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 5	
Report Date: 08 JAN 2015	**Trial No. / Doc. No.:** 1348.3/ c02968933-02	**Dates of Trial:** 07 May 2014 - 02 August 2014	**Date of Revision:** 02 FEB 2015

Title of Trial:	Bioequivalence of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed-dose combination tablet compared to concomitant administration of telmisartan 80 mg/amlodipine 5 mg fixed-dose combination tablet and hydrochlorothiazide 12.5 mg tablet in healthy male subjects: an open-label, randomised, single-dose, two-sequence, four-period replicated crossover study
Principal/Coordinating Investigator:	[redacted]
Trial Site:	[redacted] Japan
Publications:	Data of this trial has not been published
Clinical Phase:	I
Objectives:	The primary objective of this trial is to investigate bioequivalence of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed-dose combination tablet (T80/A5/H12.5 mg FDC tablet) and concomitant use of telmisartan 80 mg/amlodipine 5 mg fixed-dose combination tablet and hydrochlorothiazide 12.5 mg tablet (T80/A5 mg FDC tablet and H12.5 mg tablet) in healthy Japanese male subjects.
Methodology:	This was an open-label, randomised, single-dose, two-sequence, four-period replicated crossover design.
No. of Subjects:	
Planned:	Entered: 72
Actual:	Enrolled: 72
	Entered: 72
	T80/A5/H12.5 mg FDC tablet:
	Entered: 36 Treated: 36 Analysed (for primary endpoint): 35
	T80/A5 mg FDC tablet and H12.5 mg tablet:
	Entered: 36 Treated: 36 Analysed (for primary endpoint): 36
Diagnosis:	Healthy Japanese male subjects
Main Criteria for Inclusion:	Male subjects at the age of ≥20 and ≤35 years, with body weight: ≥50 kg and ≤80 kg, and body mass index: ≥18.0 and ≤25.0 kg/m^2

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BI Investigational Product:	telmisartan/amlodipine/hydrochlorothiazide (HCTZ) FDC tablet
Dose:	80 mg telmisartan, 5 mg amlodipine, 12.5 mg HCTZ
Mode of Admin.:	Oral administration with 150 mL water after an overnight fast
Batch No.:	14001
Comparator Products:	telmisartan/amlodipine FDC tablet and HCTZ tablet
Dose:	80 mg telmisartan, 5 mg amlodipine, 12.5 mg HCTZ
Mode of Admin.:	Oral administration with 150 mL water after an overnight fast
Batch No.:	T80/A5 mg FDC tablet: 13006 H12.5 mg tablet: 13007
Duration of Treatment:	One day (single oral dose) for each treatment period The trial consisted of a screening period (within 30 days of the first study drug administration), 4 treatment periods (periods 1 to 4) for 8 days (Day -1 to Day 7) per period, and 3 washout periods (14 days or more between study drug administrations).
Criteria for Evaluation:	Primary endpoints: AUC_{0-tz}, C_{max}
Clinical Pharmacology:	Secondary endpoint: $AUC_{0-\infty}$
Safety:	adverse events (AEs), laboratory tests, vital signs (blood pressure, pulse rate and body temperature)
Statistical Methods:	Two-sided 90% confidence intervals for the intra-subject ratio (as estimated by the geometric mean of the ratio) of each of all pharmacokinetics endpoints were calculated for telmisartan, amlodipine and HCTZ to determine whether the confidence intervals were contained in the acceptance range of 80% to 125% for bioequivalence (the acceptable range for t_{max}: 80% to 120%). Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios were provided. The statistical model based on a four-period replicated crossover design was mixed model on original or log transformed parameters including "sequence" "period" and "treatment" as fixed effect and "subjects nested within sequence" as random effect. Confidence intervals were based on the residual error from mixed model. Descriptive statistics for all other parameters were calculated.

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SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 72 subjects with mean (SD) age of 26.7 (4.8) was enrolled in the trial, was randomised to the Treatment sequence 1 or 2 in a 1:1 ratio. Subjects in the Treatment sequence 1 were treated with the study drug(s) in the order of the test drug (T: T80/A5/H12.5 mg FDC tablet) - the reference drugs (R: T80/A5 mg FDC tablet and H12.5 mg tablet) - R - T from period 1 to 4. Meanwhile, those subjects in the Treatment sequence 2 were treated in the order of R (period 1) - T (period 2) -T (period 3) -R (period 4). Of 72 subjects, 70 (97.2%) subjects completed the trial. Two subjects (2.8%) were withdrawn from the trial either after completing period 1 or period 3 due to withdrawal of consent. All 72 randomised and treated subjects (100.0%) were included in the treated set. Of 72 subjects, 71 subjects (98.6%) have evaluable pharmacokinetic (PK) data for at least 1 analyte for both the test drug and the reference drugs, and were included in the PK set.

Clinical Pharmacology Results:

PK parameters were shown in Table 1.

Table 1 Comparison of PK parameters between T80/A5/H12.5 mg FDC tablet (test) and T80/A5 mg FDC tablet and H12.5 mg tablet in concomitant use (reference)

		T80/A5/H12.5 mg FDC tablet			T80/A5 mg FDC tablet and H12.5 mg tablet		
Parameter	Unit	N	gMean	gCV [%]	N	gMean	gCV [%]
Telmisartan							
C_{max}	[ng/mL]	141	718	56.4	142	694	55.2
AUC_{0-tz}	[ng·h/mL]	141	2850	52.0	141	2790	54.9
$AUC_{0-\infty}$	[ng·h/mL]	140	3090	54.5	136	3120	58.8
Amlodipine							
C_{max}	[ng/mL]	141	3.69	22.0	141	3.68	20.7
AUC_{0-tz}	[ng·h/mL]	141	171	24.3	140	172	25.0
$AUC_{0-\infty}$	[ng·h/mL]	141	184	25.2	139	185	26.0

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

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Table 1(cont'd) Comparison of PK parameters between T80/A5/H12.5 mg FDC tablet (test) and T80/A5 mg FDC tablet and H12.5 mg tablet in concomitant use (reference)

HCTZ							
C_{max}	[ng/mL]	141	104	23.0	142	94.7	23.4
AUC_{0-tz}	[ng·h/mL]	141	638	19.3	142	611	19.6
$AUC_{0-\infty}$	[ng·h/mL]	141	661	18.7	142	634	18.9

Relative bioavailability of the test treatment (T80/A5/H12.5 mg FDC tablet) to the reference treatment (T80/A5 mg FDC tablet and H12.5 mg tablet in concomitant use) based on the primary endpoints (C_{max} and AUC_{0-tz}) is summarised in Table 2. The 90% CIs of the adjusted gMean ratio for C_{max} and AUC_{0-tz} of telmisartan, amlodipine, and HCTZ were within the acceptance range for bioequivalence (80% to 125%). Therefore, bioequivalence of telmisartan, amlodipine, and HCTZ was demonstrated between T80/A5/H12.5 mg FDC tablet (test treatment) and T80/A5 mg FDC tablet and H12.5 mg tablet in concomitant use (reference treatment) in this trial.

Table 2 Relative bioavailability for the two formulations (T80/A5/H12.5 mg FDC tablet [test] and T80/A5 mg FDC tablet and H12.5 mg tablet in concomitant use [reference]) based on the log-transformed C_{max} and AUC_{0-tz}

	Adjusted gMean ratio (Test/Reference)	Two-sided 90% CI	
		Lower limit	Upper limit
Parameter	[%]	[%]	[%]
Telmisartan			
C_{max}	103.8	97.0	111.0
AUC_{0-tz}	102.0	98.9	105.1
Amlodipine			
C_{max}	100.1	98.5	101.7
AUC_{0-tz}	99.5	98.1	100.9
HCTZ			
C_{max}	110.2	106.9	113.5
AUC_{0-tz}	104.3	102.5	106.1

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Safety Results:	Adverse event profiles of T80/A5/H12.5 mg FDC tablet and concomitant use of T80/A5 mg FDC tablet and H12.5 mg tablet were similar. AEs were reported for 5 (6.9%) of 72 subjects: 3 (4.2%) subjects when treated with T80/A5/H12.5 mg FDC tablet, and 2 (2.8%) subjects when treated with T80/A5 mg FDC tablet and H12.5 mg tablet. All AEs were related to the study drug(s), mild in severity, and were later resolved. The most frequently reported AEs were alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased. No death, no serious AEs or no AEs leading to discontinuation of the study drug(s) were reported in the trial. Thus, no notable safety concerns were reported in the treatment with T80/A5/H12.5 mg FDC tablet or concomitant use of T80/A5 mg FDC tablet and H12.5 mg tablet.
Conclusions:	The 90% confidence intervals of the adjusted gMean ratio for C_{max} and $AUC_{0\text{-}tz}$ of telmisartan, amlodipine, and hydrochlorothiazide were within the acceptance range for bioequivalence (80% to 125%). Therefore, T80/A5/H12.5 mg FDC tablet (test treatment) and concomitant use of T80/A5 mg FDC tablet and H12.5 mg tablet (reference treatment) are bioequivalent. Safety assessments demonstrated that both T80/A5/H12.5 mg FDC tablet and concomitant use of T80/A5 mg FDC tablet and H12.5 mg tablet appeared to be safe and well tolerated in the healthy Japanese male subjects in the trial.