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 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

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/hydrochlorothiazide 12.5 mg fixed-dose combination tablet and amlodipine 5 mg capsule in healthy male subjects (an open-label, randomised, single-dose, two-sequence, four-period replicated crossover study), with influence of food on the bioavailability of telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg fixed-dose combination tablet
Principal Investigator:	[redacted]
Trial Site:	[redacted] Japan
Publications:	Data from this trial have not been published.
Clinical Phase:	I
Objectives:	To investigate the bioequivalence between telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide (HCTZ) 12.5 mg (T80/A5/H12.5 mg) fixed-dose combination (FDC) tablet and concomitant administration of telmisartan 80 mg/HCTZ 12.5 mg (T80/H12.5 mg) FDC tablet and amlodipine 5 mg (A5 mg) capsule in healthy Japanese male subjects. To assess the relative bioavailability and pharmacokinetics of T80/A5/H12.5 mg FDC tablet in the fed condition compared with those in the fasted condition in healthy Japanese male subjects.
Methodology:	Bioequivalence: open-label, randomised, single-dose, two-sequence, four-period replicated crossover design Effect of food on bioavailability: open-label, single-dose, additional-period add-on design
No. of Subjects:	
Planned:	Entered: 72 subjects (36 subjects per sequence)
Actual:	Entered: 72 subjects <Treatment sequence 1: Subjects were treated with the study drug(s) in the order of test product (T: T80/A5/H12.5 mg FDC tablet) - the reference products (R: T80/H12.5 mg FDC tablet and A5 mg capsule) - R - T - T from period 1 to period 5.>:

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 2 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

	Entered: 36 Treated: 36 Analysed (for primary endpoint): 36
	< Treatment sequence 2: Subjects were treated in the order of R (period 1) – T (period 2) -T (period 3) -R (period 4).>: Entered: 36 Treated: 36 Analysed (for primary endpoint): 35
Diagnosis:	Healthy Japanese male subjects
Main Criteria for Inclusion:	Healthy Japanese male subjects, age ≥20 and ≤35 years; body weight ≥50 and ≤80 kg; body mass index (BMI) ≥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 (periods 1 to 4) Oral administration with 150 mL of water after a Japanese-style breakfast (period 5 for the effect of food on bioavailability)
Batch No.:	14002
Comparator Products:	T80/H12.5 mg FDC tablet Amlodipine, DBcaps® (capsule [over-encapsulated two amlodipine 2.5 mg tablets])
Dose:	T80/H12.5 mg FDC: telmisartan 80 mg and HCTZ 12.5 mg Amlodipine: 5 mg
Mode of Admin.:	Oral administration with 150 mL of water after an overnight fast
Batch No.:	T80/H12.5 mg FDC: 13008 Amlodipine: 13009
Duration of Treatment:	One day (single dose) for each treatment period Screening period: within 30 days before the first drug administration Treatment period: consisted of 4 periods (for subjects assigned to treatment sequence 2) or 5 periods (for subjects assigned to treatment sequence 1), with 8 trial days in each period Washout period: at least 14 days from drug administration in the previous period End of trial: safety to be confirmed 144 hours after the last drug administration

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 3 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

Criteria for Evaluation:

Pharmacokinetics: Primary endpoints (bioequivalence and food effect): AUC_{0-tz} and C_{max}
Secondary endpoint (bioequivalence and food effect): $AUC_{0-\infty}$
Further endpoints (bioequivalence): t_{max}, λ_z, $t_{1/2}$, and MRT_{po}

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

Statistical Methods:

For bioequivalence (periods 1 to 4):

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 bioequivalence criteria (80% to 125% for parameters with log-transformation). 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 analysis of variance (ANOVA) on original or log-transformed parameters including “sequence”, “period”, and “treatment” as fixed effects and “subjects nested within sequence” as a random effect. Confidence intervals were based on the residual error from ANOVA.

Descriptive statistics for all other parameters were calculated.

For effect of food on bioavailability (period 5):

Point estimators (geometric means) of the median intra-subject ratios of AUC_{0-tz}, C_{max}, and $AUC_{0-\infty}$ and their two-sided 90% confidence intervals were calculated, separately for telmisartan, amlodipine, and HCTZ. The statistical model was an ANOVA on log-transformed parameters including “fasting status” as a fixed effect and “subjects” as a random effect. Confidence intervals were based on the residual error from ANOVA.

In general, for continuous parameters, descriptive statistics were calculated by treatment or by treatment and period; for categorical (or categorised) parameters, frequencies were tabulated by treatment or by treatment and period.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 4 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 72 subjects entered the trial and were randomly assigned to either treatment sequence 1 (36 subjects) or treatment sequence 2 (36 subjects). The subjects received the test product (T80/A5/H12.5 mg FDC tablet) and the reference products (T80/H12.5 mg FDC tablet and A5 mg capsule) in the specified order until period 4 or 5. Of the 72 subjects who took the study drug in period 1, 71 completed the trial. One subject in treatment sequence 2 withdrew his consent and prematurely discontinued participation in the trial after completing the period 1.

Of the 72 subjects, 1 (1.4%) had an important protocol violation and was excluded from analyses of bioequivalence. The data for the primary endpoints were missing for the subject because he prematurely withdrew from the trial after completing the period 1.

All subjects met the inclusion criteria with respect to age, body weight, and BMI. The overall mean (SD) age was 26.6 (4.0) years, the mean (SD) body weight was 61.89 (6.15) kg, and the mean (SD) BMI was 21.12 (1.76) kg/m^2. No apparent difference was noted between the treatment sequences.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 5 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

Clinical Pharmacology Results:

Relative bioavailability

Table 1 shows PK parameters after administration of T80/A5/H12.5 mg FDC tablet and concomitant use of T80/H12.5 mg FDC tablet and A5 mg capsule.

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

		T80/A5/H12.5 mg FDC tablet			T80/H12.5 mg FDC tablet and A5 mg capsule		
Parameter	Unit	N	gMean	gCV [%]	N	gMean	gCV [%]
Telmisartan							
C_{max}	[ng/mL]	142	697	75.5	142	726	74.9
AUC_{0-tz}	[ng·h/mL]	142	2580	76.8	142	2600	76.1
$AUC_{0-\infty}$	[ng·h/mL]	142	2750	79.2	140	2730	73.7
Amlodipine							
C_{max}	[ng/mL]	142	3.62	20.2	142	3.57	19.9
AUC_{0-tz}	[ng·h/mL]	142	159	23.4	142	157	24.0
$AUC_{0-\infty}$	[ng·h/mL]	142	172	25.4	142	170	26.0
HCTZ							
C_{max}	[ng/mL]	142	98.5	25.1	142	96.6	25.8
AUC_{0-tz}	[ng·h/mL]	142	600	21.0	142	598	19.1
$AUC_{0-\infty}$	[ng·h/mL]	141	626	20.2	142	624	18.2

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 FDC tablet and A5 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/H12.5 mg FDC tablet and A5 mg tablet in concomitant use (reference treatment) in this trial.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 6 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

Table 2 Relative bioavailability for the two formulations (T80/A5/H12.5 mg FDC tablet [test] and concomitant use of T80/H12.5 mg FDC tablet and A5 mg tablet [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}	95.8	88.9	103.2
AUC_{0-tz}	99.2	96.1	102.4
Amlodipine			
C_{max}	101.4	99.7	103.1
AUC_{0-tz}	101.4	99.8	103.0
HCTZ			
C_{max}	101.8	98.5	105.2
AUC_{0-tz}	100.3	98.3	102.4

Abbreviations: gMean=geometric mean, CI=confidence interval

Food effect

Table 3 shows PK parameters after administration of T80/A5/H12.5 mg FDC tablet in the fed/fasted condition. Relative bioavailability of fed condition to the fasted condition based on the primary endpoints (C_{max} and AUC_{0-tz}) is summarised in Table 4.

The 90% CIs of the adjusted gMean ratio suggests C_{max} and AUC_{0-tz} of telmisartan, and C_{max} of HCTZ were reduced when T80/A5/H12.5 mg FDC tablet was administered in the fed condition. On the other hand, no food effect was observed in the pharmacokinetics of amlodipine.

Table 3 Comparison of pharmacokinetic parameters after single oral

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 7 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

administration of T80/A5/H12.5 mg FDC tablet in the fed/fasted condition

		Fed			Fasted		
Parameter	Unit	N	gMean	gCV [%]	N	gMean	gCV [%]
Telmisartan							
C_{max}	[ng/mL]	36	182	75.9	36	605	84.4
AUC_{0-tz}	[ng·h/mL]	36	1500	98.3	36	2350	93.6
$AUC_{0-\infty}$	[ng·h/mL]	35	1670	108	36	2530	98.3
Amlodipine							
C_{max}	[ng/mL]	36	3.54	20.6	36	3.60	22.4
AUC_{0-tz}	[ng·h/mL]	36	156	23.9	36	157	26.1
$AUC_{0-\infty}$	[ng·h/mL]	36	168	26.0	36	169	28.6
HCTZ							
C_{max}	[ng/mL]	36	75.4	16.5	36	94.6	20.1
AUC_{0-tz}	[ng·h/mL]	36	515	18.9	36	575	19.2
$AUC_{0-\infty}$	[ng·h/mL]	36	542	18.3	36	603	18.3

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

Table 4 Relative bioavailability after administration of T80/A5/H12.5 mg FDC tablet in the fed/fasted condition based on the log-transformed C_{max} and

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 8 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

	AUC_{0-tz}		
	Adjusted gMean ratio (Fed/Fasted)	Two-sided 90% CI	
		Lower limit	Upper limit
Parameter	[%]	[%]	[%]
Telmisartan			
C_{max}	30.2	25.0	36.4
AUC_{0-tz}	63.7	59.0	68.7
Amlodipine			
C_{max}	98.2	94.6	102.0
AUC_{0-tz}	99.7	97.1	102.5
HCTZ			
C_{max}	79.7	75.0	84.7
AUC_{0-tz}	89.7	85.8	93.7

Abbreviations: gMean=geometric mean, CI=confidence interval

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 9 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

Safety Results:

Of the 72 treated subjects, 24 (33.3%) had at least one AE during the course of the trial. The incidence of AEs was 22.5% (16 of 71 subjects) after treatment with T80/A5/H12.5 mg FDC tablet and 13.9% (10 of 72 subjects) after treatment with T80/H12.5 mg FDC tablet and A5 mg capsule.

The reported AEs were in the system organ classes, Nervous system disorders, Vascular disorders, Infections and infestations, and Musculoskeletal and connective tissue disorders. On a preferred term basis, the most frequently reported AEs (i.e., those reported for >5% of subjects overall) were headache (10 of 72 subjects, 13.9%) and orthostatic hypotension (6 of 72 subjects, 8.3%). Most AEs were mild in intensity. No severe AEs occurred during the trial. The only treatment-emergent AE of moderate intensity reported for 1 subject was nasopharyngitis, which was not related to the study drug. None of the AEs led to discontinuation of the study drug.

Drug-related AEs were reported in 16 of 72 subjects (22.2%) overall. These AEs included headache (9 of 72 subjects, 12.5%), orthostatic hypotension (6 of 72 subjects, 8.3%), and dizziness (1 of 72 subjects, 1.4%).

No death, SAEs, or other significant AEs were reported.

No clinically relevant changes from baseline were found in any of the laboratory parameters including haematology, blood chemistry, and urinalysis.

As expected from antihypertensive effect of telmisartan, amlodipine, and HCTZ the mean systolic and diastolic blood pressure decreased after each dose of the study drug irrespective of treatment (test product/reference products) or feeding condition (fasted/fed). Then, the values returned to the baseline level. No clinically relevant changes were noted for either pulse rate or body temperature.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable			
BI Investigational Product: telmisartan / amlodipine / hydrochlorothiazide (BIBR277 TCT)		**Page:** 10 of 10	
Report Date: 24 Feb 2015	**Trial No. / Doc. No.:** 1348.4 / c02861413-01	**Dates of Trial:** 8 May 2014 - 16 September 2014	**Date of Revision:** Not applicable

Conclusions:

The 90% confidence intervals 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, T80/A5/H12.5 mg FDC tablet (test treatment) and T80/H12.5 mg FDC tablet and A5 mg capsule in concomitant use (reference treatment) are bioequivalent.

Food effect was observed in pharmacokinetics of telmisartan and HCTZ. C_{max} and AUC_{0-tz} of telmisartan, and C_{max} of HCTZ were reduced when T80/A5/H12.5 mg FDC tablet was administered in the fed condition. On the other hand, no food effect was observed in the pharmacokinetics of amlodipine.

Both T80/A5/H12.5 mg FDC tablet and concomitant use of T80/H12.5 mg FDC tablet and A5 mg capsule were safe and well tolerated in healthy Japanese male subjects.