1 hours under fed conditions and 9.4 hours under fasted conditions.

CONCLUSION:

The rate, but not the extent, of appearance of CV-11974 in serum was increased when candesartan cilexetil was administered 30 minutes after completing a high-fat breakfast rather than during a complete fast. The net effect was an increase of C_{max}, and an earlier T_{max} under fed conditions. The PK analysis indicates that either candesartan cilexetil absorption or candesartan cilexetil conversion to CV-11974 is faster after food.

TABLE 1: A & B Centre Data, SCV-116/NC 027, Clinical Trial Report, Final version of 8 April, 1996

Figure 5
Serum CV-11974 Concentration versus Time
(Mean at Each Time)



APPENDIX II

DRUG INTERACTION STUDIES

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ASSESSMENT OF PHARMACOKINETIC INTERACTION BETWEEN TCV-116 AND AN ORAL CONTRACEPTIVE (MICROGYNON® 21) IN 12 HEALTHY FEMALE VOLUNTEERS (Phase I)

Investigator:

Study Centre:

Objectives:

Main objective: assessment of a possible interaction of TCV116 with the oral contraceptive; secondary objective: evaluation of possible changes on the serum concentrations of the endocrine parameters FSH and LH with concomitant application of TCV116 and the oral contraceptive

Methodology:

Multipledose, placebo controlled, randomized two-way cross-over bioavailability study with enrollment of 12 healthy, female volunteers. The first and second treatment period (= cycle 1 and 2) of 21 days each were separated by a 7 day washout period. Regarding TCV116 the study was doubleblinded.

Test Product:

Name: TCV116
Dosage Form: Tablet
Strength: 8 mg
Lot No.: Z 5429021
Batch No.: E 1160261

Criteria for evaluation:

Pharmacokinetics:

Pharmacokinetic parameters from ethinylestradiol (EE), levonorgestrel (L), CV11974 concentrations and amounts of CV11974 excreted in urine were compared statistically in order to determine a possible interaction of TCV116 with the oral contraceptive.

Statistical methods:

For the pharmacokinetic analysis of AUC, Cmax and Tmax data from ethinylestradiol and levonorgestrel plasma concentrations and AUC, Cmax, Tmax, and (Ae) data from CV11974 serum concentrations, an analysis of variance (ANOVA) was used in order to determine a possible interaction of TCV116 with the oral contraceptive after concomitant dosing of the oral contraceptive + TCV116 or the oral contraceptive + placebo. 90% conventional confidence intervals were given for the ratios.

SUMMARY-CONCLUSIONS

The coadministration of TCV116 did not influence the pharmacokinetics of ethinylestradiol or levonorgestrel to any noticeable degree.

Mean values for AUC(0-24) as well as individual minimal and maximal values are similar for the different treatments and different days. Thus, impairment of the efficacy of Microgynon® 21 (as a typical representative of oral contraceptives) together with daily concomitant administration of 8 mg of TCV116 was not evident.

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In addition, no hormone peaks around midcycle (day 14 and 42) were observed, indicating that ovulation did not occur during the study. A continued oral contraceptive efficacy of Microgynon® 21 with concomitant administration of TCV116 therefore can be concluded.

CONCLUSION:

Based on the study data it can be concluded that the coadministration of TCV116 did not influence the pharmacokinetics of ethinylestradiol or levonorgestrel.

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Table 4
 Summary of Statistical Parameters
 data : plasma concentrations of Ethinylestradiol
 test treatment:
 AC : Microgynon 21 and TCV-116 coadministration
 reference treatment:
 BD : Microgynon 21 and Placebo coadministration

Parameter	AUC24	Cmax	Tmax (A/B)	Tmax (C/D)
Unit	h*pg/ml	pg/ml	h	h
Mean - test	982.6	108.03	1.8333	1.7500
Mean - reference	1064.7	114.29	1.6667	1.5833
%CV - test	41.4%	31.3%	39.1%	49.5%
%CV - reference	41.5%	37.4%	46.7%	42.2%
ANOVA by GLM:				Nonparam.
see Table No.	12	13	14a	14b
ln-transformation ?	yes	yes	no	no
MS(error)	0.0468	0.0413		
DF(error)	33	33		
Number of Subjects	12	12	12	12
Number of Treatments	2	2	2	2
Number of Periods	2	2	2	2
balanced design ?	yes	yes		
Least Square Means				Medians
Mean - test	899.8	103.09	2.0	2.0
Mean - reference	977.7	107.42	1.5	1.5
Difference	-0.083	-0.041	0.0	0.0
SE of Difference	0.0625	0.0586		
ratio	92.03%	95.97%	100.00%	100.00%
90 % Confidence Intervals				
lower limit	82.79%	86.90%	66.66%	66.66%
upper limit	102.28%	105.98%	200.00%	200.00%

For analyses of data after ln-transformation:
 LS-means given back-transformed, i.e. as geometric means,
 MS(error), difference and SE of difference on ln-scale.

AUC24 : AUC(0-24) by trapezoidal rule [h*pg/ml]
 Cmax : observed maximal concentration [pg/ml]
 Tmax : time of peak concentration [h]

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Table 2
 Summary of Statistical Parameters
 data : plasma concentrations of Levonorgestrel
 test treatment:
 AC : Microgynon 21 and TCV-116 coadministration
 reference treatment:
 BD : Microgynon 21 and Placebo coadministration

Parameter	AUC24	Cmax	Tmax (A/B)	Tmax (C/D)
Unit	h*ng/ml	ng/ml	h	h
Mean - test	102.48	9.029	1.1667	1.0889
Mean - reference	110.39	9.955	1.1667	1.0955
%CV - test	44.5%	36.1%	33.4%	26.4%
%CV - reference	44.2%	38.8%	33.4%	27.4%
ANOVA by GLM:				Nonparam.
see Table No.	9	10	11a	11b
ln-transformation ?	yes	yes	no	no
MS(error)	0.0165	0.0154		
DF(error)	33	33		
Number of Subjects	12	12	12	11
Number of Treatments	2	2	2	2
Number of Periods	2	2	2	2
balanced design ?	yes	yes		
Least Square Means				Medians
Mean - test	91.40	8.461	1.0	1.0
Mean - reference	99.60	9.283	1.0	1.0
Difference	-0.086	-0.093	0.0	0.0
SE of Difference	0.0371	0.0358		
ratio	91.77%	91.15%	100.00%	100.00%
90 % Confidence Intervals				
lower limit	86.18%	85.79%	100.00%	50.00%
upper limit	97.71%	96.84%	150.00%	150.00%

For analyses of data after ln-transformation:
 LS-means given back-transformed, i.e. as geometric means,
 MS(error), difference and SE of difference on ln-scale.

AUC24 : AUC(0-24) by trapezoidal rule [h*ng/ml]
 Cmax : observed maximal concentration [ng/ml]
 Tmax : time of peak concentration [h]

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Double-blind, Crossover, Randomized, Placebo-Controlled, Pharmacokinetic Interaction Study of TCV-116, 12 mg Capsule, and Hydrochlorothiazide, 25 mg Capsule, after Repeated Oral Dose Administration in 18 Healthy Male Subjects.

Investigator(s) :

Study centre(s) :

Clinical Phase : Pk interaction study (Phase I)

Objectives : To evaluate, in 18 healthy male subjects, the pharmacokinetic interaction and safety between TCV-116 and hydrochlorothiazide after repeated, once-daily, administration.

Methodology : Double blind, placebo-controlled, randomized, balanced 3-way crossover, repeated dose study

Number of subjects : 18

Diagnosis and criteria for inclusion : healthy male subjects (aged 18-45 y)

Test product, dose and mode of administration, batch no. : TCV-116 12 mg capsules once daily batch no. : E1160281; manufacturer : Pharmakapsel GmbH & Co KG.

Duration of treatment : 3 × 7 days.

Interaction therapy, dose and mode of administration, batch no. : Hydrochlorothiazide 25 mg capsules and placebo capsules.

Criteria for evaluation : Pharmacokinetic parameters obtained after the last administration of each treatment for HCTZ and TCV-116 and its metabolites (CV-11974 and CV-15959). General tolerability of the treatments (vital signs, adverse events).

Statistical methods : For continuous pk parameters : ANOVA (model : formulations, sequences and periods of administration, subjects) after log transform. Standard 90% confidence interval for the ratio test/reference (test = drug given in association; reference = drug given alone). Inclusion of the 90%CI within 80-125% is taken as demonstration for lack-of-interaction. Equivalent nonparametric methods for T_{max}.

SUMMARY - CONCLUSIONS :

The frequency of adverse events (headache, dizziness, fatigue) was higher with the combination TCV-116 and HCTZ than with TCV-116 or HCTZ alone.

The bioavailability of TCV-116 metabolites at steady-state was increased by HCTZ : the mean ratios and CI were 118% (105-133%) for AUC_τ, and 123%, (106-143%) for C_{max}. Other pharmacokinetic parameters (T_{max}, MRT_τ and T_{1/2el}) remained unmodified.

The bioavailability of HCTZ at steady-state was slightly diminished (difference statistically significant) by concomitant administration of TCV-116. AUC_τ decrease of 14% in geometric

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mean (7% in median) and C_{max} decrease by 6%; the 90% confidence interval for combined/monotherapy ratio remained included within the 80-125%. Other pharmacokinetic parameters of HCTZ (T_{max}, MRT_τ and T_{1/2el}) remained unmodified.

Repeated once-daily oral intake of 12 mg TCV-116 has minor influence on the steady-state HCTZ serum concentrations, but HCTZ at therapeutic serum concentrations (25 mg once daily) influences the TCV-116 disposition kinetics, by increasing the bioavailability of both major metabolites (active CV-11974 and inactive CV-15959) by about 20% on the average. The mechanism of this interaction is not known as an IV dose was not investigated. If absorption changes can be eliminated as a mechanism for this interaction, changes in distribution or even elimination could cause the observed increases in bioavailability.

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GLOSSARY

ACE = Angiotensin-converting-enzym

Ang II = Angiotensin II

AUC = Area under the curve

C_{max} = maximum concentration

DBP = Diastolic blood pressure

HCTZ = Hydrochlorothiazide

HR = Heart rate

M-I (CV-11974) = metabolite I of TCV-116

M-II (CV-15959) = metabolite II of TCV-116

MRT = Mean residence time

% PTF = Percent peak trough fluctuation

RAS = Renin-angiotensin system

SBP = Systolic blood pressure

T_{max} = Time corresponding to C_{max}

$T_{1/2el}$ = Elimination half-life

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SUMMARY

Study objective : To evaluate, in 18 healthy male subjects, the pharmacokinetic interaction and safety between TCV-116 and hydrochlorothiazide after repeated, once-daily, administration.

Methods : The clinical trial was conducted as a double blind, placebo-controlled, randomized, fully balanced three-way crossover, repeated dose study in 18 subjects. The subjects were randomly assigned to one of 6 administration sequences to receive, at the occasion of 3 identical sessions, each of the following treatments once daily for 7 days : either TCV-116 12 mg capsule + placebo capsule, or HCTZ 25 mg capsule + placebo, or TCV-116 12 mg + HCTZ 25 mg. On the 7th day of each session, serum samples were drawn for 24 h after administration, for the determination of HCTZ and of TCV-116 and its metabolites M-I (CV-11974) and M-II (CV-15959). No wash-out period separated the different sessions.

Results : The 3 treatments were generally well tolerated with only minor side effects related to the hypotensive potency of the drugs (headache, dizziness, fatigue) occurring during the study. The frequency of adverse events in subjects receiving the combination of TCV-116 and HCTZ was higher than with TCV-116 or HCTZ alone. The following values were obtained for the pharmacokinetic parameters of the two drugs (or metabolic moieties) administered alone (with placebo) or in association.

Drug or metabolite Parameter	Drug administered		P-value	Means ratio (90% CI)	
	alone	in association			
HCTZ	C _{max} (ng/mL)	112 (93 - 135)	105 (86 - 129)	0.14	94 % (88 - 101 %) ✓
	T _{max} (h)	3 (2 - 4)	3 (2 - 6)	0.50	100 % (94 - 122 %) ✓
	AUC ₀₋₂₄ (ng.h/mL)	877 (708-1085)	732 (601-940)	<0.01	86 % (79 - 93 %) ✓
	MRT ₀₋₂₄ (h)	7.2 (6.5 - 8.1)	6.9 (6.0 - 8.1)	0.26	96 % (90 - 102 %) ✓
	T _{1/2el} (h)	9.7 (6.5 - 14.5)	9.1 (5.4 - 15.1)	0.66	94 % (72 - 121 %) ↓
CV-11974	C _{max} (ng/mL)	78 (58 - 106)	96 (64 - 145)	0.04	123 % (106 - 143 %) ↑
	T _{max} (h)	4 (2 - 4)	4 (2 - 6)	0.41	100 % (82 - 115 %) ✓
	AUC ₀₋₂₄ (ng.h/mL)	750 (596 - 942)	886 (654 - 1201)	0.02	118 % (105 - 133 %) ✓
	MRT ₀₋₂₄ (h)	8.4 (7.4 - 9.5)	8.4 (7.4 - 9.4)	0.92	100 % (94 - 105 %) ✓
	T _{1/2el} (h)	9.9 (6.6 - 14.9)	10.7 (8.5 - 13.6)	0.40	108 % (90 - 129 %) ↑
CV-15959	C _{max} (ng/mL)	11.4 (7.6-17.1)	14.1 (9.2 - 21.7)	0.04	124 % (107 - 148 %) ✓
	AUC ₀₋₂₄ (ng.h/mL)	189 (128-280)	228 (152 - 343)	0.07	121 % (105 - 143 %) ✓
	T _{1/2el} (h)	17.3 (11.1-26.9)	17.9 (11.4 - 28.3)	0.62	103 % (91 - 117 %) ✓

Values are median (range) for T_{max}; geometric means (mean - 1 SD; mean + 1 SD) (N=18 for HCTZ and 17 for CV-11974 and CV-15959) for other parameters.

The bioavailability of TCV-116 metabolites was augmented by HCTZ : the mean ratios for AUC₀₋₂₄ and C_{max}, and their associated confidence intervals, were significantly shifted above unity. Other pharmacokinetic parameters (T_{max}, MRT₀₋₂₄ and T_{1/2el}) remained unmodified.

On the other hand, the bioavailability of HCTZ was slightly diminished (difference statistically significant) by concomitant administration of TCV-116, but to an extent apparently lacking any clinical relevance : AUC₀₋₂₄ decrease of 14% in geometric mean (7% in median) and C_{max} decrease by 6%; the 90% confidence interval for combined/monotherapy ratio remained included within the 80-125% limits considered to decide for lack of interaction [Steinijans VW *et al.* Int J Clin Pharmacol Ther Toxicol 29 : 323-328, 1991]. Other pharmacokinetic parameters of HCTZ (T_{max}, MRT₀₋₂₄ and T_{1/2el}) remained unmodified.

Conclusion : Repeated once-daily oral intake of 12 mg TCV-116 has no clinically relevant influence on the steady-state HCTZ serum concentrations, but HCTZ at therapeutic serum concentrations (25 mg once daily) influences the TCV-116 disposition kinetics, by increasing the bioavailability of both major metabolites (active CV-11974 and inactive CV-15959) by about 20% on the average.

inactive

At discharge, no clinically significant modifications were observed in the blood and urine laboratory parameters of the subjects (see details in table C.4).

The vital signs recorded during each session are presented in table C.3. The time course of blood pressure (both systolic and diastolic, recorded in standing and supine positions) and heart rate during the 24 h period following the last (7th) administration of each treatment are illustrated in figure C.1.a-c (average curves) and C.2.a-e (individual curves). The average measure of each vital sign during the dosing interval are given in table 2 below.

Table 2 : average measure of blood pressure (BP) and heart rate (HR) during the 24 h period following the last administration after 7 days of repeated once-daily dosing of TCV-116 12 mg + placebo or HCTZ 25 mg + placebo or TCV-116 12 mg + HCTZ 25 mg in healthy subjects (values are mean (SD); N = 18).

	TCV-116 + placebo	HCTZ + placebo	TCV-116 + HCTZ
Standing systolic BP (mmHg)	116.6 (5.4)	118.3 (4.2)	115.1 (6.9)
Standing diastolic BP (mmHg)	72.9 (4.6)	75.7 (3)	72.8 (4.4)
Supine systolic BP (mmHg)	112.7 (4.8)	115.7 (6)	112.8 (6.7)
Supine diastolic BP (mmHg)	69.7 (3.7)	74.4 (3.7)	68.8 (5)
HR (beats/min)	72.7 (4.1)	73.8 (5)	75.2 (6.1)

3.3 Interaction of TCV-116 with the pharmacokinetics of HCTZ

The individual HCTZ serum concentrations, measured over the 24 h dosing interval on day 7 after once daily administration of either HCTZ alone (administration with placebo) or in combination with TCV-116, are presented in Table A.1, appendix A.

The individual profiles are given per treatment in Figures B.2.a-b, and by subject in Figures B.7.a-r, in appendix B. The mean serum concentration profiles are illustrated in Figure 1 below (see also Figure B.1, appendix B).

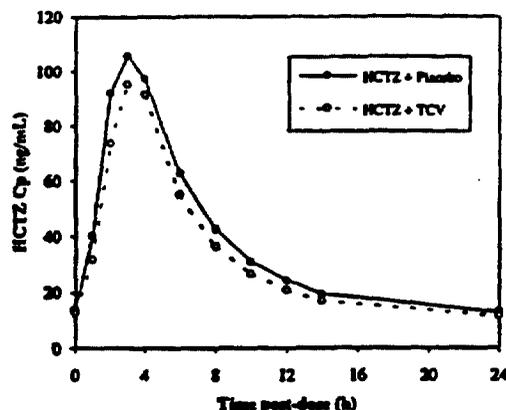


Fig. 1 : Average HCTZ serum concentration vs. time profiles (geometric means; n=18) at steady-state after once daily administration for 7 days of 25 mg HCTZ given with placebo (o) or with 12 mg TCV-116 (o) in healthy subjects.

The pharmacokinetic parameters derived from the HCTZ serum concentration-time profiles are summarized in Table 3 below (individual values are given in Tables A.1.c, appendix A; statistical printouts are given in Tables A.2.a-g).

Table 3 : Pharmacokinetic parameters of HCTZ at steady-state after once daily administration for 7 days of 25 mg HCTZ given with placebo or with 12 mg TCV-116 in healthy subjects.

Parameter	HCTZ + placebo	HCTZ + TCV-116	p *	90%CI for combin/alone ratio **
C _{max} (ng/mL)	112 (93 - 135)	105 (86 - 129)	0.14	88 - 101 % ✓
T _{max} (h)	3 (2 - 4)	3 (2 - 6)	0.50	94 - 122 % ✓
C _{min} (ng/mL)	5.8 (6.9)	4.4 (5.8)	0.45	24 - 129 % ✓
AUC _t (ng.h/mL)	877 (708-1085)	752 (601-940)	<0.01	79 - 93 % ✗
MRT _t (h)	7.2 (6.5 - 8.1)	6.9 (6.0 - 8.1)	0.26	90 - 102 % ✓
%PTF (%)	291 (246 - 345)	323 (268 - 388)	0.04	102 - 120 % ✓
T _{1/2el} (h)	9.7 (6.5 - 14.5)	9.1 (5.4 - 15.1)	0.66	72 - 121 % ✗

T_{max} values are median (range). C_{min} values are means (SD). Other values are geometric means (mean - 1 SD; mean + 1 SD) (N=18).

* : Statistical significance of the difference between formulation means.

** : Standard 90% confidence interval for the expected mean of the (HCTZ+TCV)/(HCTZ alone) ratio, derived from ANOVA for continuous parameters, and from a nonparametric method for T_{max}.

Statistical analysis of the results indicated no significant sequence and period effects for any parameter except T_{max} (significant sequence effect). A significant subject effect was observed for C_{max}, AUC_t and %PTF (tendency : p=0.06).

A statistically significant difference between the two treatments (HCTZ + TCV-116 vs. HCTZ + placebo) was detected for AUC_t and %PTF.

The results indicate an interaction of TCV-116 leading to a slightly but statistically significantly dampened bioavailability of HCTZ (as indicated by AUC_t) : The relative bioavailability compared to administration with placebo was 86% (90%CI : 79 - 93%).

A similar trend (not statistically significant) to lower values when HCTZ was combined with TCV-116 was observed for C_{max} (ratio : 94%; 90%CI : 88-101%) and also for C_{min} (ratio : 76%; 90%CI : 24-129%).

For AUC_{τ} and C_{max} ; the 90% confidence intervals around the (HCTZ + TCV-116)/(HCTZ + placebo) ratio remained almost entirely enclosed within the 80-125% range considered to decide for lack-of-interaction.

The influence of TCV-116 on HCTZ bioavailability was variable from subject to subject (individual combined/monotherapy ratios ranging for AUC_{τ}), as indicated in Figure 2 below.

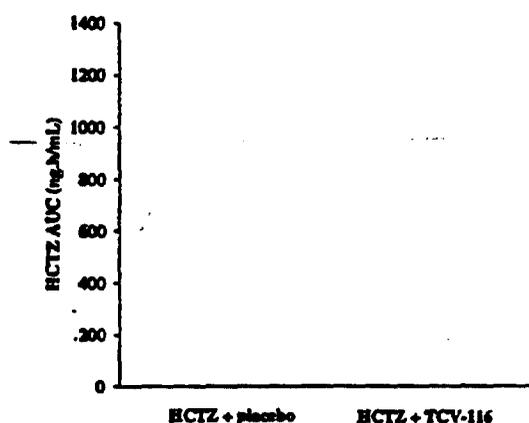


Fig. 2 : Individual HCTZ AUC_{τ} values at steady-state after once daily administration for 7 days of 25 mg HCTZ given with placebo or with 12 mg TCV-116 in healthy subjects.

The other parameters exhibited slight trends (not statistically significant) above or below the unit ratio, T_{max} (94-122%), MRT_{τ} (90-102%) and %PTF (102-120%), but the intervals also remained enclosed within the 80-125% range. A larger interval, centered over the unit ratio, was obtained for $T_{1/2el}$ (72-121%).

3.4 Interaction of HCTZ with the pharmacokinetics of TCV-116

The parent drug TCV-116 was never detected (limit of detection : 0.5 ng/mL) in any serum sample (Table A.3.b). The individual serum concentrations of TCV-116 metabolites M-I (CV-11974) and M-II (CV-15959), measured over the 24 h dosing interval on day 7 after once daily administration of either TCV-116 alone (administration with placebo) or in combination with HCTZ, are presented in Tables A.4.a and A.6.a, appendix A.

The individual profiles are given per treatment in Figures B.4.a-b and 6.a-b, and by subject in Figures B.7.a-r, in appendix B. The mean serum concentration profiles are illustrated in Figure 3 below (see also Figures B.3 and B.5, appendix B).

The pharmacokinetic parameters derived from the serum concentration-time profiles of the two metabolites are summarized in Table 4 below (individual values are given in Tables A.4.b and A.6.b, appendix A; statistical printouts are given in Tables A.5.a-g and A.7.a-g).

Important remark : The profiles obtained for both metabolites indicate that subject no.7 did not take TCV-116 on morning of day 7 on session 2 (see "Deviations from the Protocol", section 3.1). The results obtained for that subject (with both treatments) were disregarded in all calculations (average curves, statistics).

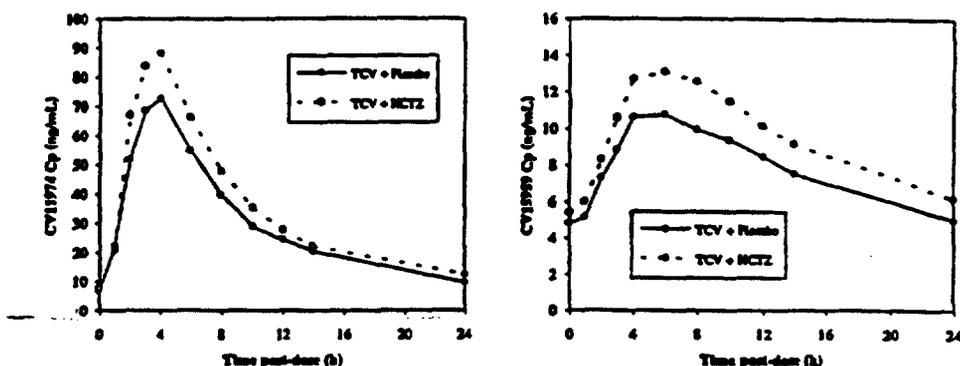


Fig. 3 : Average serum concentration vs. time profiles of TCV-116 metabolites MI (CV-11974; left) and MII (CV-15959; right) at steady-state after once daily administration for 7 days of 12 mg TCV-116 given with placebo (●) or with 25 mg HCTZ (○) in healthy subjects. Values are geometric means (n=17).

Statistical analysis of the results indicated no significant sequence and period effects for any parameter of both moieties. A significant subject effect was observed for all parameters except $T_{1/2el}$ for CV-11974 and MRT_{τ} for CV-15959 (not tested for T_{max}).

Statistically significant differences between the two treatments (TCV-116 + HCTZ vs. TCV-116 + placebo) were detected for C_{max} and AUC_{τ} of CV-11974 and C_{max} of CV-15959 (only tendency, $p = 0.07$, for AUC_{τ} of CV-15959).

These results indicate an interaction of HCTZ leading to a larger bioavailability of both metabolites of TCV-116 :

The relative bioavailability (as indicated by AUC_{τ}) compared to administration with placebo was 118% (90%CI : 105-133%) for CV-11974 and 121% (90%CI : 105-143%).

The influence of HCTZ on TCV-116 bioavailability was variable from subject to subject, as indicated in Figure 4 below : individual ratios ranged for CV-11974 (with 8 subjects among 17 exhibiting a ratio upper than 1.2), and from for CV-15959 (10 subjects with a ratio > 1.2), as indicated in Figure 4 below.

Similarly, C_{max} was increased by 23% for both metabolites (90%CI : 106-143% for CV-11974 and 107-148% for CV-15959).

A similar trend above the unit ratio (but not statistically significant) was observed for C_{min} (mean increase for CV-11974 : 13%; 90%CI : 89-136%; mean increase for CV-15959 : 19%; 90%CI : 100-149%).

For the parameters representing the rate of absorption and elimination (%PTF, T_{max} , MRT_{τ} and $T_{1/2el}$), the intervals remained almost entirely enclosed within the 80-125% considered to decide for lack-of-interaction.

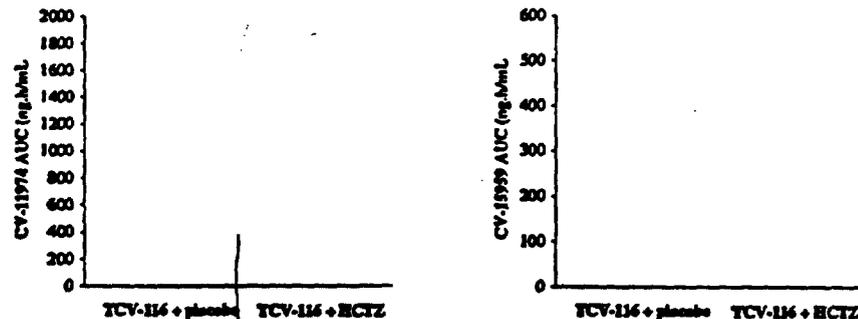


Fig. 4 : Individual AUC values of CV-11974 (left) and CV-15959 (right) at steady-state after once daily administration for 7 days of 12 mg TCV-116 given with placebo or with 25 mg HCTZ in healthy subjects.

Table 4 : Pharmacokinetic parameters of TCV-116 metabolites MI (CV-11974) and MII (CV-15959) at steady-state after once daily administration for 7 days of 12 mg TCV-116 given with placebo or with 25 mg HCTZ, in healthy subjects.

CV-11974				
Parameter	TCV-116 + placebo	TCV-116 + HCTZ	p *	90%CI for combin./alone ratio **
C _{max} (ng/mL)	78 (58 - 106)	96 (64 - 145)	0.04	106 - 143 % ↑
T _{max} (h)	4 (2 - 4)	4 (2 - 6)	0.41	82 - 115 % ✓
C _{min} (ng/mL)	6.8 (4.1 - 11.1)	7.7 (4.8 - 12.2)	0.21	89 - 136 %
AUC _t (ng.h/mL)	750 (596 - 942)	886 (654 - 1201)	0.02	105 - 133 % ↑
MRT _t (h)	8.4 (7.4 - 9.5)	8.4 (7.4 - 9.4)	0.92	94 - 105 % ✓
%PTF (%)	227 (173 - 296)	238 (185 - 307)	0.36	97 - 115 % ✓
T _{1/2el} (h)	9.9 (6.6 - 14.9)	10.7 (8.5 - 13.6)	0.40	90 - 129 % ↑
CV-15959				
Parameter	TCV-116 + placebo	TCV-116 + HCTZ	p *	90%CI for combin./alone ratio **
C _{max} (ng/mL)	11.4 (7.6 - 17.1)	14.1 (9.2 - 21.7)	0.04	107 - 148 %
T _{max} (h)	6 (4 - 12)	4 (4 - 10)	0.22	82 - 105 %
C _{min} (ng/mL)	4.2 (2.5 - 7.1)	5.0 (3.2 - 7.8)	0.23	100 - 149 %
AUC _t (ng.h/mL)	189 (128 - 280)	228 (152 - 343)	0.07	105 - 143 %
MRT _t (h)	10.8 (10.2 - 11.4)	10.9 (10.1 - 11.6)	0.73	97 - 104 %
%PTF (%)	89 (66 - 121)	96 (70 - 130)	0.18	98 - 117 %
T _{1/2el} (h)	17.3 (11.1 - 26.9)	17.9 (11.4 - 28.3)	0.62	91 - 117 %

T_{max} values are median (range). Other values are geometric means (mean - 1 SD ; mean + 1 SD) (N=17 except for C_{min} : N=16).

* : Statistical significance of the difference between formulation means.

** : Standard 90% confidence interval for the expected mean of the (TCV+HCTZ)/(TCV alone) ratio, derived from ANOVA for continuous parameters, and from a nonparametric method for T_{max}.

ATACAND

An open label multiple dose study to evaluate the effect of 16 mg candesartan cilexetil on the steady state pharmacodynamics and pharmacokinetics of warfarin

Investigators:

Study centre:

Objectives:

To investigate the effect of multiple dose oral administration of candesartan cilexetil on the steady state pharmacodynamics and pharmacokinetics of warfarin

Methodology:

Multiple dose, open label, single period study

Number of subjects (planned and analysed):

The 12 subjects planned completed all treatments; 2 subjects were withdrawn from the study after the warfarin run-in as per protocol; the 14 subjects who entered the study were included in the safety evaluation and 12 of them in the pharmacodynamic and pharmacokinetic evaluation

Diagnosis and main criteria for inclusion:

Healthy male volunteers aged 18-45 years; body weight within $\pm 15\%$ of normal body weight range; having given written informed consent; final inclusion of 12 out of 14 volunteers based on value and stability of the international normalized ratio of prothrombin time (INR) during the warfarin run-in

Test product, dose and mode of administration, batch number/lot number:

candesartan cilexetil; 8 mg tablet; oral administration; E1160321/Z5429061

Duration of treatment:

Multiple dose oral administration of warfarin once daily for 30 days according to the following dosing schedule: 10 mg on day 1, 5 mg on day 2, 4 mg on days 3, 4 and 5, individual dose adjustment on day 6 and/or 9 to obtain and maintain an INR value between 1.2 and 1.8. For six subjects the warfarin run-in (days 1-14; phase W1) was extended with two days after which two subjects were withdrawn from the study. On days 15-24 (or days 17-26; phase W+T) 16 mg candesartan cilexetil was co-administered once daily after a continental breakfast; warfarin treatment alone continued until day 30 (day 32; phase W2)

Reference product, dose and mode of administration, batch number:

warfarin; 1 mg tablet; oral administration; BN 49700

Criteria for evaluation:

Pharmacodynamics: prothrombin time (INR)

Pharmacokinetics: warfarin trough concentration

Statistical methods: The mean of the last four INR values before changing to another treatment (=INR_{pre}) subjected to two-factor ANOVA and subsequent construction of estimates of the difference of means and their 95% confidence intervals for the stability of INR during the study and possible influence of candesartan cilexetil on INR; the mean of the last four warfarin trough concentrations before changing to another treatment (=c_{pre}) analysed similarly.

SUMMARY - CONCLUSIONS

PHARMACODYNAMIC AND PHARMACOKINETIC RESULTS: Subtherapeutic stabilized INR values, generally between 1.2 and 1.8 were seen for all 12 subjects after an appropriate warfarin run-in period. A slight but insignificant decrease of the INR value was observed during combined treatment compared to warfarin treatment alone (W₁), which was accompanied by significantly lower warfarin trough plasma concentrations.

The primary pharmacodynamic and pharmacokinetic parameters are tabulated below:

parameter	treatment phase	arithmetic mean	min - max			
INR _{pre}	W ₁	1.55	1.21-1.86			
	W+T	1.54	1.28-1.85			
	W ₂	1.41	1.16-1.90			
	treatment phase	geometric mean	min - max			
c _{pre} (µg.L ⁻¹)	W ₁	672.7	383.2-1170.9			
	W+T	629.0	369.9-1028.1			
	W ₂	704.7	469.9-1346.0			
parameter	95% confidence interval		point estimate		p-value	
	W ₂ /W ₁	W+T/W ₁	W ₂ /W ₁	W+T/W ₁	W ₂ /W ₁	W+T/W ₁
INR _{pre} *	-0.24 - -0.03	-0.12-0.09	-0.14	-0.01	0.0146	0.8039
c _{pre} (µg.L ⁻¹)**	0.99 - 1.11	0.88-0.99	1.05	0.93	0.1246	0.0305

* 95% confidence interval for the difference of means

** 95% confidence interval for the ratio of geometric means (from ANOVA on logarithmically transformed data)

All adverse events were of a mild intensity. The incidence of adverse events occurring during combined treatment was not higher than during mono-treatment with warfarin.

CONCLUSION:

Despite a small (7%) but significant decrease in warfarin trough plasma concentrations during combined dosing of warfarin and candesartan cilexetil, no interaction could be demonstrated regarding the INR values (anti-coagulation). Based on the results of the present study dose adaptation does not seem necessary.

The treatments were well tolerated by twelve healthy male volunteers.



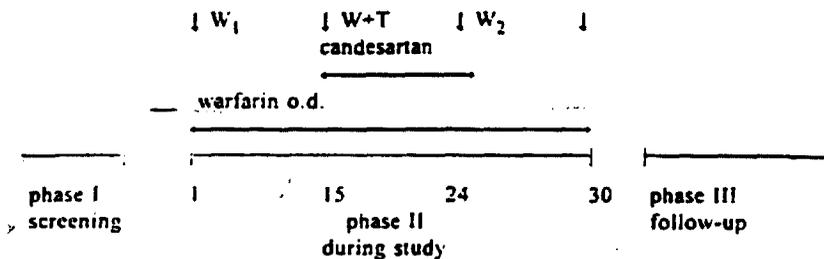
TAKEDA Euro R&D Centre GmbH, TCV-116/EC 032, Clinical Trial Report, final version of 12 April, 1996

6 METHODS AND INVESTIGATIONAL PLAN

6.1 Study Design and Plan

The trial was designed as a multiple dose, open label, single period study. The study consisted of three phases; phase I was the eligibility screening phase, phase 2 involved administration of multiple doses of candesartan cilexetil and warfarin and phase 3 was the follow-up phase.

The treatment consisted of multiple dose oral administration of warfarin for 30 days and co-administration of candesartan cilexetil for 10 days (from days 15-24). If necessary the warfarin run-in (days 1-14) could be extended with a maximum of five days (see Section 6.3).



Twelve (12) healthy young male caucasian volunteers participated in the study.

The target parameters were:

Pharmacodynamic Parameter:

Prothrombin time (INR)

Pharmacokinetic Parameter:

warfarin trough concentration

Safety Parameters:

adverse events, vital signs, physical examination and clinical laboratory tests.

6.2 Ethics Committee / Declaration of Helsinki

The Clinical Trial Protocol (including Written Informed Consent Forms) version-2, dated September 20, 1994, was approved by the Medical Ethics Committee of the "Stichting Beoordeling Ethiek Bio-medisch Onderzoek", Assen, The Netherlands, on September 30, 1994. The list of changes leading to version-3 of the Protocol, dated October 05, 1994 was approved on October 06, 1994 (see Appendix III).

The procedures and ethical precautions of the study were in compliance with the "Declaration of Helsinki" (as lately revised in Hong Kong, 1989) and in accordance with the rules of Good Clinical Practice and Good Laboratory Practice.

6.3 Study Population

Within three weeks prior to the start of the study, volunteers reported to the clinical research facility in Groningen for the eligibility screening. To be eligible for the study, volunteers had to meet the inclusion and exclusion criteria as specified on the next page.

1994.100.04

TAKEDA Euro R&D Centre GmbH, TCV-116/EC 032, Clinical Trial Report, final version of 12 April, 1996

of this report, while individual concentrations on warfarin and candesartan are given in Appendix IX.13.

7.6.3 Pharmacokinetics

Calculations and statistics concerning the pharmacokinetic results of the study were performed during the months

of December, 1994 and January, 1995.

The individual concentration-time profiles of the 12 subjects for warfarin are presented in Section 10.1 as graphs and in Appendix IX.13 as tables. There was a large variability in the warfarin trough plasma concentrations, which was inherent to the warfarin dose administered. A mean plasma concentration-time curve is given in Figure 3. A slight decrease in the warfarin trough plasma concentration was seen during combined treatment.

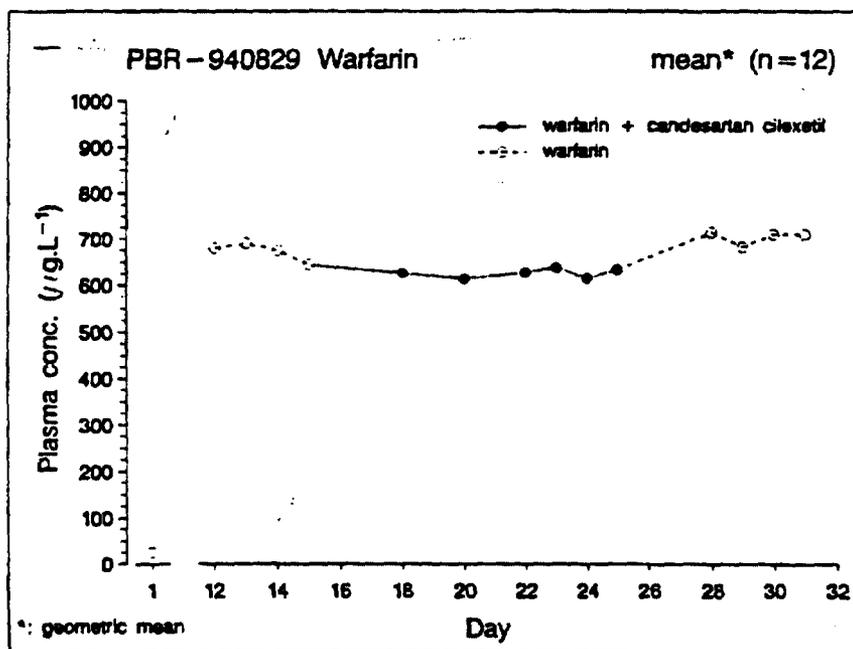


Figure 3 Geometric mean warfarin plasma concentration-time profile as observed during multiple dose oral administration of warfarin for 30 days and co-administration of candesartan cilexetil for 10 days

- phase W₁ = 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 (if applicable)
- phase W+T = individual warfarin dose o.d. and candesartan cilexetil 16 mg o.d. on days 15-24
- phase W₂ = individual warfarin dose o.d. on days 25-30

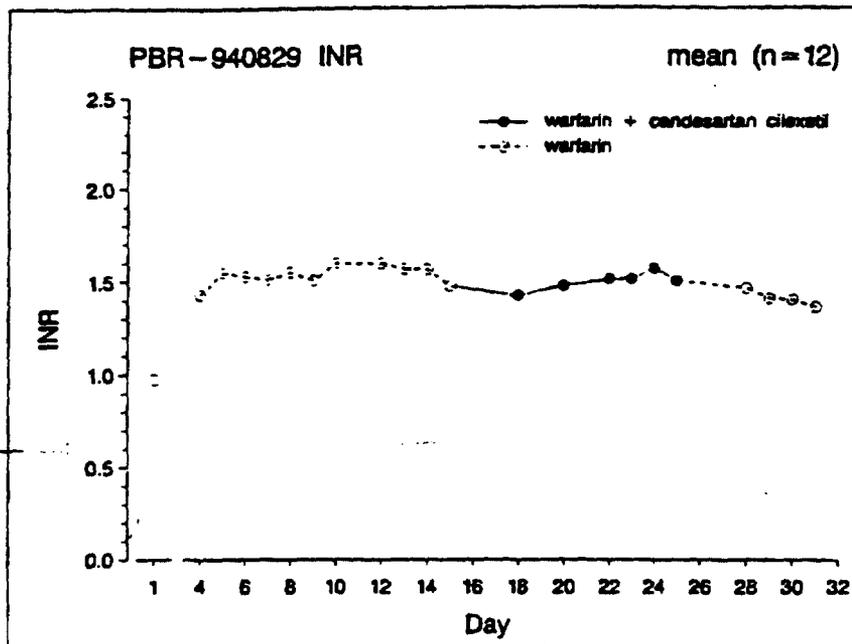


Figure 2 Mean INR values versus time profile as observed during multiple dose oral administration of warfarin for 30 days and co-administration of candesartan cilexetil for 10 days
 phase W₁ = warfarin o.d. on days 1-14: 10 mg on day 1, 5 mg on day 2, 4 mg on days 3-5 and individual dose adjustment on day 6 and/or 9 (if applicable)
 phase W+T = individual warfarin dose o.d. and candesartan cilexetil 16 mg o.d. on days 15-24
 phase W₂ = individual warfarin dose o.d. on days 25-30

The individual INR_{pre} values with their means are listed in Section 10.2. A summary of statistics on this parameter can be found in Table 1.

Statistical evaluation of the INR_{pre} values (see Section 10.4) confirmed the visually observed decline.

Apparently, warfarin treatment alone, both before and after the combined treatment period (W₁ and W₂), resulted in significantly different INR_{pre} values.

No significant interaction could be observed when comparing the INR_{pre} values during combined treatment (W+T) versus baseline warfarin INR_{pre} values (W₁) (see ANOVA in Section 10.4). However, when the INR values during warfarin treatment alone (i.e. before and after combined treatment) were interpolated visually, the INR values during combined treatment tended to be slightly above the interpolation line.

ATACAND

An open label multiple dose randomized three-way crossover study to evaluate the effect of 16 mg candesartan cilexetil on glibenclamide pharmacokinetics at steady state and vice versa

Investigators:

Study centre:

Clinical Phase: I

Objectives:

To investigate the effect of multiple dose oral administration of candesartan cilexetil on the steady state pharmacokinetics of glibenclamide, and vice versa

Methodology:

Multiple dose, open label, three-period, randomized, crossover study with an interval of at least seven days between the treatments

Number of subjects (planned and analysed):

The 12 subjects planned completed the three treatments; 13 subjects who entered the study were included in the safety evaluation and 12 of them in the pharmacokinetic evaluation

Diagnosis and main criteria for inclusion:

Healthy male volunteers aged 18-45 years; body weight within $\pm 15\%$ of normal body weight range; having given written informed consent

Test product, dose and mode of administration, batch number/lot number:

candesartan cilexetil; 8 mg tablet; oral administration; E1160481/Z5429061

Duration of treatment:

Multiple dose oral administration (for 7 days) after a standardized continental breakfast of

- A = combination of candesartan cilexetil 16 mg o.d. and glibenclamide 3.5 mg o.d.
- B = candesartan cilexetil 16 mg o.d.
- C = glibenclamide 3.5 mg o.d.

Reference product, dose and mode of administration, batch number:

glibenclamide (Euglucon N®); 3.5 mg tablet; oral administration; B.752464-01

Criteria for evaluation:

Pharmacokinetics: primary parameters (for glibenclamide and candesartan): c_{max} and AUC₁₄₄₋₁₆₈

secondary parameters (for glibenclamide and candesartan): c_{pre} , t_{max} and c_{min}

Safety: adverse events, vital signs, ECG recordings, glucose levels in capillary blood, physical examination and clinical laboratory tests

Name of Active Ingredient: candesartan cilexetil (TCV-116)

Statistical methods:

Steady state analysis on logarithmically transformed cpre concentrations using ANOVA followed by Dunnett's t-test; four-factor ANOVA on logarithmically transformed primary pharmacokinetic parameters; 90% confidence intervals for ratios of geometric means of A over B and A over C; no-interaction range for cmax and for AUC.

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS:

For glibenclamide no accumulation occurred due to the relatively short half-life. For candesartan (the active metabolite of candesartan cilexetil) serum concentration-time profiles generated on day 7 appeared to be a reflection of a steady state situation. For both glibenclamide and candesartan the mean profiles were similar for the combined treatment and the corresponding mono-treatment. The primary pharmacokinetic parameters are tabulated below:

parameter		treatment	geometric mean	min-max	90% confidence interval and point estimate of ratio*	
glibenclamide						
c _{max}	(ng.mL ⁻¹)	A	161.5	109 - 210	0.93 - 1.22	1.07
		C	151.4	112 - 206		
AUC ₁₄₄₋₁₆₈	(ng.mL ⁻¹ .h)	A	521.3	311 - 872	0.98 - 1.07	1.02
		C	509.1	292 - 789		
candesartan						
c _{max}	(ng.mL ⁻¹)	A	108.9	87.4 - 164	1.04 - 1.21	1.12
		B	96.8	78.9 - 143		
AUC ₁₄₄₋₁₆₈	(ng.mL ⁻¹ .h)	A	762	626 - 1101	0.99 - 1.11	1.05
		B	727	545 - 1131		

*90% confidence interval for the ratio of geometric means of A (test) and B or C (references) (from ANOVA on logarithmically transformed data)

There was no statistically significant difference in blood glucose levels between combined treatment and glibenclamide treatment alone, indicating the absence of a pharmacodynamic interaction.

CONCLUSION:

- There was no pharmacokinetic interaction when glibenclamide and candesartan cilexetil were co-administered for seven days to 12 healthy male volunteers.
- There was no pharmacodynamic interaction (blood glucose levels).
- The three treatments were well tolerated by twelve male volunteers.

7.5.3 Pharmacokinetics

Calculations and statistics concerning the pharmacokinetic results of the study were performed by the Biometrics Department of Pharma Bio-Research Consultancy B.V. during the months of January and February, 1995. The individual serum concentration-time profiles of the 12 subjects both for glibenclamide and candesartan are presented as graphs in Section 10.2 and as tables in Appendix X. Variability plots are given in Section 10.2. A relatively small inter-individual variation in the serum profiles was found for both glibenclamide and candesartan. Graphs of the mean serum concentrations after combined treatment and after administration of each drug alone are given in Figures 2 and 3.

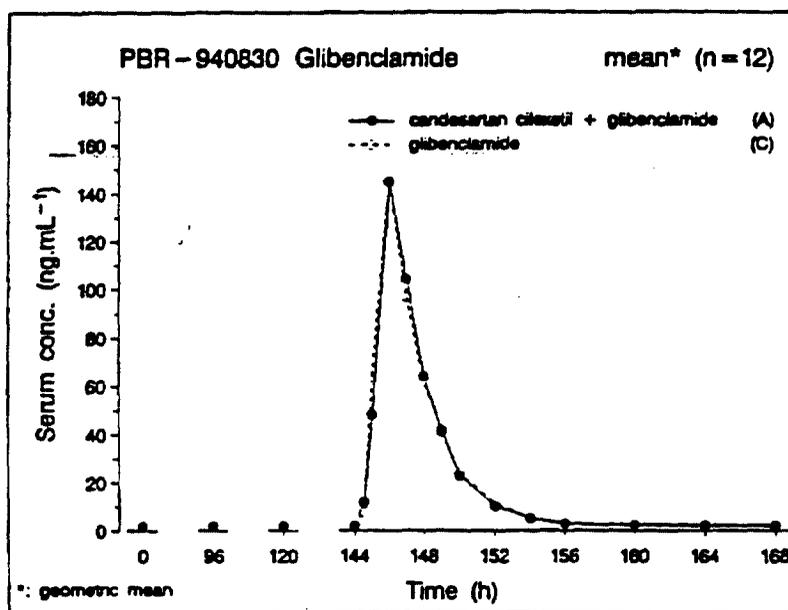


Figure 2 Geometric mean glibenclamide serum concentration-time profiles as observed during multiple dose oral administration (for 7 days) to 12 subjects
 A = combination of candesartan cilexetil 16 mg o.d. and glibenclamide 3.5 mg o.d.
 B = candesartan cilexetil 16 mg o.d.
 C = glibenclamide 3.5 mg o.d.

Upon visual inspection of the plots it was evident that no accumulation occurred during glibenclamide treatment which is in line with the relatively short terminal half-life of the drug. In contrast, the candesartan trough (c_{pre}) serum concentrations on days 5, 6, 7 and 8 were at a comparable level of around 7 ng.mL⁻¹. The latter was confirmed by two-factor ANOVA, followed by Dunnett's test on the logarithmically transformed candesartan trough concentrations (see Section 10.3) with day 7 as the control, which did not show a significant difference during both treatments (A and B). Based on the above-mentioned results the serum concentration-time profiles for candesartan generated on day 7 appeared to be a reflection of a steady state situation.

The pharmacokinetic parameters for the individual subjects as well as means for the total of 12 subjects are listed in Section 10.4. A summary of the primary pharmacokinetic parameters is given in Table 1.

An open label multiple dose randomized three-way crossover study to evaluate the effect of 16 mg candesartan cilexetil on nifedipine pharmacokinetics at steady state and vice versa

Investigators:

Study centre:

Clinical Phase: I

Objectives:

To investigate the effect of multiple dose oral administration of candesartan cilexetil on the steady state pharmacokinetics of nifedipine, and vice versa

Methodology:

Multiple dose, open label, three-period, randomized, crossover study with an interval of at least seven days between the treatments

Number of subjects (planned and analysed):

The 12 planned subjects completed the three treatments; 13 subjects who entered the study were included in the safety evaluation and 12 of them in the pharmacokinetic evaluation

Diagnosis and main criteria for inclusion:

Healthy male volunteers aged 18-45 years; body weight within $\pm 15\%$ of normal body weight range; having given written informed consent

Test product, dose and mode of administration, batch number/lot number:

candesartan cilexetil; 8 mg tablet; oral administration; E1160511/Z5429061

Duration of treatment:

Multiple dose oral administration (for 7 days) after a standardized continental breakfast of
A = combination of candesartan cilexetil 16 mg o.d. and nifedipine 30 mg o.d.

B = candesartan cilexetil 16 mg o.d.

C = nifedipine 30 mg o.d.

Reference product, dose and mode of administration:

nifedipine (Adalat® OROS); 30 mg sustained release tablet; oral administration.

Name of Active Ingredient: candesartan cilexetil (TCV-116)

Criteria for evaluation:

Pharmacokinetics:

primary parameters (for nifedipine and candesartan): c_{max} and AUC.

secondary parameters (for nifedipine and candesartan): c_{pre} , t_{max} and c_{min}

TAKEDA Euro R&D Centre GmbH, TCV-116/EC 048, Clinical Trial Report, final version of 16 April, 1996

The details of ANOVA on the logarithmically transformed primary pharmacokinetic parameters are given in Section 10.5. A significant period effect was demonstrated for the $AUC_{144-168}$ of glibenclamide. AUC values in the second period were approximately 15% lower than those in the first and third periods, which were comparable. However, no consistent trend could be observed and the results seemed to be independent of the treatment in period I. Moreover, since no period effect was apparent for c_{max} this period effect was considered to be irrelevant, not affecting the outcome of the study.

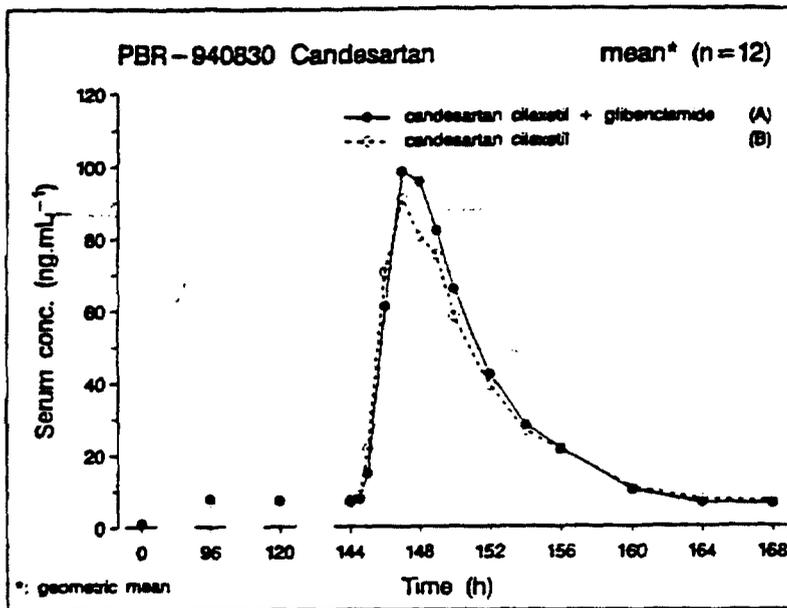


Figure 3 Geometric mean candesartan serum concentration as observed during multiple dose oral administration (for 7 days) to 12 subjects

- A = combination of candesartan cilexetil 16 mg o.d. and glibenclamide 3.5 mg o.d.
- B = candesartan cilexetil 16 mg o.d.
- C = glibenclamide 3.5 mg o.d.

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Statistical methods:

Steady state analysis on logarithmically transformed cpre concentrations using ANOVA followed by four-factor ANOVA on logarithmically transformed primary pharmacokinetic parameters; 90% confidence intervals for ratios of geometric means of A over B and A over C; no-interaction range for cmax and for AUC.

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS: Concentration-time profiles generated on day 7 appeared to be a reflection of a steady state situation. For nifedipine the profiles were rather jagged and a large interindividual variation could be observed which is in line with the literature. For candesartan the mean profiles were similar during combined treatment as compared with the corresponding mono-treatment. A non-significant decrease of 11-15% in nifedipine plasma concentrations could be observed during combined treatment as illustrated by 90% confidence intervals for cmax and AUC outside the pre-determined "no-interaction" ranges. Thus, the absence of an interaction could not be demonstrated. No interaction was observed with respect to candesartan (the active metabolite of candesartan cilexetil) pharmacokinetics. The primary pharmacokinetic parameters are tabulated below:

parameter		treatment	geometric mean	min-max	90% confidence interval and point estimate of ratio*
nifedipine					
c _{max}	(ng.mL ⁻¹)	A	18.02	12.3 - 26.2	0.68 - 1.06 0.85
		C	21.17	10.4 - 45.9	
AUC ₁₄₄₋₁₆₈	(ng.mL ⁻¹ .h)	A	229.2	115 - 486	0.70 - 1.14 0.89
		C	257.6	82 - 719	
candesartan					
c _{max}	(ng.mL ⁻¹)	A	127.9	93.2 - 185	0.95 - 1.21 1.07
		B	119.5	63.5 - 189	
AUC ₁₄₄₋₁₆₈	(ng.mL ⁻¹ .h)	A	858	660 - 1324	0.98 - 1.07 1.03
		B	836	575 - 1256	

* 90% confidence interval for the ratio of geometric means of A (test) and B or C (references) (from ANOVA on logarithmically transformed data)

CONCLUSION:

The three treatments were well tolerated by twelve male volunteers. Nifedipine steady state concentrations were slightly (11-15%) but not significantly diminished during concomitant candesartan cilexetil intake. In contrast, no effect on candesartan pharmacokinetics was observed during combined treatment.

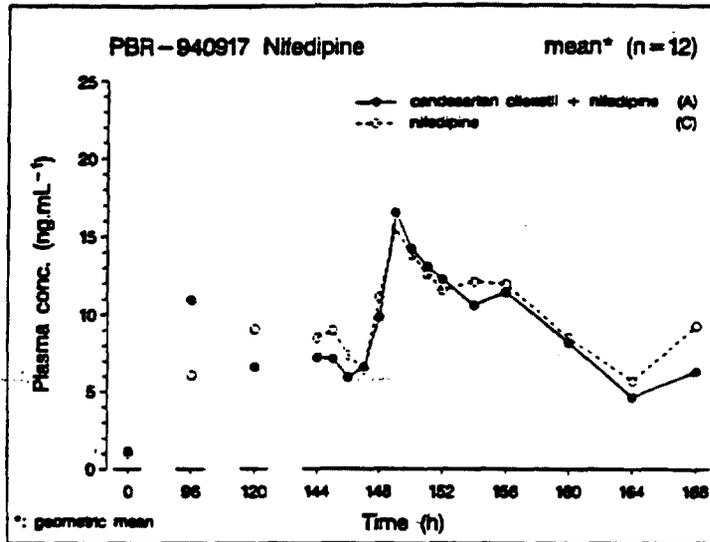


Figure 2 Geometric mean nifedipine plasma concentration-time profiles as observed during multiple dose oral administration (for 7 days) to 12 subjects
A = combination of candesartan cilexetil 16 mg o.d. and nifedipine 30 mg o.d.
C = nifedipine 30 mg o.d.

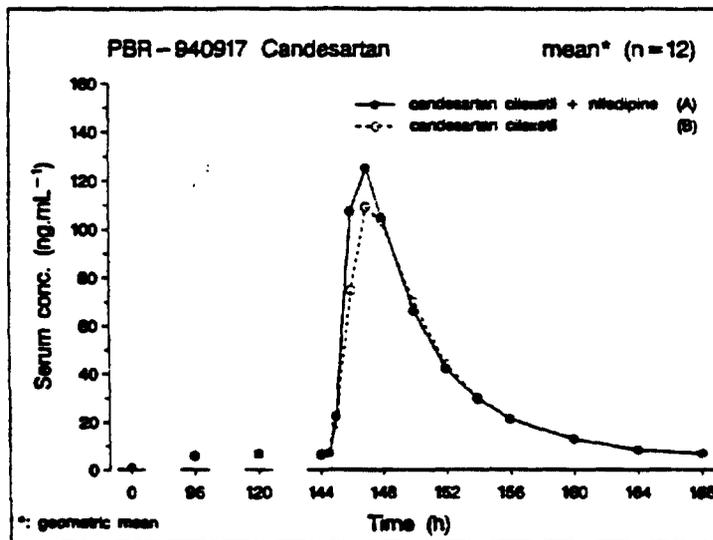


Figure 3 Geometric mean candesartan serum concentration as observed during multiple dose oral administration (for 7 days) to 12 subjects
A = combination of candesartan cilexetil 16 mg o.d. and nifedipine 30 mg o.d.
B = candesartan cilexetil 16 mg o.d.

An open label multiple dose randomized three-way crossover study to evaluate the effects of 16 mg candesartan cilexetil on digoxin pharmacokinetics at steady state and vice versa

Investigators:

Study centre:

Clinical Phase: I

Objectives:

To investigate the effect of multiple dose oral administration of candesartan cilexetil on the steady state pharmacokinetics of digoxin, and vice versa

Methodology:

Multiple dose, open-label, three-period, randomized, crossover study with an interval of at least seven days between the treatments

Number of subjects (planned and analysed):

The 12 subjects planned completed the three treatments; 13 subjects who entered the study were included in the safety evaluation and 12 of them in the pharmacokinetic evaluation

Diagnosis and main criteria for inclusion:

Healthy male (6) and female (6) volunteers aged 18-45 years; body weight within $\pm 15\%$ of normal body weight range; having given written informed consent; for female volunteers adequate contraception or no child-bearing potential

Test product, dose and mode of administration, batch number/lotnumber:

candesartan cilexetil; 16 mg capsule; oral administration; E116 6011/Z5429061

Reference product, dose and mode of administration, batch number/lotnumber:

digoxin; 0.25 mg tablet; oral administration; E116 6011/E1447A

Duration of treatment:

Multiple dose oral administration (for 9 days) after a standardized continental breakfast of

A = combination of candesartan cilexetil 16 mg o.d. and digoxin 0.25 mg o.d.*

B = candesartan cilexetil 16 mg o.d.

C = digoxin 0.25 mg o.d.*

* loading dose of 0.5 mg in the morning and 0.25 mg in the evening of day 1

Criteria for evaluation:

Pharmacokinetics: primary parameters (for digoxin and candesartan): c_{max} and AUC

secondary parameters (for digoxin and candesartan): c_{pre} , t_{max} and c_{min}

Name of Active Ingredient: candesartan cilexetil (TCV-116)

Statistical methods:

Steady state analysis on logarithmically transformed cpre concentrations using ANOVA followed by four-factor ANOVA on logarithmically-transformed primary pharmacokinetic parameters; 90% confidence intervals for ratios of geometric means of A over B and A over C; no-interaction range

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS:

Serum concentration-time profiles generated on day 9 appeared to be a reflection of a situation in steady state. Both for digoxin and candesartan (the active metabolite of candesartan cilexetil) the mean profiles were very similar for the combined treatment as compared with the corresponding mono-treatment. The primary pharmacokinetic parameters are tabulated below:

parameter		treatment	geometric mean	min-max	90% confidence interval and point estimate of ratio*	
digoxin						
c_{max}	($\mu\text{g}\cdot\text{L}^{-1}$)	A	1.32	1.04 - 1.92	0.86 - 1.05	0.95
		C	1.39	0.955 - 2.29		
AUC ₁₉₂₋₂₁₆	($\mu\text{g}\cdot\text{L}^{-1}\cdot\text{h}$)	A	13.8	9.6 - 22.4	0.90 - 1.05	0.98
		C	14.1	10.8 - 21.8		
candesartan						
c_{max}	(ng.mL ⁻¹)	A	123.7	92.3 - 220	0.96 - 1.13	1.04
		B	118.8	75.9 - 199		
AUC ₁₉₂₋₂₁₆	(ng.mL ⁻¹ .h)	A	853	532 - 1313	0.92 - 1.10	1.01
		B	849	577 - 1173		

* 90% confidence interval for the ratio of geometric means of A (test) and B or C (references) (from ANOVA on logarithmically-transformed data)

When primary parameters for each gender were corrected for (dose per) body weight there were no differences between genders.

CONCLUSION:

The three treatments were well tolerated by six male and six female volunteers. With respect to safety and tolerability there was no difference between the treatments.

No pharmacokinetic interaction could be demonstrated when digoxin and candesartan cilexetil were administered concomitantly for nine days. There was no gender difference when primary pharmacokinetic parameters were corrected for (dose per) body weight.

TAKEDA Euro R&D Centre GmbH, TCV-116/EC 601, Clinical Trial Report, final version of 23 April, 1995

10.6 Pharmacokinetic Evaluation by Gender

Geometric mean serum concentration-time curves of digoxin and candesartan as observed during multiple dose oral administration (for 9 days) to 12 subjects

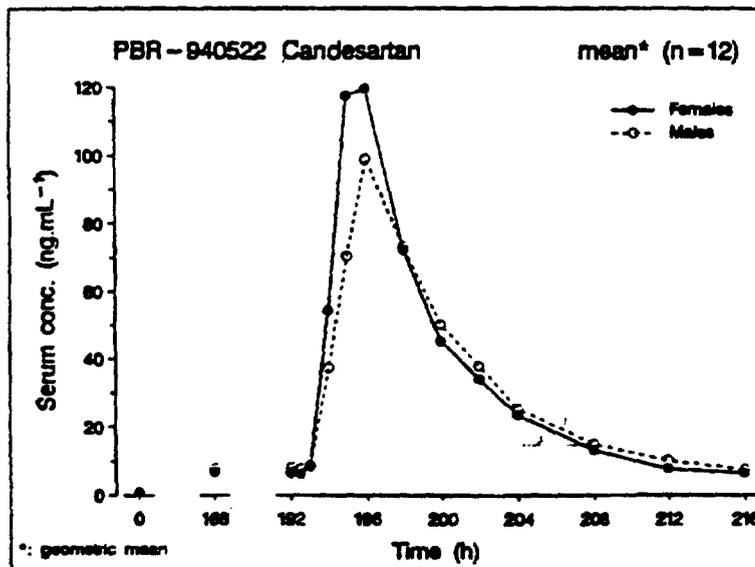
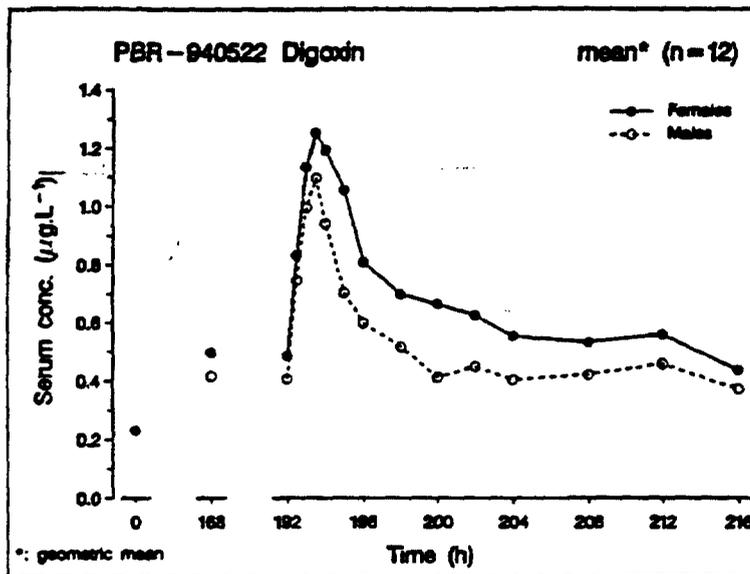
A = combination of candesartan cilexetil 16 mg o.d. and digoxin 0.25 mg o.d.*

B = candesartan cilexetil 16 mg o.d.

C = digoxin 0.25 mg o.d.*

* loading dose of 0.5 mg in the morning and 0.25 mg in the evening of day 1

Subjects 01-11, 16



APPENDIX III

POPULATION PHARMACOKINETIC ANALYSIS

POPULATION PHARMACOKINETIC ANALYSIS OF CANDESARTAN CILEXETIL

Studies #AM113, AM119, EC002 and EC002A

Report Prepared by:

II. SYNOPSIS

Population pharmacokinetic analysis was performed on pooled data from Studies AM113 (Study 113), AM 119 (Study 119), and EC002 and EC002A (collectively, Study 002), in which candesartan cilexetil doses within the range of 2 to 64 mg were administered once daily to individuals with essential hypertension (Studies 113 and 119) or to healthy individuals (Study 002). Study 113 was a parallel dose study, Study 119 a forced-dose titration study and Study 002 a crossover study, with a washout period between treatments.

A 2-compartment open model with a lag time and first-order input reasonably describes the pharmacokinetics of candesartan after oral administration of candesartan cilexetil. The model that was used allows for differences in interindividual variability in clearance (CL) of candesartan and in intraindividual (and residual) variability in plasma concentrations among studies.

The only covariate that was statistically significant through the final stage of testing was a study effect (Studies 113 and 119 vs. Study 2) on CL/F . While linear models for body weight effects on CL/F and V_d/F and for age effect on CL/F were initially identified as potentially significant covariates, finally they were able to be removed from the model without significantly ($p < 0.01$) worsening the goodness-of-fit. No significant effects of gender or race (nonblack vs. black) on CL/F and V_d/F were detected.

Clinical Performance of Studies

In Study 113, PK data were collected from men and women with hypertension who received once daily doses of either 2, 4, 8, 16, 32 mg candesartan cilexetil tablet for 8 weeks. At Week 2, a trough blood sample was collected prior to taking the daily dose and another sample was collected 2 to 6 h after the dose was administered. One additional blood samples were collected at Week 8 between 6 and 24 h after the dose was administered. (Nearly all of the final samples were collected near 24 h.)

In Study 119, PK data were collected from individuals with hypertension who received forced-titration once daily doses of 8, 16, 32 and then 64 mg candesartan cilexetil, for 2 weeks each, for a total of 8 weeks. Three blood samples per person were collected during each visit; the visits occurred with the last dose of each dose level. A trough blood sample was collected just prior to taking the daily dose, another sample 2 to 6 h after the dose was administered, and a third sample between 8 and 24 h after the dose. (Nearly all of the third samples were taken at 24 h.)

In study 002, The PK data were collected in healthy volunteers who received once daily doses of 2, 4 or 8 mg candesartan cilexetil on Day 1 and Days 3-9. Blood samples were collected on Day 9 just before the dose, and at 1, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, 30 and 36 h after the dose. After a 2-week washout period, the subjects received another dose level, until they received all dose levels. Twelve of the 19 subjects also received 16 mg doses after finishing the above 3 dose levels.

Data Analysis Methods

A 2-compartment open model with a lag time and first-order input was used to describe the candesartan plasma concentration vs. time relationship.

The general form of the model is as follows:

$$C_{mij} = (f(X_{mij}; \bar{P}_{mi})) \exp(\epsilon_{mij}) \quad (1)$$

in which C_{mij} is the observed concentration at steady-state in the i th individual from the m th study (in which $m=1$ for Study 113, 2 for Study 119 and 3 for Study 002) at the j th observation, $f(\cdot)$ is a function of known form, X_{mij} are all the concomitant data (e.g., time and dose), \bar{P}_{mi} is a vector of PK parameters. ϵ_{mij} are random differences between the log of the observed and the log of the predicted concentrations and are attributable to intraindividual (within-individual) variability and other sources of error (e.g., assay variability). The magnitude of the residual random variability in each of the studies is given by the variance of the vectors $\bar{\epsilon}_1$, $\bar{\epsilon}_2$ and $\bar{\epsilon}_3$, σ_1^2 , σ_2^2 and σ_3^2 , respectively.

The model also includes interindividual (between-individual) variability in CL , V_c , t_{lag} , k_a , Q , V_{ss} and F . The magnitude of interindividual variability in V_{ss} was modeled as being identical to that in V_c . By recognizing that there is interindividual variability in F (although absolute F cannot be estimated) we have, in essence, included a correlation between volume and clearance terms. This aspect of the model improved the goodness of fit significantly ($p < 0.001$). The general model for interindividual variability is as follows:

$$P_{kmi} = \bar{P}_{ki} \cdot \exp(\eta_{kmi}), \quad (2)$$

in which η_{kmi} is the individual random effect of the k th PK parameter in the m th study and accounts for the difference between the log of the population prediction (\bar{P}_{ki}) and the log of the subject-specific value of this parameter in the i th individual. The magnitude of interindividual variability of the k th parameter in the m th study is given by the variance of the vector $\bar{\eta}_{km}$ (ω_{km}^2). For all PK parameters except CL , V_c and F , $\omega_{k1}^2 = \omega_{k2}^2 = \omega_{k3}^2$. The estimates of interindividual variability in CL were allowed to differ among studies, and for V_c and F $\omega_{k1}^2 = \omega_{k2}^2$.

The following covariates were tested for their influence on the parameters CL/F and V_c/F : age, body weight, gender, race (nonblack vs. black), study effect, dose level (within Study 113) and time since beginning the drug (within Study 113). If a covariate is shown to be significant for both CL/F and V_c/F in the same direction (negative or positive) and in approximately the same magnitude, testing of this covariate on F would be performed.

In the first step, covariates were tested by their separate inclusion in the models of CL/F and V_c/F . At this point, the criterion for a significant $\Delta[-2 \ln(\text{likelihood})]$ with the fuller model relative to the reduced (nested) model is the χ^2 value that corresponds to $p < 0.05$. The continuous covariates are introduced as simple linear functions. Categorical covariates are modeled by allowing a fractional change in $(\bar{CL}/F)_i$ or $(\bar{V}_c/F)_i$ depending on the covariate attribute [e.g., $(\bar{CL}/F)_i = \theta_1 \cdot GEND_i$, in which $GEND_i = 1$ if the i th individual is male and $GEND_i = \theta_2$ if female]. During the initial covariate testing, CL/F was allowed to be estimated separately for each of the studies and the estimate of V_c/F for Studies 113 and 119 was allowed to differ from that of Study 2.

All significant covariates (and their associated parameters) from the first step were included in a full model. Then in the second step, each covariate (and associated parameter) was deleted separately from this model. In the third step, stepwise deletion of the covariates (and their associated parameters) from the full model was done, retaining only those covariates/parameters that caused a significant decrease in the goodness-of-fit when they are deleted. At this stage, the criterion for statistically significant is a $p < 0.01$. In this last stage, study effect on V_c/F was the first covariate tested; then, the order of covariate testing was based on the results from the second step, with the least significant covariates deleted first. Attempts to refine the models for CL/F and V_c/F (i.e., use of a nonlinear model) would be made for any significant covariate effects.

VI. RESULTS

A 2-compartment open model with a lag time and first-order input reasonably describes the PK of candesartan after oral administration of candesartan cilexetil.

In the first stage of model building age, body weight and time since beginning active treatment were shown to have significant ($p < 0.05$) effects on CL/F , and body weight was shown to have a significant effect on V_c/F . Thus, the full model combined these covariate effects together with study effects.

In the second stage (separate deletion of each covariate from the full model), the time effect on CL/F and the body weight effect on V_c/F were no longer significant ($p > 0.05$). In the third step of the analysis, the effects of age and weight on CL/F were no longer significant ($p > 0.05$). The only covariate which remained statistically significant was a study effect (Studies 113 and 119 vs. Study 002) on CL/F ($p < 0.001$).

Because of the strong study effect (Studies 113 and 119 vs. Study 002) on CL/F , and the correlation between study and age (Study 002 was conducted in young, healthy subjects, whereas Studies 113 and 119 were conducted in individuals with essential hypertension), When age effect (without study effect) is included in the model for CL/F , the $-2\ln(\text{likelihood})$ is not as low as when study effect (without age effect) is included in the model, suggesting that the effect of Study 002 is not attributable exclusively (and perhaps not at all) to age. The parameter estimates of the final model (and 95% confidence intervals) are as follows:

$$\begin{aligned} CL/F_{113,119} &= 303.8 (283.6, 324.1) \text{ ml/min,} \\ CL/F_{002} &= 387.4 (346.2, 428.5) \text{ ml/min,} \\ V_c/F &= 66.0 (58.5, 73.5) \text{ L} \\ t_{lag} &= 0.701 (0.656, 0.746) \text{ h,} \\ k_a &= 0.508 (0.430, 0.587) \text{ h}^{-1}, \\ Q &= 131.8 (99.2, 164.3) \text{ ml/min, and} \\ V_{ss} &= 566 (286.0, 846.0) \text{ L.} \end{aligned}$$

VII. CONCLUSION

The pharmacokinetics of the candesartan after oral administration of candesartan cilexetil are reasonably well described by a 2-compartment open model with a lag time and first-order input. The population parameters were well estimated.

Covariate results:

There was a significant difference in CL/F in Study 002 relative to Studies 113 and 119.

- Weight (which is lower in Study 002) and gender (Study 002 consisted of males only) were not significant covariates overall for either CL/F or V_c/F .

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- Age (which is lower in Study 002), when tested for a linear relationship with *CL/F* (and *V_c/F*) overall, and with *CL/F* within Studies 113 and 119, was not shown to be significant.
- race, dose level and duration receiving the candesartan cilexetil had no significant influences on *CL/F* and *V_c/F*.

The population analysis was submitted very recently and thus a through analysis at this time is practically impossible. Although, the effect of all covariates were found to be insignificant, age appear to affect CL. The reviewer will analyze these data in the near future exploring non-linear relationships between CL and Age, WT.

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Table I
Summary of Characteristics of Subjects

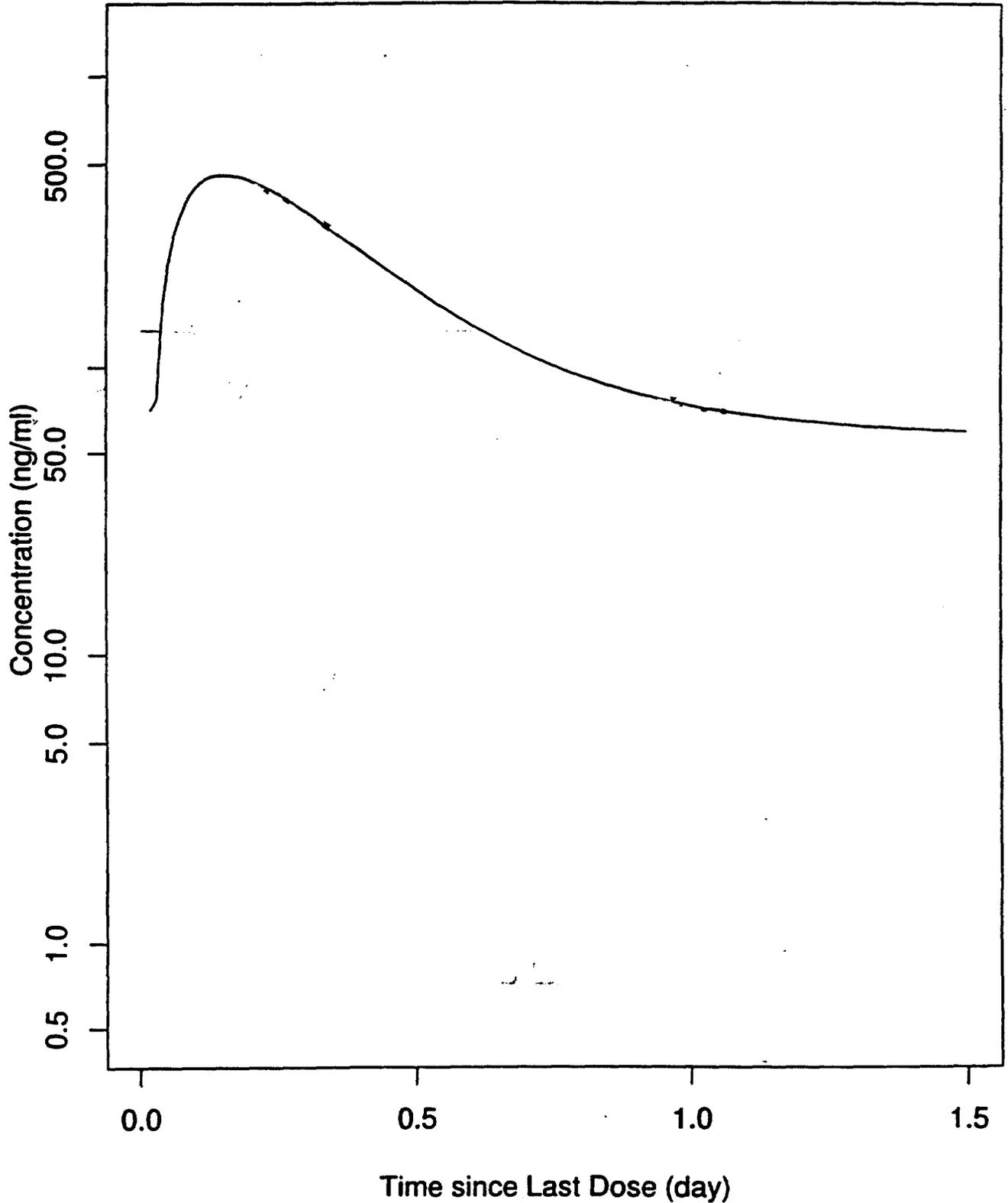
Characteristic	Mean	Median	SD	Minimum Value	Maximum Value
<u>All Studies</u>					
Age (yr)	51.6	52.0	12.8	19.0	87.0
Weight (lb)	197.5	193.0	44.5	105.0	350.0
<u>Study 113 (n=126)</u>					
Age (yr)	54.6	53.0	11.4	31.0	87.0
Weight (lb)	201.5	198.0	42.7	117.0	314.0
<u>Study 119 (n=92)</u>					
Age (yr)	52.7	52.0	10.0	27.0	75.0
Weight (lb)	200.7	196.0	46.1	105.0	314.0
<u>Study 002 (n=19)</u>					
Age (yr)	26.5	26.0	4.6	19.0	37.0
Weight (lb)	155.4	154.0	20.9	128.0	198.0
Characteristic	Number of Subjects				
<u>All Studies</u>					
Gender	male=139		female=98		
Race	nonblack=177		black=60		
<u>Study 113</u>					
Gender	male=75		female=51		
Race	nonblack=92		black=34		
<u>Study 119</u>					
Gender	male=45		female=47		
Race	nonblack=66		black=26		
<u>Study 002</u>					
Gender	male=19		female=0		
Race	nonblack=19		black=0		

Parameter Estimates of Final Model

Parameter	Variability (coefficient of variation)	
	Estimate	95% Confidence interval
Clearance/F (ml/min)		
Studies 113 and 119	313.9	(284.8, 343.0)
Study 002	416.2	(307.9, 524.4)
Central volume of distribution/F (L)	68.1	(52.6, 83.6)
Lag time (h)	0.694	(0.646, 0.742)
First-order input rate constant (h ⁻¹)	0.492	(0.415, 0.569)
Intercompartmental clearance (ml/min)	112.9	(41.2, 184.6)
Volume of distribution at steady-state/F (L)	585.1	(270.6, 763.4)
<i>Interindividual Variability</i>		
Clearance		
Study 113	25.3 %	(-0, 37.3 %)
Study 119	19.9 %	(8.2, 27.0 %)
Study 002	NE*	NE
Central volume of distribution and volume of distribution at steady-state		
Study 113 and 119	19.4 %	(-0, 64.9 %)
Study 002	NE	NE
Lag time	NE	NE
First-order input rate constant	34.1 %	(19.4, 44.1 %)
Bioavailability		
Study 113 and 119	30.3 %	(19.2, 38.4 %)
Study 002	26.5 %	(-0, 41.1 %)
Intercompartmental clearance	48.7 %	(-0 %, 107.7 %)
<i>Residual Variability</i>		
Study 113	72.2 %	(56.2 %, 85.3 %)
Study 119	69.1 %	(50.0 %, 84.0 %)
Study 002	33.2 %	(28.5 %, 37.2 %)
Low Concentrations (All studies)†	72.3 %	(18.7 %, 100.5 %)

*Not reportable. Estimate approaches zero. † Estimate of mean low concentration=0.46 (-0,0.93) ng/ml.

Figure 3e. Predicted Candesartan Plasma Concentration vs. Time
(Study 119, Week 8, 64 mg)



circles: observations
curve: population prediction at Day 56

APPENDIX IV

(DETAILS OF MARKET FORMULATION & DISSOLUTION)

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The conditions employed for the dissolution testing were as follows:

The test was evaluated for its discriminatory ability in regards to particle size, changes in dissolution profiles upon storage, and to manufacturing process. The dissolution conditions was found to be appropriate as a discriminating quality control tool. Please refer to Attachment I for more details.

The following information was communicated in a telecon between Dan Cushings, Maria Suazel, ameeta Parekh on 4/2/98:

- 4, 8mg Tablets manufactured by Takeda were used in pivotal clinical trial #113.
- 8, 16 mg tablets manufactured by Astra jin
pivotal clinical trial #119.
- Two tablets of 8 mg tablets (Takeda formulation used in study #113) was bioequivalent to 1 tablet of 16 mg tablet (Astra formulation used in study #119).

Based on invitro dissolution profiles, 4 mg tablets (Astra) has an apparent faster dissolution than higher strengths, especially at 30 min. Since this formulation was used in pivotal clinical trials, the higher dissolution at 30 minutes appears to have no clinical relevance. Wavier of BE studies for 4, 8 mg tablets is granted.

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APPENDIX V

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