Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan/amlodipine/hydrochlorothiazide (BIBR277 TCT)		**Page:** 1 of 6	
Report Date: 12 March 2015	**Trial No. / Doc. No.:** 1348.5 / c02749535-01	**Dates of Trial:** 19 Jul 2014 - 23 Oct 2014	**Date of Revision:** Not applicable

Title of Trial:	Pharmacokinetics of multiple oral doses of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed-dose combination tablet, telmisartan 80 mg/hydrochlorothiazide 12.5 mg fixed-dose combination tablet and telmisartan 80 mg/amlodipine 5 mg fixed-dose combination tablet at steady state in healthy male subjects: an open-label, randomised, multiple-dose, three-treatment, three-period, six-sequence crossover study
Principal Investigator:	[redacted]
Trial Site:	[redacted] Japan Phone: [redacted] Fax: [redacted]
Publications:	Data from this trial have not been published.
Clinical Phase:	I
Objectives:	To investigate the steady state pharmacokinetics (PK) of telmisartan, amlodipine, and hydrochlorothiazide (HCTZ) in three different ways: telmisartan 80 mg/amlodipine 5 mg/HCTZ 12.5 mg (T80/A5/H12.5 mg) fixed-dose combination (FDC) tablet, telmisartan 80 mg/HCTZ 12.5 mg (T80/H12.5 mg) FDC tablet and telmisartan 80 mg/amlodipine 5 mg (T80/A5 mg) FDC tablet in healthy Japanese male subjects
Methodology:	Open-label, randomised, multiple-dose, three-treatment, three-period, six-sequence crossover design
No. of Subjects:	
Planned:	Entered: 36 (6 per sequence)
Actual:	Entered: 36 Treatment sequence 1 (A-B-C): Entered: 6, Treated: 6, Analysed (for primary endpoints): 6 Treatment sequence 2 (B-C-A): Entered: 6, Treated: 6, Analysed (for primary endpoints): 6 Treatment sequence 3 (C-A-B): Entered: 6, Treated: 6, Analysed (for primary endpoints): 6

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	Treatment sequence 4 (C-B-A): Entered: 6, Treated: 6, Analysed (for primary endpoints): 6 Treatment sequence 5 (A-C-B): Entered: 6, Treated: 6, Analysed (for primary endpoints): 6 Treatment sequence 6 (B-A-C): Entered: 6, Treated: 6, Analysed (for primary endpoints): 6 A=T80/A5/H12.5 mg, B=T80/H12.5 mg, C=T80/A5 mg
Diagnosis:	Healthy Japanese male subjects
Main Criteria for Inclusion:	Healthy male subjects aged ≥20 and ≤35 years; body weight: ≥50 and ≤80 kg; body mass index: ≥18.0 and ≤25.0 kg/m^2
BI Investigational Product:	T80/A5/H12.5 mg FDC tablet
Dose:	telmisartan 80 mg, amlodipine 5 mg, and HCTZ 12.5 mg
Mode of Admin.:	Oral administration with 150 mL of water after an overnight fast (at least 10 hours)
Batch No.:	14005
Comparator Product:	T80/H12.5 mg FDC tablet (Micombi® Combination Tablets BP)
Dose:	telmisartan 80 mg, HCTZ 12.5 mg
Mode of Admin.:	Oral administration with 150 mL of water after an overnight fast (at least 10 hours)
Batch No.:	14003
Comparator Product:	T80/A5 mg FDC tablet (Micamlo® Combination Tablets BP)
Dose:	telmisartan 80 mg, amlodipine 5 mg
Mode of Admin.:	Oral administration with 150 mL of water after an overnight fast (at least 10 hours)
Batch No.:	14004
Duration of Treatment:	10 days (once daily) for each treatment period

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Criteria for Evaluation:

Pharmacokinetics:

Primary endpoints: $C_{max,ss}$, $AUC_{\tau,ss}$ for telmisartan, amlodipine and HCTZ

Secondary endpoint: $Ae_{0-24,ss}$ only for HCTZ

Further endpoints: $t_{max,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $C_{pre,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$ for telmisartan, amlodipine and HCTZ

Safety: Adverse events (AEs), clinical laboratory tests, vital signs (blood pressure, pulse rate and body temperature)

Statistical Methods:

Point estimates (geometric means) of the median intra-subject ratios of $C_{max,ss}$ and $AUC_{\tau,ss}$ and their two-sided 90% confidence intervals (CIs) were calculated for telmisartan, amlodipine and HCTZ.

The statistical model used was an analysis of variance (ANOVA) model on log transformed parameters including "sequence", "subjects within sequences", "period" and "treatment" as effects. Confidence intervals were based on the residual error from the ANOVA.

Descriptive statistics were calculated for all other continuous parameters. Frequencies were tabulated for all categorical parameters.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 36 subjects were entered in the trial and were randomly assigned to one of the six treatment sequences (6 subjects for each). Of these, 34 subjects (94.4%) completed the three treatment periods as scheduled, and 2 subjects (5.6%) in the treatment sequence 6 who completed periods 1 and 2 were withdrawn from the trial before starting the treatment in period 3 due to an AE. All the 36 subjects received at least one dose of the study drug and were included in the safety and pharmacokinetic analyses.

The mean (SD) age of the 36 subjects was 28.0 (4.6) years, the mean (SD) body weight was 65.23 (6.86) kg and the mean (SD) body mass index (BMI) was 21.82 (1.86) kg/m^2.The demographic characteristics were generally comparable among the treatment sequences.

No important protocol violations were identified in the trial. All doses of the study drugs were administered orally under supervision by the investigator in compliance with the clinical trial protocol.

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Efficacy / Clinical Pharmacology / Other Results:

Pharmacokinetic parameters were shown in Table 1.

Table 1 Comparison of PK parameters between T80/A5/H12.5 mg and T80/H12.5 mg or T80/A5 mg FDC tablet

		T80/A5/H12.5 mg		T80/H12.5 mg		T80/A5 mg	
Parameter	Unit	N	gMean (gCV [%])	N	gMean (gCV [%])	N	gMean (gCV [%])
Telmisartan							
$C_{max,ss}$	[ng/mL]	36	970 (69.3)	36	895 (75.0)	34	857 (70.7)
$AUC_{\tau\ ss}$	[ng*h/mL]	36	2510 (72.1)	36	2580 (81.4)	34	2570 (70.8)
Amlodipine							
$C_{max,ss}$	[ng/mL]	36	11.8 (21.8)	-	-	34	11.3 (22.3)
$AUC_{\tau\ ss}$	[ng*h/mL]	36	230 (23.4)	-	-	34	223 (21.8)
HCTZ							
$C_{max,ss}$	[ng/mL]	36	107 (28.5)	36	102 (28.0)	-	-
$AUC_{\tau,ss}$	[ng*h/mL]	36	584 (23.8)	36	565 (23.4)	-	-
$Ae_{0\text{-}24\ ss}$	[mg]	36	10.4 (11.4)	36	9.91 (12.2)	-	-

Abbreviations: gMean=geometric mean, gCV=geometric coefficient of variation

Relative bioavailability of the test treatment (T80/A5/H12.5 mg FDC tablet) to the reference treatment (T80/H12.5 mg or T80/A5 mg FDC tablet) based on the primary endpoints ($C_{max,ss}$ and $AUC_{\tau,ss}$) is summarised in Table 2. The 90% CIs of the adjusted gMean ratio for $C_{max,ss}$ and $AUC_{\tau,ss}$ were within the acceptance range for bioequivalence (80% to 125%), except for $C_{max,ss}$ of telmisartan. The upper limits of 90% CI of adjusted gMean ratio of $C_{max,ss}$ for telmisartan was slightly higher than those of the acceptance range for bioequivalence both in comparison with T80/H12.5 mg and T80/A5 mg; however, 90% CIs of adjusted gMean ratio of $C_{max,ss}$ included 100%. On the basis of these results, no clinically relevant pharmacokinetic drug-drug interaction was demonstrated for the three active ingredients, i.e., telmisartan, amlodipine, and HCTZ, at steady state.

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Efficacy / Clinical Pharmacology / Other Results (continued):

Table 2 Relative bioavailability for the two formulations (T80/A5/H12.5 mg [test] and T80/H12.5 mg or T80/A5 mg FDC tablet [reference]) based on the log-transformed $C_{max,ss}$ and $AUC_{\tau,ss}$

	Adjusted gMean ratio (Test/Reference)	Two-sided 90% CI	
		Lower limit	Upper limit
Parameter	[%]	[%]	[%]
Telmisartan (v.s. T80/H12.5 mg)			
$C_{max,ss}$	108.4	93.1	126.2
$AUC_{\tau,ss}$	97.5	90.4	105.2
Telmisartan (v.s. T80/A5 mg)			
$C_{max,ss}$	114.9	98.2	134.3
$AUC_{\tau,ss}$	102.0	96.9	107.4
HCTZ (v.s. T80/H12.5 mg)			
$C_{max,ss}$	105.4	99.2	111.8
$AUC_{\tau,ss}$	103.4	98.7	108.3
Amlodipine (v.s. T80/A5 mg)			
$C_{max,ss}$	104.0	101.0	107.0
$AUC_{\tau,ss}$	102.5	100.2	104.9

Safety Results:

Overall summary of AEs is presented in Table 3. AEs occurred in 7 of 36 subjects (19.4%) overall: 5 of 36 subjects (13.9%) with T80/A5/H12.5 mg FDC tablet, 3 of 36 subjects (8.3%) with T80/H12.5 mg FDC tablet, and 2 of 34 subjects (5.9%) with T80/A5 mg FDC tablet. All AEs except one hand fracture (moderate intensity) were mild in intensity. No deaths or other serious AEs occurred. AEs leading to discontinuation of study drug occurred in 2 of 36 subjects (5.6%) during the treatment with T80/A5/H12.5 mg FDC tablet. These 2 events were considered not drug-related by the investigator.

The most frequent AEs on preferred term level was alanine aminotransferase increased (4 of 36 subjects [11.1%]; 3 subjects [8.3%] with T80/A5/H12.5 mg, 2 subjects [5.6%] with T80/H12.5 mg and 2 subjects [5.9%] with T80/A5 mg) followed by C-reactive protein increased (2 of 36 subjects [5.6%]; 1 subject [2.8%] with T80/A5/H12.5 mg and 1 subject

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Safety Results (continued):

[2.8%] with T80/H12.5 mg).

Drug-related AEs occurred in 3 of 36 subjects (8.3%) overall. These AEs included alanine aminotransferase increased in 2 subjects (2 subjects with T80/A5/H12.5 mg, 2 subjects with T80/H12.5 mg, and 1 subject with T80/A5 mg) and C-reactive protein increased in 1 subject (T80/H12.5 mg).

As expected from the antihypertensive effect of telmisartan, amlodipine and HCTZ, the mean systolic and diastolic blood pressure tended to decrease during treatment periods. However, blood pressure showed a tendency to return toward baseline after drug intake was completed at the end of each treatment period. No clinically meaningful changes were found in the data of laboratory tests, pulse rate, body temperature or body weight.

Table 3 AEs overall summary – treated set

	T80/A5/H12.5 FDC tablet N (%)	T80/H12.5 FDC tablet N (%)	T80/A5 FDC tablet N (%)	Total N (%)
Number of subjects	36	36	34	36
Subjects with any AE	5 (13.9)	3 (8.3)	2 (5.9)	7 (19.4)
Subjects with severe AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with investigator defined drug-related AEs	2 (5.6)	3 (8.3)	1 (2.9)	3 (8.3)
Subjects with other significant AEs	2 (5.6)	0 (0.0)	0 (0.0)	2 (5.6)
Subjects with AEs leading to discontinuation of study drug	2 (5.6)	0 (0.0)	0 (0.0)	2 (5.6)
Subjects with serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are calculated using total number of subjects per treatment as the denominator.

Conclusions:

On the basis of the pharmacokinetic results obtained in this trial, no clinically relevant pharmacokinetic interaction was demonstrated for the three active ingredients, telmisartan, amlodipine, and HCTZ at steady state.

Multiple-dose treatment of T80/A5/H12.5 mg FDC tablet, as well as two reference products (T80/H12.5 mg and T80/A5 mg FDC tablets), was safe and well tolerated in healthy Japanese male subjects.