CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-162

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 15 2000

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation I

NDA 21-162

Telmisartan/Hydrochlorothiazide Combination Tablets (40/12.5 mg and 80/12.5 mg)
Boehringer Ingelheim Pharmaceuticals Inc.
Ridgefield, CT

SUBMISSION DATES:

Original Submission: December 29, 1999
Original Amendment BB: May 10, 2000
Original Amendment BB: August 4, 2000

TYPE OF SUBMISSION: Original NDA

REVIEWER: Angelica Dorantes, Ph.D.

I. SUBMISSION:

On December 29, 1999, Boehringer Ingelheim submitted original NDA 21-162 for telmisartan/hydrochlorotiazide (HCTZ) fixed dose combination tablets. The present NDA seeks approval of two strengths of telmisartan/HCTZ combination dosage form containing 40/12.5 mg and 80/12.5 mg. The proposed indication for telmisartan/HCTZ is the treatment of hypertension.

Telmisartan and hydrochlorothiazide (HCTZ) are approved products and their pharmacokinetics are well known. As a result, only a very limited clinical pharmacology and biopharmaceutic information was provided to support the approval of telmisartan/HCTZ combination tablets. The following three studies were submitted in this NDA.

- **Study 502.114**, was an open label, randomized, 3-way crossover trial designed to compare the steady state pharmacokinetics of telmisartan with and without the co-administration of hydrochlorothiazide, and the steady state pharmacokinetics of HCTZ with and without the co-administration of telmisartan. The results of this drug-interaction study showed that concomitant administration of telmisartan and HCTZ do not present a clinically relevant interaction.

  It should be noted that study 502.114 was previously reviewed and deemed acceptable by Dr. Emmanuel Fadiran (OCPB's Bio-review for NDA 20-850/Telmisartan dated August 7, 1998), therefore, further evaluation of this study was not warranted.

- **Study 502.136**, was an open-label, randomized, 4-way crossover replicate design trial conducted to demonstrate the bioequivalence of telmisartan and hydrochlorothiazide administered as fixed dose combination T80/H12.5 mg in comparison to the single unit formulations (T80 mg and H12.5 mg), and to asses the pharmacokinetic profile of hydrochlorothiazide and telmisartan in the fixed dose combination tablet.

- **Study 502.324**, was an open-label, randomized, 4-way crossover replicate design conducted to demonstrate the bioequivalence of telmisartan and hydrochlorothiazide administered as fixed dose combination T40/H12.5 mg in comparison to the single unit formulations (T40 mg and H12.5 mg), and to asses the pharmacokinetic profile of hydrochlorothiazide and telmisartan in the fixed dose combination tablet.

The overall results of bioequivalence studies 502.136 and 502.324 showed that the fixed dose combination and the individual tablet formulations were bioequivalent with respect to telmisartan's AUC, but not with respect to C_{max}. For T40/H12.5 and T80/12.5 mg tablets, the 90% CI for the "test/reference" mean ratio of telmisartan's AUC_{0-inf} were 95.8% to 110.2% and 100.0% to 111.0%, and for telmisartan's C_{max} were 102.5% to 126.0% and 106.8% to 129.0%, respectively.

For HCTZ, the results of bioequivalence studies 502.136 and 502.324 showed that the fixed dose combination and the individual tablet formulations were bioequivalent with respect to all pharmacokinetic variables. All confidence intervals fall in the 80-125% range.

II. RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the information included in original NDA 21-162 dated December 29, 1999 for Telmisartan/Hydrochlorothiazide Combination Tablets and has the following Comments:

Dissolution:

- Based on the review of the submitted dissolution data, OCPB considers that the proposed specifications of Q=( )at( )minutes and Q=( )at( )minutes for telmisartan and HCTZ, respectively, are less than appropriate and are not acceptable. It is recommended that the dissolution specifications be changed to Q=( )at( )minutes for both, telmisartan and HCTZ components.

Bioequivalence:

- Although the results of the bioequivalence studies showed that the fixed dose combination and the individual tablet formulations are not bioequivalent with respect to telmisartan's Cmax, OCPB shares the opinion of DCRP that the failure to pass the upper bounder of the 90% CI for Cmax will not have any clinical consequences because telmisartan has a very wide therapeutic range and the to-be-marketed 80/12.5 telmisartan/HCTZ combination product was used in clinical study No. 502.261. Therefore, bioequivalence studies No. 502.136 and 502.324 submitted to support the approval of NDA 21-162, are acceptable.

Labeling:

- The clinical pharmacology and biopharmaceutic information included in the proposed labeling of the telmisartan/HCTZ combination product is appropriate and acceptable.

Please convey Recommendation and Comments as appropriate to the sponsor.

/S/ 9/15/2000

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick J. Marroum, Ph.D. /S/ 9/15/2000
Briefing held on 9/15/00. Attendees: Sahajwalla, Marroum, Dorantes, and Westelinck

cc: NDA 21-162, HFD-110, HFD-860 (Dorantes, Metha), and CDR (Biopharm).

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III. BACKGROUND

Telmisartan is an angiotensin II antagonist that lowers blood pressure through blockade of the Renin Angiotensin Aldosterone System (RAA). Telmisartan is marketed in the United States as MICARDIS® Tablets 40 mg and 80 mg. It was approved by the Agency under NDA 20-850 on November 10, 1998. Hydrochlorotiazide is an approved diuretic of the benzothiazide class that is thought to lower blood pressure through an alteration in sodium balance. The combination of the two drugs represents a rational therapeutic extension in the treatment of hypertension.

IV. DRUG PRODUCT/FORMULATION

Telmisartan/HCTZ tablets are oblong, two-layer, biconvex, uncoated tablets for oral administration. The HCTZ layer is red and unmarked, and the telmisartan layer is white to off-white marked with the Boehringer Ingelheim (BI) logo. The telmisartan layer is prepared from a common blend that is used for both tablet strengths, the quantity of each ingredient in the blend is doubled in the 80/12.5 mg tablets. The HCTZ layer is identical in composition for both tablet strengths.

TABLE 1

INGREDIENT	MG PER TABLET (40/12.5 MG)	MG PER TABLET (80/12.5 MG)
Telmisartan Layer		
Telmisartan		
Sodium hydroxide		
Meglumine		
Sorbitol		
Magnesium sterate		
Total telmisartan layer		
hydrochlorothiazide Layer		
Hydrochlorothiazide		
Lactose monohydrate		
Microcrystalline cellulose		
Maize starch		
Iron oxide red		
Sodium starch glycolate		
Magnesium sterate		
Total hydrochlorothiazide la		
Total Tablet Weight	440.000	680.000

*Does not appear in the final product

REVIEWER COMMENTS:

1. *None of the Phase II/III studies provided in the original NDA to support the registration of telmisartan/HCTZ combination tablets were conducted with the proposed commercial combination product. Instead, the studies were conducted with the single/individual telmisartan and HCTZ tablets.*
2. *To link the clinical-tablets to the to-be-marketed combination tablet, bioequivalence studies No. 502.136 and No. 502.324 were conducted, comparing to-be-marketed telmisartan/HCTZ 80/12.5 and 40/12.5 combination tablets, to the individual telmisartan and HCTZ tablets used in the clinical studies, respectively.*

3. *It should be noted that on May 12, 2000, the sponsor submitted Amendment No. 6 to NDA 21-162, which provided the final report for clinical study No. 502.261. This clinical trial was conducted using the to-be-marketed 80/12.5 telmisartan/HCTZ combination product. Therefore, this study is providing clinical data to support the approval of the above formulation.*

V. ANALYTICAL METHODOLOGY

3. *It should be noted that on May 12, 2000, the sponsor submitted Amendment No. 6 to NDA 21-162, which provided the final report for clinical study No. 502.261. This clinical trial was conducted using the to-be-marketed 80/12.5 telmisartan/HCTZ combination product. Therefore, this study is providing clinical data to support the approval of the above formulation.*

V. ANALYTICAL METHODOLOGY

Telmisartan: Determination of telmisartan concentrations in plasma samples was accomplished using a)The assay was validated in a range from( )elmisartan. The study validation resulted in an assay precision within( )and an assay accuracy within( )n quality control samples. Assay precision during daily sample assay was within and assay accuracy within( )espectively. The assay precision and accuracy are summarized in Table 2. The( )was( )HCTZ did not interfere with telmisartan analysis.

TABLE 2. Assay Precision and Accuracy During the Analysis of Telmisartan Plasma Samples

TELMISARTAN-QUALITY CONTROL SAMPLES (ng/r	N	MEAN	PRECISION %	ACCURACY %
	37	2.05		
	38	39.85		
	37	154.4		

Hydrochlothiazide:

Plasma HCTZ: Determination of HCTZ concentration in plasma samples was accomplished using a [ ]The assay involved( ) The assay was validated in a range from( )was The ( )n quality control samples. The assay precision and accuracy are summarized in Table 3.

TABLE 3. Assay Precision and Accuracy During the Analysis of HCTZ Plasma & Urine Samples

HCTZ-QUALITY CONTROL SAMPLES (ng/mL)	N	MEAN	PRECISION (CV%)	ACCURACY (BIAS%)
PLASMA				
	22	2.81		
	23	29.7		
	23	119		
URINE				
	12	0.157		
	12	7.33		
	12	14.4		

Urine HCTZ: Determination of HCTZ concentration in urine samples was accomplished using a ( )The assay involved( )

The assay was validated in a range from [redacted] was [redacted] The assay precision and accuracy are summarized in Table 3.

REVIEWER COMMENT:

1. *It should be noted that the complete validation information for the analytical methodologies used to quantify telmisartan and HCTZ was provided in original NDA No. 20-850 for* MICARDIS®. *This submission only includes Quality Control Data for the determination of telmisartan in plasma and HCTZ in plasma and urine. The provided Quality Control data showed that the accuracy and precision for both telmisartan and HCTZ are* [redacted]

VI. DISSOLUTION

- ***Telmisartan:*** For dissolution testing of telmisartan in the telmisartan/HCTZ combination tablets, the same dissolution procedure is used as for testing of telmisartan in MICARDIS® tablets. This procedure uses [redacted] The proposed specification for telmisartan from the bilayer tablets is Q= [redacted] after [redacted] minutes.
- ***Hydrochlorothiazide:*** For the HCTZ component, the dissolution procedure described in the USP was used. The dissolution test is performed in 900 mL of 0.1N HCl acid using Apparatus No. 1 (basket) at 100 rpm. The proposed specification for the dissolution testing of HCTZ in the bilayer tablet is Q=60% after 60 minutes.

Figure 1 illustrates the dissolution profile of telmisartan and HCTZ for the to-be-marketed biobatch of 40/12.5 mg telmisartan/HCTZ tablets, batch No. 902840.

FIGURE 1.

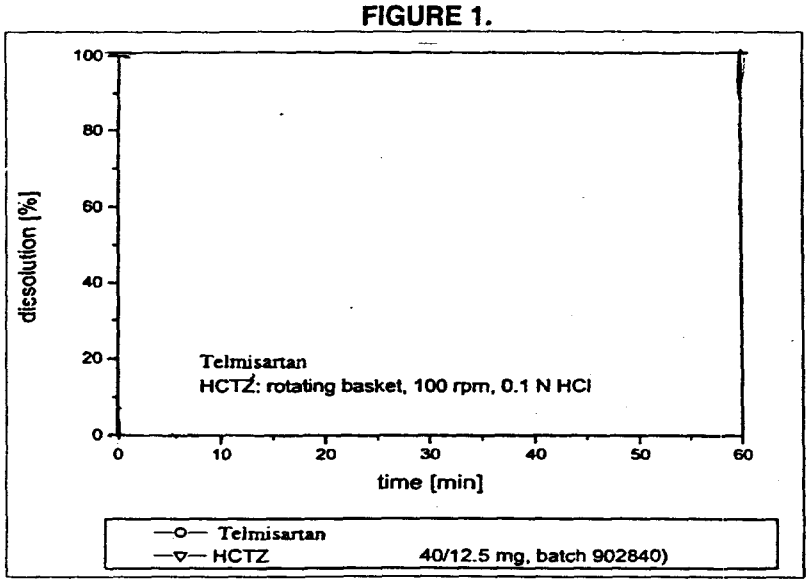


Table 4 presents the dissolution data for telmisartan and HCTZ for different batches of the T80/H12.5 mg and T40/H12.5 mg combination tablets.

TABLE 4. Dissolution Data for Telmisartan/HCTZ Combination Tablets

TABLET STRENGTH	LOT	TELMISARTAN % DISSOLVED				HCTZ % DISSOLVED			
40/12.5 mg		Time	Mean	RSD %	Min/Max	Time	Mean	RSD %	Min/Max
	902840 (n=6)	15	92.7	7.6		15	98.0	2.4	
		30	98.8	4.5		30	99.8	2.1	
		45	98.6	4.3		45	100.5	1.9	
		60	98.5	4.4		60	100.8	2.4	
	902841 (n=6)	15	95.2	4.5		15	97.5	2.5	
		30	97.9	1.5		30	100.6	2.4	
		45	98.0	1.6		45	101.1	2.9	
		60	98.0	1.7		60	101.6	2.8	
	902842 (n=6)	15	96.3	6.6		15	95.0	4.2	
		30	100.9	2.0		30	99.1	2.1	
		45	100.4	2.2		45	99.8	2.1	
		60	100.7	2.0		60	101.2	2.2	
80/12.5 mg		Time	Mean	RSD %		Time	Mean	RSD %	
	802153 (n=6)	15	77.9	7.4		15	87.2	3.1	
		30	100.6	5.0		30	93.1	4.1	
		45	102.0	4.7		45	94.0	3.9	
		60	101.6	4.8		60	94.1	4.1	
	802154 (n=12/6)	15	51.4	4.4		15	90.4	2.7	
		30	82.5	5.0		30	94.8	4.2	
		45	98.4	4.0		45	96.4	2.9	
		60	100.0	4.4		60	96.7	3.3	
	Biobatch 802155 (n=6)	15	70.1	6.9		15	83.7	2.8	
		30	96.3	4.1		30	89.7	2.7	
		45	100.9	4.2		45	91.1	2.9	
		60	100.8	4.2		60	91.1	3.2	

REVIEWER COMMENT:

1. *The proposed dissolution specifications for telmisartan and HCTZ are Q= at minutes and Q=60% at 60 minutes, respectively. Based on the review of the submitted dissolution data, OCPB considers that the proposed specifications for telmisartan and HCTZ are less than appropriate and are not acceptable. It is recommended that the dissolution specifications be changed to Q= % at minutes for both, telmisartan and HCTZ components.*

VII. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The pharmacokinetics and pharmacodynamics of both telmisartan and hydrochlorothiazide (HCTZ) are well known. Therefore, only a very limited clinical pharmacology and biopharmaceutic information was provided in this NDA submission. A listing of the clinical pharmacology and biopharmaceutic studies submitted to support the approval of telmisartan/hydrochlorothiazide combination tablets is presented in Table 5.

TABLE 5

STUDY NO.	PHARMACOKINETIC OBJECTIVES	DESIGN	DOSE FORMS	DOSE (MG)	M/F [a]
502.114	HCTZ-telmisartan interaction	7-day open label, multiple dose, randomized, 3 way crossover study	HCTZ tablet HCTZ + Telm tablets Telm tablet	25 25+(80+80) 80 + 80	7/5
502.136	Bioequivalence	Single dose, randomized, 4-period, 2-sequences, replicate design, B-C-C-B/C-B-B-C	Telm/HCTZ combo tab Telm + HCTZ tablets	801/12.5 80 + 12.5	10/10
502.324	Bioequivalence	Single dose, randomized, 4-period, 2-sequences replicate design, B-C-B-C/C-B-C-B	Telm/HCTZ combo tab Telm + HCTZ tablets	40/12.5 40 + 12.5	16/16

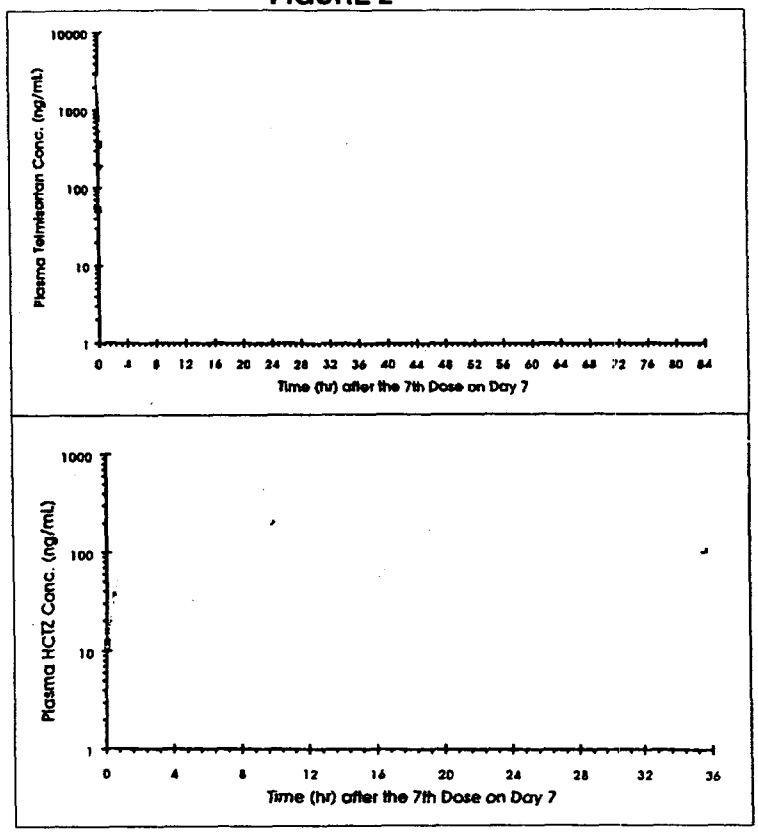
(a) = M/F = number of male subjects/number of female subjects

Due to the fact that the pharmacokinetics of telmisartan and HCTZ have been well documented and study 502.114 was previously reviewed and deemed acceptable by OCPB, this review will include only a brief summary for telmisartan and HCTZ-interaction and detail information for bioequivalence studies No. 502.136 and 502.324 that were conducted to support the approval of the 80/12.5 mg and 40/12.5 mg telmisartan/HCTZ combination tablets.

A. *Drug Interaction Between Telmisartan and Hydrochlorothiazide*

The interaction between telmisartan and HCTZ was evaluated in Study 502.114. The study aim was to assess the steady state pharmacokinetics of telmisartan with and without the co-administration of hydrochlorothiazide, and to compare the steady state pharmacokinetics of hydrochlorothiazide with and without the co-administration of telmisartan. The study was an open label, randomized, 3-way crossover trial in 14 healthy male and female subjects. The treatments were hydrochlorothiazide alone, 25 mg once a day orally for seven days; telmisartan alone, 160 mg administered once a day orally for seven days, and telmisartan 160 mg plus HCTZ 25 mg both administered once a day orally for seven days. Based on the assessment of AUC, Cmax and amount of hydrochlorothiazide excreted renally over 24 hours, it was concluded that the pharmacokinetic profile of telmisartan was not significantly affected when co-administered with hydrochlorothiazide and vice versa (Figure 2).

FIGURE 2



B. ***Bioequivalence Information for the Combination Tablets***

To demonstrate bioequivalence between the single entity tablets used in the pivotal efficacy study 502.204 and the two dosage strengths for the final combination tablets, bioequivalence studies 502.136 and 502.324 were conducted (see Attachment I and II). The telmisartan/hydrochlorothiazide combination tablets used in these studies were the to-be-marketed formulations and were produced at the proposed commercial manufacturing facilities.

- **Bioequivalence Study No. 502.136:** Was an open-label, randomized, 4-way crossover trial in 20 healthy subjects (10 male and 10 female). This replicate design trial had the sequences RTTR and TRRT. The trial objectives were to demonstrate the bioequivalence of 80 mg telmisartan and 12.5 mg hydrochlorothiazide administered as fixed dose combination in comparison to the single 80 mg telmisartan and 12.5 mg HCTZ unit tablets and to assess the pharmacokinetic profiles of hydrochlorothiazide and telmisartan in the fixed dose combination tablet. The pharmacokinetics of telmisartan and HCTZ observed in the present trial were similar to those seen in previous studies. Also, as seen in previous studies, there was a trend towards higher plasma concentrations of telmisartan and HCTZ in female subjects.

Pharmacokinetic parameters Cmax, $AUC_{0\text{-}inf}$ and $Ae_{0\text{-}48h}$ (the latter for HCTZ only) were the primary

pharmacokinetic variables for evaluation of bioequivalence of the T80/H12.5 mg fixed dose combination tablet (test formulation) and the separate T80 and H12.5 mg tablets (reference formulation). Conventional average bioequivalence, average scaled bioequivalence, and individual bioequivalence (as a secondary analysis) using a moment-based scaled approach were evaluated with respect to Telmisartan pharmacokinetic variables. With respect to HCTZ pharmacokinetic variables, conventional average bioequivalence was evaluated. It should be noted that from the regulatory viewpoint only average bioequivalence was consider to be relevant, therefore, the data analysis and results for scaled average bioequivalence and individual bioequivalence included in the study report are not presented in this review.

The results of the assessment of average bioequivalence of telmisartan and HCTZ are summarized in Table 6.

TABLE 6. Telmisartan and HCTZ Average Bioequivalence Statistics

TELMISARTAN (80 mg)					
VARIABLE	**UNIT**	**FIXED DOSE COMBINATION GEO. MEAN** [Test]	**INDIVIDUAL TABLETS GEO. MEAN** [Reference]	**MEAN RATIO (%)**	**90% CONFIDENCE INTERVAL (%)**
Cmax	(ng/ml)	167.3	196.4	117.4	106.8-129.0
AUC0-inf*	(ng.h/ml)	981.9	1034.5	105.4	100.0-111.0
AUC0-48h*	(ng.h/ml)	820.7	875.9	106.7	101.1-112.7
HCTZ (12.5 mg)					
VARIABLE	**UNIT**	**FIXED DOSE COMBINATION GEO. MEAN** [Test]	**INDIVIDUAL TABLETS GEO. MEAN** [Reference]	**MEAN RATIO (%)**	**90% CONFIDENCE INTERVAL (%)**
Cmax	(ng/ml)	74.1	73.1	98.7	90.8- 107.4
AUC0-inf*	(ng.h/ml)	574.0	575.4	100.3	91.8 - 109,5
AUC0-24h*	(ng.h/ml)	467.2	478.1	102.3	97.3- 107.6
Aex0-48h*	(mcg)	9033	8784	97.2	91.0- 103.9

* Geometric Lsmeans, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

The above results indicate that the 90% confidence intervals for the "test/reference" mean ratio for telmisartan $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}48}$ fall in the bioequivalence range of 80% to 125%, while the confidence interval for Cmax does not. With respect to HCTZ, the results indicate that the 90% confidence intervals for the "test/reference" mean ratio for $AUC_{0\text{-}inf}$, Cmax, and $Ae_{0\text{-}48h}$ fall in the bioequivalence range of 80% to 125%.

- **Bioequivalence Study No. 502.324:** Was a single dose, open-label, randomized, four-way crossover replicate design conducted in 32 subjects (16 male and 16 female). This replicate design trial had the sequences TRTR and RTRT. The trial objectives were to demonstrate the bioequivalence of 40 mg telmisartan and 12.5 mg hydrochlorothiazide administered as fixed dose combination in comparison to the single 80 mg telmisartan and 12.5 mg HCTZ unit tablets and to assess the pharmacokinetic profiles of hydrochlorothiazide and telmisartan in the fixed dose combination tablet. The pharmacokinetic parameters for telmisartan and HCTZ observed in the

present trial were similar to those seen in previous studies. This study also showed a trend towards higher plasma concentrations of telmisartan and HCTZ in female subjects.

Bioequivalence with respect to telmisartan and HCTZ pharmacokinetics between 40 mg of Telmisartan/ 12.5 mg of HCTZ fixed dose combination (test formulation) and the individual 12.5 mg of HCTZ mono-component (reference formulation) was assessed. Cmax, AUC_{0-inf} and Ae_{0-48h} (the latter for HCTZ only) were the primary pharmacokinetic variables for evaluation of bioequivalence. Conventional average bioequivalence, average scaled bioequivalence, and individual bioequivalence (as a secondary analysis) using a moment-based scaled approach were evaluated with respect to Telmisartan pharmacokinetic variables. With respect to HCTZ pharmacokinetic variables, conventional average bioequivalence was evaluated. It should be noted that from the regulatory viewpoint only the results from average bioequivalence were considered to be relevant and are the only results that are presented in this review.

Because of the presence of this clear outlier, all analyses of Telmisartan pharmacokinetic variables were performed both including and excluding this outlier (note that not all data of subject 7 were deleted, but only the outlying single data point). The 90% confidence intervals for the "test/reference" mean ratio for pharmacokinetic variables AUC_{0-inf} and AUC_{0-48h} fall in the bioequivalence range of 80% to 125%, while the confidence interval for Cmax extends slightly over the 125% upper bound of bioequivalence criteria. With respect to HCTZ, all confidence intervals fall in the bioequivalence range of 80% to 125%. The results of the assessment of average bioequivalence of telmisartan are summarized in Table 7.

TABLE 7. Telmisartan and HCTZ Average Bioequivalence Statistics

TELMISARTAN (40 mg)						
VARIABLE	**UNIT**		**FIXED DOSE COMBINATION GEO. MEAN** [Test]	**INDIVIDUAL TABLETS GEO. MEAN** [Reference]	**MEAN RATIO (%)**	**90% CONFIDENCE INTERVAL (%)**
Cmax	(ng/ml)	2	30.6	26.9	113.1	102.5-126.6
		3	30.6	27.5	110.2	100.3-123.1
AUC0-inf*	(ng.h/ml)	2	204.9	189.7	107.7	101.2-115.2
		3	204.8	194.0	105.3	99.5-112.0
AUC0-48h*	(ng.h/ml)	2	306.0	297.9	102.6	95.8-110.2
		3	305.9	304.4	100.4	94.3-107.1

HCTZ (12.5 mg)					
VARIABLE	**UNIT**	**FIXED DOSE COMBINATION GEO. MEAN** [Test]	**INDIVIDUAL TABLETS GEO. MEAN** [Reference]	**MEAN RATIO (%)**	**90% CONFIDENCE INTERVAL (%)**
Cmax	(ng/ml)	76.5	71.4	107.1	99.7-115.1
AUC0-inf*	(ng.h/ml)	465.6	453.7	102.6	97.8-107.6
AUC0-24h*	(ng.h/ml)	556.2	552.5	100.7	94.6-107.1
Aex0-48h*	(mcg)	7651.2	7798.7	98.1	93.2-103.2

- *Geometric Lsmeans, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.
- 2: All data
- 3: Excluding data from subject 7, period 4 (replicate observation of reference formulation)

REVIEWER COMMENTS:

1. *In study No. 502.136, average bioequivalence could be shown for the Telmisartan pharmacokinetic variables AUC_{0-inf} and AUC_{0-24}, but bioequivalence could not be demonstrated for Cmax.*
2. *In study No. 502.324, bioequivalence could be shown for the Telmisartan pharmacokinetic variables AUC_{0-inf} and AUC_{0-24}. Average bioequivalence could be shown also for the variable Cmax, on exclusion of one outlier value. With all data included, the upper bound of the 90% confidence interval for Cmax was 126.6% which is only marginally exceeding the upper limit of the bioequivalence acceptance range of 125%.*
3. *With respect to HCTZ, both studies demonstrated that the fixed dose combination formulation and the individual tablet formulations are bioequivalent with respect to all pharmacokinetic variables.*
4. *Although the results of the bioequivalence studies showed that the fixed dose combination and the individual tablet formulations are not bioequivalent with respect to telmisartan's Cmax, it is not expected that the failure to pass the upper bounder of the 90% CI for Cmax will have any clinical consequences, because telmisartan has a very wide therapeutic range and the to-be-marketed 80/12.5 telmisartan/HCTZ combination product was used in clinical study No. 502.261.*
5. *It should be noted that the effect of food on the bioavailability of the T80/H12.5 combination tablets was not studied. Therefore, there is not information available for the combination product regarding this issue.*

XIII. PROPOSED LABELING

A copy of the proposed labeling for telmisartan/HCTZ combination tablets is included in Attachment III.

REVIEWER COMMENTS:

1. *It should be noted that clinical pharmacology and biopharmaceutic information included in the in the different sections of the proposed labeling for the telmisartan/HCTZ combination product, is exactly the same information included in the individual labelings of previously approved telmisartan and HCTZ products.*
2. *The package insert for MICARDIS was used to obtain the information for telmisartan and the package inserts for HydroDIURIL, AVALIDE, HYZAAR, and DIOVAN HCT were used to obtain the information for hydrochlothiazide.*
3. *Due to the fact that the overall format of the proposed labeling is similar to the format of previously approved combination products and to the fact that the proposed labeling does not include any new clinical pharmacology information, this reviewer is of the opinion that the proposed labeling is appropriate and acceptable.*

ATTACHMENT I

Includes

NDA 21-162

Bioequivalence Study 502.136

"Relative Bioavailability of 80 mg Telmisartan / 12.5 mg HCTZ Fixed Dose Combination Compared with its Mono-Components in Healthy Subjects".

STUDY SUMMARY

Protocol Number: 502.136

Title of Study: Relative bioavailability of 80 mg Telmisartan / 12.5 mg HCTZ fixed dose combination compared with its mono-components in healthy subjects.

Investigators: C A P F Su, Biberach/Boehringer Ingelheim Pharma KG, Germany

Study Site: Human Pharmacology Centre, Boehringer Ingelheim Pharma KG,

Objective:

To demonstrate the bioequivalence of 80 mg telmisartan and 12.5 mg hydrochlorothiazide (HCTZ) administered as fixed dose combination in comparison to the individual 80 mg telmisartan and 12.5 mg HCTZ tablet.

Subjects: Twenty male and female subjects meeting the inclusion/exclusion criteria participated in the study. Table 1 describes the mean demographic characteristics of the subjects that participated in the study.

TABLE 1. Demographic Data of Study Subjects

PARAMETER	UNITS	MEAN	SD	CV (%)	MEAN	SD	CV (%)
		FEMALE SUBJECTS (N=10)			MALE SUBJECTS (N=10)		
Age	[years]	32.6	7.1	21.8	30.2	7.0	23.2
Weight	[kg]	67.0	6.6	9.9	78.5	7.7	9.9
Height	[cm]	172.4	7.6	4.4	179.1	4.5	2.5

Formulations: Table 2 describes the specifics of the formulations used in the study.

TABLE 2. Dosage Forms, Unit Strength and Dose of Treatments

TREATMENT	SUBSTANCE	DOSAGE FORM	UNIT STRENGTH	DOSAGE	BATCH No.
A (Test)	Telmisartan HCTZ	Fixed Dose Oblong tablet	80 mg 12.5 mg	1 tablet	802155*
B (reference)	Telmisartan HCTZ	Oblong Tablet tablet	80 mg 12.5 mg	1 tablet 1 tablet	9960325 F4260

*Commercial size batch (340 kg)

Study Design:

This study was designed as a single dose open-label, randomized, four-way crossover replicate design trial. Twenty volunteers (10 male and 10 female subjects) received the individual telmisartan and HCTZ tablets or the fixed dose combination either in the sequence ABBA or BAAB. Treatment B and A denote the reference (individual tablets) and test (fixed dose tablet) formulation, respectively. The treatment

assignments were as follows:

Sequence	Period 1 Treatment	Period 2 Treatment	Period 3 Treatment	Period 4 Treatment
1	A	B	B	A
2	B	A	A	B

A = test treatment (fixed dose combination)
B = reference treatment (separate tablets)

Dietary and Other Instructions:

- Subjects were fasted for at least 10 hours before drug intake.
- Smoking, consumption of alcohol or methylxanthine-containing beverages (coffee, tea, cola, chocolate) were not allowed during the study and one day before drug administration until day 2 of each period.
- Grapefruit or grapefruit juice were not permitted 3 days preceding drug administration. Fruit juices and decaffeinated coffee were not permitted on any day that a study drug was administered.
- The study center supplied standardized meals and drinks.

Sampling Schedule:

Nine mL of blood were drawn at each time point for the determination of telmisartan and HCTZ.

- ***Telmisartan plasma samples:*** Blood samples for plasma telmisartan determination were obtained prior to drug administration and at 0.5, 17 1.5, 2, 4, 6, 8, 12, 24, 48, 72 and 96 hours after administration.
- ***HCTZ plasma samples:*** Blood samples for plasma HCTZ determination were obtained prior to drug administration and 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12, 24, 32 and 48 hours post dose.
- ***HCTZ urine samples:*** Urine specimens for HCTZ determination were collected at 0-6, 6-12, 12-24, 24-32, 32-48 hours following the dose. Total urine volumes were determined for each subject for each time period and a 4 mL volume were stored at -20°C.

The time points of sampling apply to the 4 periods of the trial for telmisartan. HCTZ blood and urine samples were collected in period 1 and 2 only.

Analytical Methodology:

DATA ANALYSIS:

- ***Pharmacokinetics:*** Drug plasma concentrations measured in this trial were used to describe the drug plasma concentration-time course and to calculate pharmacokinetic parameters. Drug plasma concentrations below the limit of quantification were excluded from the pharmacokinetic evaluation. Pharmacokinetic parameters were obtained by noncompartmental methods.
  - The drug peak concentration Cmax and the time to attain the peak concentration
  - Tmax were tabulated as observed from the drug concentration-time profile.

- The apparent terminal elimination half-life T1/2 was calculated from the elimination rate constant λz, which was estimated by log-linear regression of drug plasma concentrations during the terminal phase.
- The area under the drug plasma concentration-time curve (AUC) was calculated by the log-linear trapezoidal rule.
- Total clearance (CLtot/f) was estimated by Dose/AUC.
- The volume of distribution during the terminal phase was calculated by clearance divided by elimination rate constant λ_z.

- ***Assessment of Bioequivalence:*** Cmax, $AUC_{0\text{-}inf}$ and $Ae_{0\text{-}48h}$ (the latter for HCTZ only) were the primary pharmacokinetic variables for evaluation of bioequivalence of the fixed dose combination tablet (test formulation) and the separate tablets (reference formulation). Conventional average bioequivalence, average scaled bioequivalence, and individual bioequivalence (as a secondary analysis) using a moment-based scaled approach were evaluated with respect to Telmisartan pharmacokinetic variables. With respect to HCTZ pharmacokinetic variables, conventional average bioequivalence was evaluated.

  COMMENT: It should be noted that from the regulatory viewpoint only average bioequivalence is relevant, therefore, the data analysis and results for scaled average bioequivalence and individual bioequivalence included in the study report will not be described nor evaluated in this review.

  Average Bioequivalence for Telmisartan: Since there was no missing data in the variables Cmax, $AUC_{0\text{-}48h}$ and $AUC_{0\text{-}inf}$, the 2 replicate observations of each variable for the test and reference formulation, respectively, were averaged, after logarithmic transformation of the data. The averages of the 2 replicate observations of a given formulation are independent across subjects, and, apart from the period effect, identically distributed. Because the 2 design sequences were TRRT and RTTR (T for test and R for reference), the averaged data could be analyzed as a conventional 2 treatment, 2 period cross-over design, the 2 period effects being the average of period 1 and 4, and the average of period 2 and 3, respectively. A multiplicative model was used for the analysis of variance (ANOVA). Therefore, the data were logarithmically transformed prior to ANOVA. The following effects were included in the ANOVA model: treatment, period, sequence, and subject within sequence. From these ANOVA, the shortest two-sided 90% confidence intervals for the ratios of the primary endpoints AUC0-inf (combination)/AUC0-inf (single units) and Cmax (combination)/Cmax (single units) were calculated.

  Concerning the variable Tmax, the 2 replicate observations for the test and reference formulation, respectively, were averaged on the original scale, after which a point estimate and two-sided 90% confidence interval for the difference in medians was calculated using the non-parametric method of Hauschke et al.

- ***Average Bioequivalence HCTZ:*** Pharmacokinetic parameters were derived from plasma/urine concentration data from period 1 and 2 of the study. AUC0-inf, Cmax and Ae(0-48h) were the primary pharmacokinetic variables. A multiplicative model was used for the analysis of variance (ANOVA). Therefore all parameters were logarithmically transformed prior to ANOVA. The following effects were included in the ANOVA model: treatment, period, sequence, and subject within

sequence. From these ANOVA, the shortest two-sided 90% confidence intervals for the ratios of the following primary endpoints were calculated.

- AUC (combination)/AUC (single units)
- Cmax (combination)/Cmax (single units)
- Ae (combination)/Ae (single units)

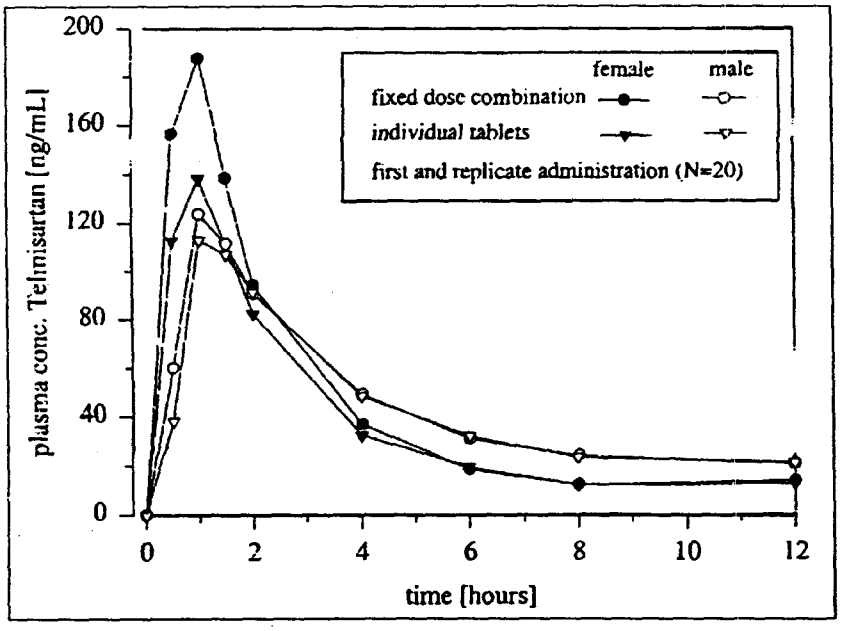
For the variable Tmax a point estimate and two-sided 90% confidence interval for the difference in medians was calculated using the non-parametric method of Hauschke et al.

- ***Confidence Intervals:*** For assessment of average bioequivalence, the shortest two-sided 90% confidence intervals for the test/reference ratios of geometric means of pharmacokinetic variables were calculated, and evaluated in relation to the conventional bioequivalence range of 80% to 125%.

RESULTS:

Plasma Telmisartan Concentrations: Geometric mean plasma telmisartan concentration-time profiles after the first and replicate administration to male and female subjects are illustrated in Figure 1. Data from first and replicate administration were combined.

FIGURE 1. Telmisartan Concentration-Time Profiles



Telmisartan Pharmacokinetic Parameters: Table 4 presents summary statistics of mean pharmacokinetic parameter values of telmisartan observed in male and female subjects after administration of the fixed dose combination and the separate tablets in a replicate design (first and replicate administration are combined).

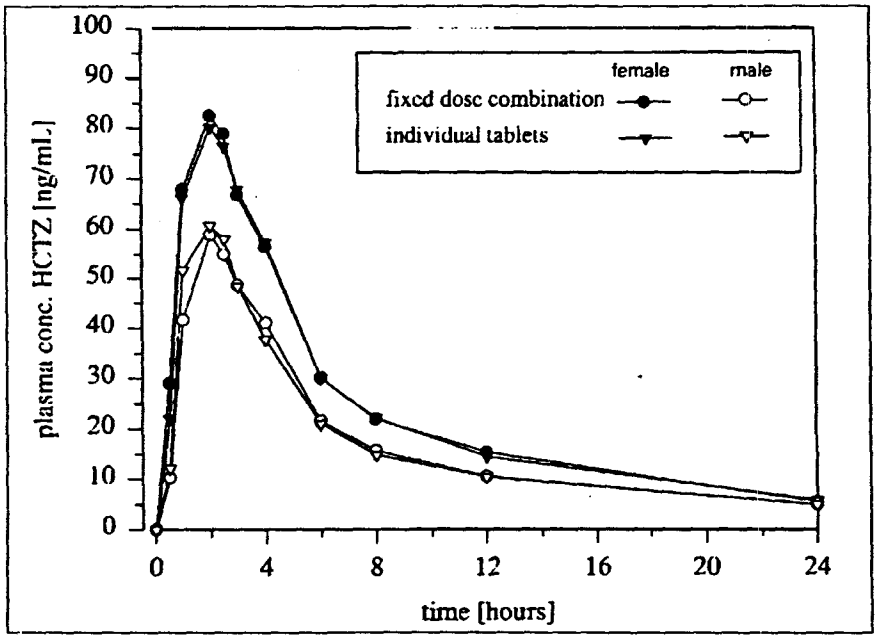
TABLE 4. Telmisartan Pharmacokinetic Parameters

FIXED DOSE COMBINATION TABLET		FEMALE SUBJECTS			MALE SUBJECTS		
PARAMETER	**UNIT**	**N**	**GEOMETRIC MEAN**	**CV (%)**	**N**	**GEOMETRIC MEAN**	**CV (%)**
Cmax	ng/ml	20	248.5	64.09	20	155.2	80.31
Tmax	h	20	0.5	-	20	1.00	-
T1/2	h	20	23.65	34.09	20	22.68	24.19
AUC0-48h	ng.h/mL	20	817.8	52.86	20	938.2	115.3
AUC0-inf	ng.h/ml	20	961.4	56.90	20	1113	122.5
MRTtot	h	20	19.79	42.72	20	22.41	28.25
CLtot/f	ml/min	20	1387	56.90	20	1198	122.5
Vz/f	L	20	2839	51.34	20	2352	117.3
INDIVIDUAL TABLETS		**FEMALE SUBJECTS**			**MALE SUBJECTS**		
PARAMETER	**UNIT**	**N**	**GEOMETRIC MEAN**	**CV (%)**	**N**	**GEOMETRIC MEAN**	**CV (%)**
Cmax	ng/ml	20	195.1	56.98	20	143.5	90.81
Tmax	h	20	0.75	-	20	1.5	-
T1/2	h	20	25.75	35.16	20	21.17	32.57
AUC0-48h	ng.h/mL	20	716.3	53.58	20	940.4	112.5
AUC0-inf	ng.h/ml	19	821.1	54.30	19	1211	117.3
MRTtot	h	19	21.38	28.25	19	22.09	40.02
CLtot/f Vz/f	ml/min	19	1624	54.30	19	1101	117.3
	L	19	3482	58.38	19	1959	92.91

* Median

Plasma HCTZ Concentrations: Geometric mean plasma concentration-time profiles of HCTZ administered as fixed dose combination with telmisartan or as individual tablets are illustrated in Figure 2.

FIGURE 2. HCTZ Concentration-Time Profiles



HCTZ Pharmacokinetic Parameters: Table 5 presents summary statistics of pharmacokinetic parameter of HCTZ in male and female subjects after administration of 80 mg Telmisartan and 12.5 mg HCTZ as fixed dose combination or individual tablets.

TABLE 5. HCTZ Pharmacokinetic Parameters

PARAMETER	UNIT	FIXED DOSE COMBINATION TABLET			INDIVIDUAL TABLETS		
		N	GEOM. MEAN	GCV (%)	N	GEOM. MEAN	GCV (%)
		MALE SUBJECTS					
Cmax	ng/ml	10	62.69	15.56	10	64.65	16.38
Tmax	h	10	2.00*	-	10	2.00*	-
T1/2	h	10	11.49	48.53	10	10.98	30.64
AUC0-inf	ng.h/mL	10	495.8	16.73	10	486.7	14.85
MRTtot	h	10	13.30	38.97	10	12.21	24.98
CLtot/f	ml/min	10	420.2	16.73	10	428.1	14.85
Vz/f	L	10	418.0	34.74	10	406.9	31.88
Ae(0-48h)	mcg	10	8327	18.23	10	8806	19.88
CLr(0-24h)	mL/min	9	299.1	23.89	10	329.3	20.01
		FEMALE SUBJECTS					
Cmax	ng/ml	10	85.40	21.93	10	84.93	16.69
Tmax	h	10	2.00*	-	10	-	-
T1/2	h	10	9.470	38.98	10	10.71	42.92
AUC0-inf	ng.h/mL	7	675.6	23.48	8	650.1	12.39
MRTtot	h	7	10.46	22.86	8	11.77	28.02
CLtot/f	ml/min	7	308.3	23.49	8	320.4	12.39
Vz/f	L	7	247.4	24.76	8	307.2	30.98
Ae(0-48h)	mcg	10	9267	6.663	10	9266	8.062
CLr(0-24h)	mL/min	7	230.9	15.62	8	252.9	7.942

*Median

Urinary Excretion of HCTZ: Figure 3 presents the geometric mean plot (N = 10) of cumulated urinary excretion [mcg] of HCTZ after administration of 80 mg telmisartan and 12.5 mg HCTZ as fixed dose combination or individual tablets.

FIGURE 3. HCTZ Cumulative Urinary Excretion-Time Profiles

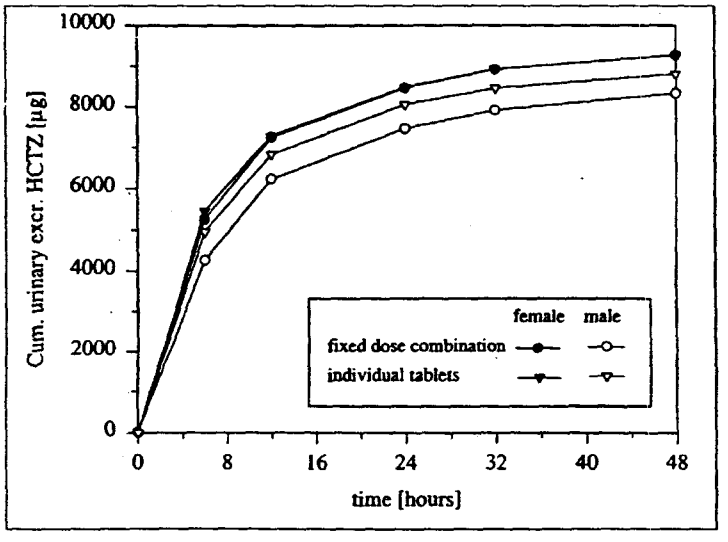


Table 6 presents the summary statistics of cumulated amount [mcg] excreted in urine of HCTZ after administration of 80 mg telmisartan and 12.5 mg HCTZ as fixed dose combination or individual tablets in male and female subjects combined.

TABLE 6. HCTZ Urinary Data

TIME (h)	MALE AND FEMALE SUBJECTS COMBINED					
	FIXED DOSE COMBINATION TABLET			INDIVIDUAL TABLETS		
	N	GEOM. MEAN (mcg)	GCV (%)	N	GEOM. MEAN (mcg)	GCV (%)
0-6	20	4738	29.85	20	5202	19.80
0-12	20	6713	19.88	20	7058	18.07
0-24	20	7956	17.02	20	8272	15.20
0-32	20	8405	15.90	20	8694	15.15
0-48	20	8784	14.42	20	9033	14.96

About 70% of the 12.5 mg HCTZ dose was excreted in the urine over the 48 hours sampling period. The geom. mean amount of HCTZ excreted was 8.8 mg (ranging from 6.3 to 10 mg) for the fixed dose combination, and 9 mg (ranging from 6.1 to 11 mg) when administered as separate tablet.

BIOEQUIVALENCE

Average Bioequivalence for Telmisartan: The results of the assessment of average bioequivalence of telmisartan are summarized in Table 7. The 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0\text{-}inf}$ and Cmax are 100.0% to 111.0% and 106.8% to 129.0%, respectively. The confidence interval for $AUC_{0\text{-}inf}$ falls within the bioequivalence range of 80% to 125%, while the confidence interval for Cmax does not. The confidence interval for the "test/reference" mean ratio of the secondary variable $AUC_{0\text{-}48h}$ falls in the bioequivalence range.

TABLE 7. Statistics for Telmisartan Average Bioequivalence

VARIABLE	UNIT	FIXED DOSE COMBINATION GEO. MEAN [Test]	INDIVIDUAL TABLETS GEO. MEAN [Reference]	MEAN RATIO (%)	90% CONFIDENCE INTERVAL (%)
Cmax	(ng/ml)	167.3	196.4	117.4	106.8-129.0
AUC0-inf*	(ng.h/ml)	981.9	1034.5	105.4	100.0-111.0
IAe0-48h*	(ng.h/ml)	820.7	875.9	106.7	101.1-112.7

* Geometric Lsmeans, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

Average Bioequivalence for HCTZ: The results of the assessment of average bioequivalence of HCTZ are summarized in Table 8. The 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0\text{-}inf}$ and Cmax are 91.8% to 109.5% and 90.8% to 107.4%, respectively. The confidence intervals for the "test/reference" mean ratio of the pharmacokinetic variable $Ae_{0\text{-}48h}$ is 91.0% to 103.9%. All confidence intervals fall in the bioequivalence range of 80% to 125%.

TABLE 8. Statistics for HCTZ Average Bioequivalence

VARIABLE	UNIT	FIXED DOSE COMBINATION GEO. MEAN [Test]	INDIVIDUAL TABLETS GEO. MEAN [Reference]	MEAN RATIO (%)	90% CONFIDENCE INTERVAL (%)
Cmax	(ng/ml)	74.1	73.1	98.7	90.8- 107.4
AUC0-inf*	(ng.h/ml)	574.0	575.4	100.3	91.8 - 109,5
AUC0-24h*	(ng.h/ml)	467.2	478.1	102.3	97.3- 107.6
IAe0-48h*	(mcg)	9033	8784	97.2	91.0- 103.9

*Geometric Lsmeans, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

REVIEWER COMMENTS:

1. *Telmisartan was rapidly absorbed from the fixed dose combination tablet and the separate tablets. In female subjects, mean Telmisartan plasma concentrations were higher than in male volunteers for both formulations. These higher levels in female subjects were also reported in telmisartan's original NDA.*

2. *For HCTZ, there was a trend towards higher AUC and Cmax in female subjects. This was observed for HCTZ administered either in fixed dose combination with telmisartan and as individual tablet, suggesting that this finding is not related to the formulation.*

3. *Bioequivalence could be shown for the telmisartan pharmacokinetic variables $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}48h}$. Average bioequivalence could not be demonstrated for the variable Cmax. With respect to HCTZ, The fixed dose combination and the individual tablet formulations were bioequivalent with respect to all pharmacokinetic variables.*

ATTACHMENT II

Includes

NDA 21-162

Bioequivalence Study 502.324

"Relative Bioavailability of 40 mg Telmisartan / 12.5 mg HCTZ Fixed Dose Combination Compared with its Mono-Components in Healthy Subjects".

STUDY SUMMARY

Protocol Number: 502.324

Title of Study: Relative oral bioavailability of 40 mg Telmisartan/12.5 mg HCTZ fixed dose combination compared with its mono-components in healthy subjects.

Investigators: Dr. M. Haaksma-Herczegh/Boehringer Ingelheim Pharma KG, Germany

Study Site: Human Pharmacology Centre, Boehringer Ingelheim Pharma KG,

Objective:

To demonstrate the bioequivalence of 40 mg telmisartan and 12.5 mg hydrochlorothiazide (HCTZ) administered as fixed dose combination in comparison to the individual 40 mg telmisartan and 12.5 mg HCTZ tablet.

Subjects: Thirty two male and female subjects meeting the inclusion/exclusion criteria participated in the study. Table 1 describes the mean demographic characteristics of the enrolled subjects.

TABLE 1. Demographic Data of Study Subjects

PARAMETER	UNITS	MEAN	SD	CV (%)	MEAN	SD	CV (%)
		FEMALE SUBJECTS (N=16)			MALE SUBJECTS (N=16)		
Age	[years]	35.3	6.36	18.0	36.3	7.61	21.0
Weight	[kg]	66.7	8.22	12.3	80.1	8.14	10.2
Height	[cm]	171	5.34	3.13	181	5.19	2.87

Formulations: Table 2 describes the specifics of the formulations used in the study.

TABLE 2. Dosage Forms, Unit Strength and Dose of Treatments

TREATMENT	SUBSTANCE	DOSAGE FORM	UNIT STRENGTH	DOSAGE	BATCH No.
A (Test)	Telmisartan HCTZ	Fixed Dose Oblong tablet	40 mg 12.5 mg	1 tablet	902840*
B (reference)	Telmisartan HCTZ	Oblong Tablet Tablet	40 mg 12.5 mg	1 tablet 1 tablet	901840 F4836

*Commercial size batch (340 kg)

Study Design:

This trial was a single dose, open-label, randomized, four way cross-over replicate design with 2 sequences: ABAB and BABA. Treatment B and A denote the reference (individual tablets) and test (fixed dose tablet) formulation, respectively.

The treatment assignments were as follows:

SEQUENCE	PERIOD 1 TREATMENT	PERIOD 2 TREATMENT	PERIOD 3 TREATMENT	PERIOD 4 TREATMENT
1	A	B	A	B
2	B	A	B	A

A = test treatment (fixed dose combination)
B = reference treatment (separate tablets)

Dietary and Other Instructions:

- Subjects were fasted for at least 10 hours before drug intake.
- Smoking, consumption of alcohol or methylxanthine-containing beverages (coffee, tea, cola, chocolate) were not allowed during the study and one day before drug administration until day 2 of each period.
- Grapefruit or grapefruit juice were not permitted 3 days preceding drug administration. Fruit juices and decaffeinated coffee were not permitted on any day that a study drug was administered.
- The study center supplied standardized meals and drinks.

Sampling Schedule:

Nine mL of blood were drawn at each time point for determination of telmisartan and HCTZ. The time points of sampling apply to the 4 periods of the trial for telmisartan. HCTZ blood and urine samples were collected in period 1 and 2 only.

- ***Telmisartan plasma samples:*** Blood samples for plasma telmisartan determination were obtained prior to drug administration and at 0.5, 1.0, 1.5, 2, 4, 6, 8, 12, 24, 48, and 72 hours after administration.
- ***HCTZ plasma samples:*** Blood samples for plasma HCTZ determination were obtained prior to drug administration and 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12, 24, 32 and 48 hours post dose.
- ***HCTZ urine samples:*** Urine specimens for HCTZ determination were collected at 0-6, 6-12, 12-24, 24-32, 32-48 hours following the dose. Total urine volumes were determined for each subject for each time period and a 4 mL volume was stored at -20°C.

Analytical Methodology:

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DATA ANALYSIS:

- ***Pharmacokinetics:*** Drug plasma concentrations measured in this trial were used to describe the drug plasma concentration-time course and to calculate pharmacokinetic parameters. Drug plasma concentrations below the limit of quantification were excluded from the pharmacokinetic evaluation.

  Pharmacokinetic parameters were obtained by noncompartmental methods. The primary variables of this study are AUC0-inf and Cmax, (Telmisartan and HCTZ) and the amount of HCTZ excreted in urine over 48 h (Ae_{0-48}). The secondary variables of this study are Tmax, Tl/2, CLtot/f, MRTtot, Vz/f (Telmisartan and HCTZ).

- ***Bioequivalence:*** This was a 2-treatment, 2-sequence, 4-period replicate design crossover study. Bioequivalence with respect to telmisartan and HCTZ pharmacokinetics between the 40 mg of Telmisartan / 12.5 mg of HCTZ fixed dose combination (test formulation) and the individual 12.5 mg of HCTZ mono-component (reference formulation) was assessed. Cmax, AUC_{0-inf} and Ae_{0-48h} (the latter for HCTZ only) were the primary pharmacokinetic variables for evaluation of bioequivalence of the fixed dose combination tablet (test formulation) and the separate tablets (reference formulation). Conventional average bioequivalence, average scaled bioequivalence, and individual bioequivalence (as a secondary analysis) using a moment-based scaled approach were evaluated with respect to Telmisartan pharmacokinetic variables. With respect to HCTZ pharmacokinetic variables, conventional average bioequivalence was evaluated.

  COMMENT: It should be noted that from the regulatory viewpoint only average bioequivalence is relevant, therefore, the data analysis and results for scaled average bioequivalence and individual bioequivalence included in the study report will not be described nor evaluated in this review.

- ***Standard Average Bioequivalence for Telmisartan:*** According to the draft FDA guidance "Average, population, and individual approaches to establishing bioequivalence" (August 1999) (http://www. fda.gov/cder/guidance/1716dft.doc) the following mixed model analysis (SAS Proc Mixed) was used for assessment of standard average bioequivalence using data from a 2-treatment, 2-sequence, 4-period cross-over study:

```
PROC MIXED;
CLASS SEQ SUBJ PER TRT;
MODEL Y = SEQ PER TRT / DDFM=SATTERTH;
RANDOM TRT / TYPE=FA0(2) SUB-SUBJ G;
REPEATED / GRP=TRT SUB=SUB J;
ESTIMATE 'T vs. R' TRT 1 -1 / CL ALPHA=0.1;
```

  Here Y is the response log (AUC_{0-24h}), log(AUC_{0-inf} and log(Cmax) being analyzed. AUC_{0-inf} and Cmax were the primary variables. Point estimates and the shortest 90% confidence intervals for the "test/reference" ratios of the above pharmacokinetic variables were calculated.

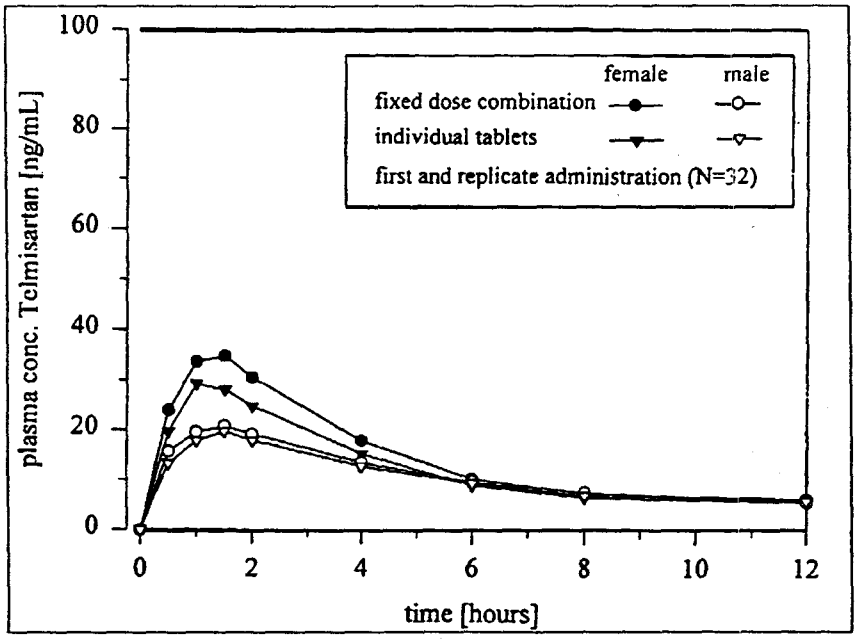
- ***Standard Average Bioequivalence for HCTZ:*** The pharmacokinetic variables $AUC_{0\text{-inf}}$, $AUC_{0.24h}$ Cmax and $Ae_{0\text{-48h}}$ of HCTZ were obtained from data from the first 2 periods of this study. The ANOVA model for the assessment of standard average bioequivalence using data from a 2-period, 2-treatment cross-over study included the factors sequence, subject (sequence), treatment and period. $AUC_{0\text{-inf}}$, Cmax and $Ae_{0\text{-48h}}$ were the primary variables. Point estimates and the shortest 90% confidence intervals for the "test/reference" ratios of the above pharmacokinetic variables were calculated.

- ***Confidence Intervals:*** For assessment of conventional average bioequivalence, shortest two-sided 90% confidence intervals for the test/reference ratios of the geometric means of pharmacokinetic variables were calculated, and evaluated in relation to the conventional bioequivalence range of 80% and 125%.

RESULTS:

Plasma Telmisartan Concentrations: Geometric mean plasma telmisartan concentration-time profiles either as separate individual tablets or as fixed dose combination tablet are illustrated in Figure 1. Data from first and replicate administration were combined.

FIGURE 1. Telmisartan Concentration-Time Profiles



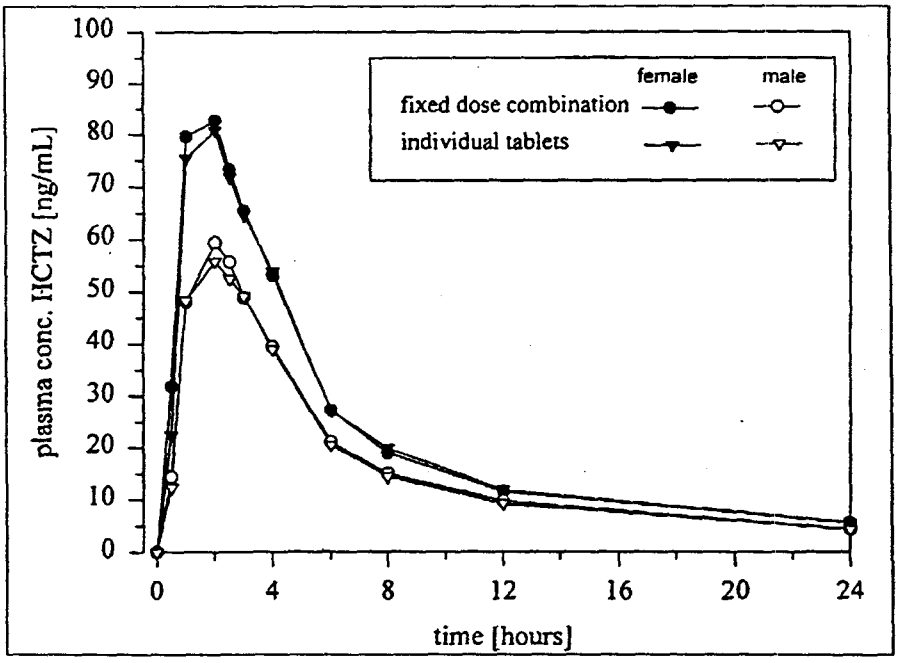
Telmisartan Pharmacokinetic Parameters: Table 4 present summary statistics of mean pharmacokinetic parameter values of telmisartan observed in male and female subjects after administration of the fixed dose combination and the separate tablets in a replicate design (first and replicate administration are combined).

TABLE 4. Telmisartan Pharmacokinetic Parameters

PARAMETER	UNIT	FIXED DOSE COMBINATION TABLET					
		FEMALE SUBJECTS			MALE SUBJECTS		
		N	GEOM. MEAN	CV (%)	N	GEOM. MEAN	CV (%)
Cmax	ng/ml	32	39.4	45.6	31	24.4	73.8
Tmax	h	32	1.09	58.4	31	1.18	73.5
T1/2	h	31	20.1	24.6	28	20.2	26.2
AUC0-24h	ng.h/mL	32	233	50.4	31	192	74.7
AUC0-inf	ng.h/ml	32	338	52.6	28	301	81.6
AUCtf-inf	%	32	7.34	55.6	28	9.65	61.6
MRTtot	h	32	20.8	34.7	28	23.0	35.1
CLtot/f	ml/min	32	1970	52.5	28	2210	79.8
Vz/f	L	32	3280	57.4	28	3630	71.6
		INDIVIDUAL TABLETS					
Cmax	ng/ml	32	33.2	55.8	31	22.2	72.0
Tmax	h	32	1.15	60.1	31	1.11	75.9
T1/2	h	31	21.2	34.9	31	21.1	25.0
AUC0-24h	ng.h/mL	32	203	53.6	31	184	78.6
AUC0-inf	ng.h/ml	29	313	54.7	26	341	72.0
AUCtf-inf	%	29	7.52	64.5	26	9.06	40.6
MRTtot	h	29	21.7	39.3	26	25.1	22.8
CLtot/f	ml/min	29	2130	54.7	26	1950	72.0
Vz/f	L	29	3610	56.3	26	3460	73.2

Plasma HCTZ Concentrations: Geometric mean plasma concentration-time profiles of HCTZ administered as fixed dose combination with telmisartan or as individual tablets are illustrated in Figure 2.

FIGURE 2. HCTZ Concentration-Time Profiles



HCTZ Pharmacokinetic Parameters: Table 5 presents summary statistics of pharmacokinetic parameter of HCTZ in male and female subjects after administration of 40 mg Telmisartan and 12.5 mg HCTZ as fixed dose combination or individual tablets.

TABLE 5. HCTZ Pharmacokinetic Parameters

PARAMETER	UNIT	FIXED DOSE COMBINATION TABLET					
		FEMALE SUBJECTS			MALE SUBJECTS		
		N	GEOM. MEAN	CV (%)	N	GEOM. MEAN	CV (%)
Cmax	ng/ml	16	91.1	15.5	16	64.3	20.0
Tmax	h	16	1.48	36.7	16	1.61	40.4
T1/2	h	16	13.8	34.2	16	10.1	24.2
AUC0-24h	ng.h/mL	16	537	12.5	16	403	14.7
AUC0-inf	ng.h/mL	15	649	17.1	16	469	15.3
AUCtf-inf	ng.h/mL	15	6.17	59.8	16	5.96	35.9
MRTtot	h	15	12.6	29.5	16	11.1	22.7
CLtot/f	ml/min	15	321	17.1	16	445	15.3
Vz/f	L	15	366	23.8	16	388	28.3
Ae(0-48h)	mcg	16	7540	18.3	16	7770	17.0
CLr(0-24h)	mL/min	16	12.7	24.9	16	17.4	24.1
		INDIVIDUAL TABLETS					
Cmax	ng/ml	16	86.3	25.8	16	59.1	21.1
Tmax	h	16	1.60	40.9	16	2.09	34.5
T1/2	h	16	13.6	42.8	16	11.6	32.0
AUC0-24h	ng.h/mL	16	535	22.3	16	385	21.3
AUC0-inf	ng.h/mL	15	625	21.8	16	461	24.7
AUCtf-inf	ng.h/mL	15	6.49	62.3	16	6.47	46.1
MRTtot	h	15	12.4	34.5	16	12.2	28.0
CLtot/f	ml/min	15	333	21.8	16	452	24.8
Vz/f	L	15	366	31.9	16	455	29.6
Ae(0-48h)	mcg	16	7620	21.1	16	7980	11.3
CLr(0-24h)	mL/min	16	13.1	28.1	16	18.9	20.9

Urinary Excretion of HCTZ: Figure 3 presents the geometric mean plot (N = 10) of cumulated urinary excretion [mcg] of HCTZ after administration of 80 mg telmisartan and 12.5 mg HCTZ as fixed close combination or individual tablets.

FIGURE 3. HCTZ Cumulative Urinary Excretion-Time Profiles

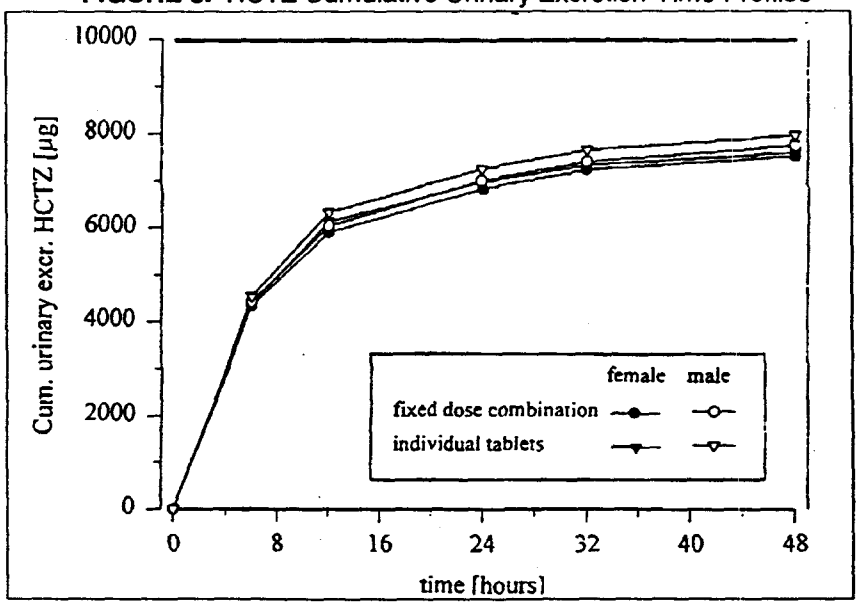


Table 6 presents the summary statistics of cumulated amount [mcg] excreted in urine of HCTZ after administration of 40 mg telmisartan and 12.5 mg HCTZ as fixed dose combination or individual tablets in male and female subjects combined.

TABLE 6. HCTZ Urinary Data

TIME (h)	MALE AND FEMALE SUBJECTS COMBINED					
	FIXED DOSE COMBINATION TABLET			INDIVIDUAL TABLETS		
	N	GEOM. MEAN	GCV (%)	N	GEOM. MEAN	GCV (%)
0-6	32	4390	31.4	32	4550	30.9
0-12	32	5980	22.1	32	6230	17.9
0-24	32	6930	19.3	32	7120	17.0
0-32	32	7340	18.5	32	7520	17.0
0-48	32	7650	17.4	32	7800	16.8

It should be noted that about 60% of the HCTZ dose is recovered in urine within 48 hours after drug administration. There was no relevant difference in urinary HCTZ excretion between the two formulations.

ASSESSMENT OF BIOEQUIVALENCE

Average Bioequivalence for HCTZ: The results of the assessment of average bioequivalence of HCTZ are summarized in Table 7. The 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0\text{-}inf}$ and Cmax are 94.6% to 107.1% and 99.7% to 115.1%, respectively. The confidence intervals for the "test/reference" mean ratio of the pharmacokinetic variable $Ae_{0\text{-}48h}$ is 93.2% to 103.2%. All confidence intervals fall in the bioequivalence range of 80% to 125%.

TABLE 7. Statistics of HCTZ Average Bioequivalence

VARIABLE	UNIT	FIXED DOSE COMBINATION GEO. MEAN [Test]	INDIVIDUAL TABLETS GEO. MEAN [Reference]	MEAN RATIO (%)	90% CONFIDENCE INTERVAL (%)
Cmax	(ng/ml)	76.5	71.4	107.1	99.7-115.1
AUC0-inf*	(ng.h/ml)	465.6	453.7	102.6	97.8-107.6
AUC0-24h*	(ng.h/ml)	556.2	552.5	100.7	94.6-107.1
Ae0-48h*	(mcg)	7651.2	7798.7	98.1	93.2-103.2

*Geometric Lsmeans, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.

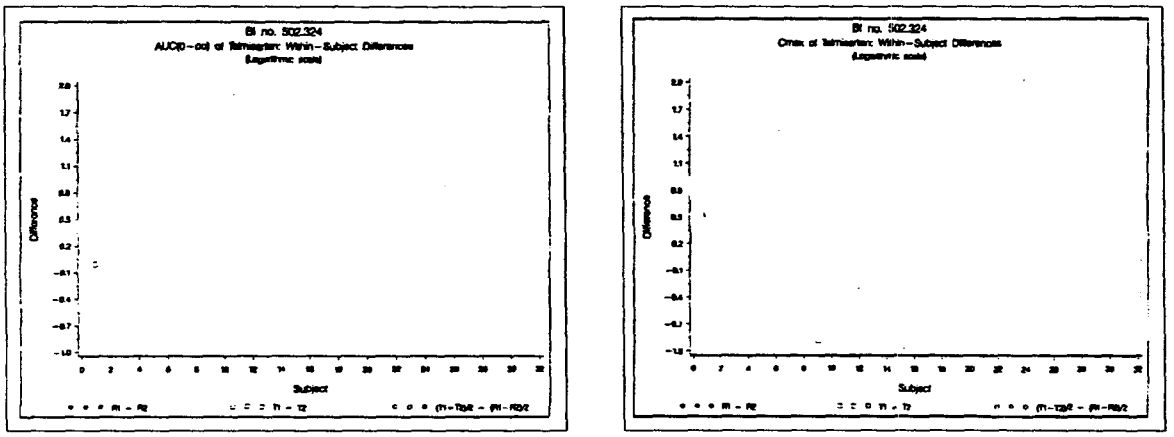
Outlier in Telmisartan data

Figure 4 presents two scatterplots of the within-subject differences of Telmisartan pharmacokinetic variables versus subject number (difference of first and second replicate of the test formulation, difference of first and second replicate of the reference formulation, and the difference of the average test and reference values). These plots indicate a gross outlier in subject 7, namely in the difference of first and second replicate of the reference formulation, which is considerably larger than all other differences. This is the result of the second replicate of the reference formulation, in period 4, having an

extraordinarily low value. For AUC(0-inf) the 4 readings for subject 7 are as follows: test 495 ng.h/mL; test 488 ng.h/mL; reference 581 ng.h/mL and reference 121 ng.h/mL. The corresponding values for AUC(0-24h) are: 359 ng.h/mL, 398 ng-h/mL, 437 ng.h/mL and 83 ng-h/mL, and for Cmax 58.8 ng/mL, 69.8 ng/mL, 67.2 ng/mL and 9.3 ng/mL.

Because of the presence of this clear outlier, all analyses of Telmisartan pharmacokinetic variables were performed both including and excluding this data point (note that not all data of subject 7 were deleted, but only the outlying single data point).

FIGURE 4



Average Bioequivalence for Telmisartan: The results of the assessment of average bioequivalence of telmisartan are summarized in Table 8. The 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0\text{-}inf}$ and Cmax are 95.8% to 110.2% and 102.5% to 126.0%, respectively. The confidence interval for $AUC_{0\text{-}inf}$ falls in the bioequivalence range of 80% to 125%, while the confidence interval for Cmax extends slightly over the 125% upper bound of bioequivalence criteria. The confidence interval for the "test/reference" mean ratio of the secondary variable $AUC_{0\text{-}48h}$ falls in the bioequivalence range.

TABLE 8. Statistics of Telmisartan Average Bioequivalence

VARIABLE	UNIT		FIXED DOSE COMBINATION GEO. MEAN [Test]	INDIVIDUAL TABLETS GEO. MEAN [Reference]	MEAN RATIO (%)	90%CONFIDENCE INTERVAL (%)
Cmax	(ng/ml)	2	30.6	26.9	113.1	102.5-126.6
		3	30.6	27.5	110.2	100.3-123.1
AUC0-inf*	(ng.h/ml)	2	204.9	189.7	107.7	101.2-115.2
		3	204.8	194.0	105.3	99.5-112.0
IAe0-48h*	(ng.h/ml)	2	306.0	297.9	102.6	95.8-110.2
		3	305.9	304.4	100.4	94.3-107.1

- Geometric Lsmeans, estimate and 90% conventional confidence interval for the "test/reference" mean ratio from analysis of variance of log-transformed data.
- 2: All data
- 3: Excluding data from subject 7, period 4 (replicate observation of reference formulation)

Safety Results:

Fourteen of the 32 subjects (8 male and 6 female) reported a total of 23 adverse events. These events

included 8 episodes of headache, 3 episodes of upper respiratory tract infection, one episode of thrombophlebitis, vomiting, neurosis, tooth disorder, rash erythematous, haematoma, accident vehicular, dizziness, dermatitis fungal, pharyngitis, arrhythmia atrial and epistaxis. All of the episodes were mild to moderate in intensity. There was no serious adverse event. One subject discontinued prematurely because of the adverse event accident vehicular. There was no reasonable causal relationship between the above listed adverse events and the test drug.

Overall, telmisartan at a dose of 40 mg and HCTZ 12.5 mg administered concomitantly to healthy subjects were well tolerated. There were no adverse reactions that could be attributed to the use of the test drug (fixed dose combination of Telmisartan and HCTZ) or to the reference therapy (single components of Telmisartan and HCTZ). There were no significant changes in laboratory parameters, vital signs, ECG and physical findings after treatment at the post-examination compared to baseline at screening.

COMMENTS:

1. *It should be noted that complete analytical validation information was submitted under the original NDA. This study report only included Quality Control data for the determination of telmisartan in plasma and HCTZ in plasma and urine. The provided Quality Control data showed adequate assay accuracy and precision for both drugs.*

2. *The within-subject variability of telmisartan pharmacokinetic variables is documented to be high, in particular with regard to Cmax. In two previous studies with Telmisartan (studies 502.128 and 502.114), the within-subject coefficient of variation of Cmax was 50 % and 57 %, respectively, with corresponding values for AUC of 25 % and 24 %.*

3. *The pharmacokinetics of telmisartan and HCTZ observed in the present trial were similar to those seen in previous studies. There was a trend towards higher plasma concentrations of telmisartan and HCTZ in female subjects.*

4. *Bioequivalence could be shown for the Telmisartan pharmacokinetic variables AUC_{0-inf} and AUC_{0-24}. Average bioequivalence could be shown also for the variable Cmax, on exclusion of one outliner value. With all data included, the upper bound of the 90 % confidence interval for Cmax was 126.6% which is only marginally exceeding the bioequivalence acceptance range of 125%. With respect to HCTZ, the fixed dose combination and individual tablet formulations were bioequivalent with respect to all pharmacokinetic variables.*

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