Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
Name of active ingredient: 80 mg telmisartan; 25 mg ASA/200 mg ER-DP		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 03 JUN 2005	**Number:** U05-1694	**Study period (dates):** 26-May 04 to 30-Jul 04		

Title of study:	Relative bioavailability of telmisartan in Micardis® and of dipyridamole in Aggrenox® after co-administration compared to the bioavailability of telmisartan respectively of dipyridamole after oral administration of 80 mg telmisartan respectively of 25 mg ASA/200 mg extended-release dipyridamole alone. An open-label, randomised, single-dose, four-way crossover study in 24 healthy female and male subjects
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Str. 65 D-88397 Biberach/Riss
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of telmisartan (BIBR 277SE) respectively of dipyridamole after concomitant administration of 80 mg telmisartan in Micardis® and 25 mg acetylsalicylic acid (ASA) /200 mg extended release dipyridamole (ER-DP) in Aggrenox® (Test 1) relative to ER-DP in Aggrenox® alone (Reference 1), respectively relative to telmisartan in Micardis® alone (Reference 2). To investigate the relative bioavailability of dipyridamole respectively of telmisartan administered as 25 mg ASA/200 mg ER-DP 30 minutes after intake of 80 mg telmisartan (Test 2) relative to dipyridamole in Aggrenox® alone (Reference 1), respectively relative to telmisartan in Micardis® alone (Reference 2).
Methodology:	This study was performed as an open-label, randomised, four-way crossover trial with four single-dose treatments and six sequences.
No. of subjects: **planned:**	entered: 24
actual:	enrolled: 39; entered: 24; dropped out: 1 Treatment 1: Telmisartan and ASA/ER-DP (concomitant) entered: 23 treated: 23 analysed (for primary endpoint): 23 Treatment 2:ASA-ER-DP entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment 3: Telmisartan given 30 minutes before ASA/ER-DP entered: 23 treated: 23 analysed (for primary endpoint): 23 Treatment 4: Telmisartan entered: 23 treated: 23 analysed (for primary endpoint): 23

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Diagnosis and main criteria for inclusion:	Healthy female and male subjects, age ≥21 and ≤65 years, BMI range: ≥18.5 and ≤29.9 kg/m2
Test product:	Micardis® (telmisartan) and Aggrenox® (acetylsalicylic acid /extended-release dipyridamole)
dose:	80 mg and 25 mg/200 mg
mode of admin.:	Oral administration after an overnight fast with 240 mL mineral water
batch no.:	telmisartan batch no.: 206065; ASS/ER-DP batch no.: 304377
Duration of treatment:	One day (single dose per os) for each treatment, total 4 treatment days
Reference therapy:	Micardis® (telmisartan) or Aggrenox® (acetylsalicylic acid /extended-release dipyridamole)
dose:	80 mg or 25 mg/200 mg
mode of admin.:	Oral administration after an overnight fast with 240 mL mineral water
batch no.:	telmisartan batch no.: 206065; ASS/ER-DP batch no.: 304377
Criteria for evaluation:	
Efficacy:	There are no efficacy endpoints.
	primary endpoints: $AUC_{0-\infty}$, and C_{max} for telmisartan and dipyridamole secondary endpoints: AUC_{0-tz}, t_{max}, λ_Z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F for telmisartan and dipyridamole
Safety:	Physical examination, vital signs (BP, HR), 12-lead ECG, laboratory tests, adverse events, tolerability
Statistical methods:	Point estimators of the intra-subject ratios of geometric means $AUC_{0-\infty}$ and C_{max} and their two-sided 90% CIs.
	The statistical model was ANOVA on log transformed parameters. CIs will be based on the residual error from ANOVA.
	Descriptive statistics for all other parameters will be calculated.
SUMMARY – CONCLUSIONS:	
Efficacy results:	There were no efficacy endpoints.
	PK results: Co-administration of telmisartan and dipyridamole (treatment 1) increased

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gMean $AUC_{0-\infty}$ for telmisartan from 943 to 1060 ng·h/mL. Administration of dipyridamole 30 minutes after telmisartan (treatment 3) further increased the total exposure of telmisartan ($AUC_{0-\infty}$ raised to 1150 ng·h/mL). Accordingly, the 90% CI for the test/reference ratio for gMean $AUC_{0-\infty}$ telmisartan following dipyridamole 30 min after telmisartan vs. telmisartan alone (treatment 4) was not contained within the 80 – 125% limits (110 – 135%).

For C_{max} of telmisartan the 90% CI was always contained within the 80 - 125 % limits and the 90% CI included 100% irrespective of the different co-administrations of dipyridamole.

The gMean AUC_{0-tz} of dipyridamole was increased after concurrent administration of telmisartan from 7570 to 8540 ng·h/mL and to 9750 ng·h/mL when given 30 min after telmisartan. Although the ratio of gMean AUC_{0-tz} comparing concomitantly telmisartan (treatment 1) vs. dipyridamole alone (treatment 2) was within the 80 -125% boundaries, the 90% CI did not contain 100%. Furthermore, the 90% CI (119 – 140%) for the comparison of telmisartan 30 min before dipyridamole (treatment 3) vs. dipyridamole alone for AUC_{0-tz} was not contained within the 80 – 125% limits, indicating even greater exposure for dipyridamole following the treatment telmisartan 30 min before dipyridamole.

Concomitantly given telmisartan increased gMean C_{max} for dipyridamole from 1100 to 1320 ng/mL. Telmisartan given 30 min before dipyridamole further increased gMean C_{max} of dipyridamole to 1500 ng/mL. For gMean C_{max}, the 90% CI (110 – 131%) was not contained within the 80-125% limits for the comparison of co-administration vs. dipyridamole alone, showing significant evidence that C_{max} is greater for co-administration than dipyridamole alone. Similarly, for C_{max}, the 90% CI (125 – 147%) for comparison of telmisartan 30 min before dipyridamole vs. dipyridamole alone, was not contained within the 80 – 125% limits indicating a greater C_{max} for dipyridamole following administration of telmisartan 30 min before dipyridamole.

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Statistical evaluation of telmisartan (BIBR 277 SE) C_{max} and $AUC_{0-\infty}$ by treatment

Parameter	Unit	Test	Ref.	intra-indiv. gCV	Adjusted Mean Ratio (Test/ Reference)	Two sided 90% Confidence Interval	
						Lower limit	Upper limit
				[%]	[%]	[%]	[%]
C_{max}	[ng/mL]	Treatment 1 (N=23)	Treatment 4 (N=23)	28.86	100.77	87.25	116.40
		Treatment 3 (N=23)	Treatment 4 (N=23)	25.14	96.93	85.51	109.87
$AUC_{0-\infty}$	[ng·h/mL]	Treatment 1 (N=23)	Treatment 4 (N=23)	15.85	112.22	103.57	121.60
		Treatment 3 (N=23)	Treatment 4 (N=23)	20.05	121.68	110.04	134.55

Statistical evaluation of dipyridamole C_{max} and AUC_{0-tz} by treatment

Parameter	Unit	Test	Ref.	intra-indiv. gCV	Adjusted Mean Ratio (Test/ Reference)	Two sided 90% Confidence Interval	
						Lower limit	Upper limit
				[%]	[%]	[%]	[%]
C_{max}	[ng/mL]	Treatment 1 (N=23)	Treatment 2 (N=23)	17.14	119.86	109.90	130.72

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Cont: Statistical evaluation of dipyridamole C_{max} and AUC_{0-tz} by treatment

Parameter	Unit	Test	Ref.	intra-indiv. gCV	Adjusted Mean Ratio (Test/ Reference)	Two sided 90% Confidence Interval	
						Lower limit	Upper limit
				[%]	[%]	[%]	[%]
C_{max}	[ng/mL]	Treatment 3 (N=23)	Treatment 2 (N=23)	16.07	135.96	125.40	147.41
AUC_{0-tz}	[ng·h/mL]	Treatment 1 (N=23)	Treatment 2 (N=23)	14.63	111.91	103.91	120.52
		Treatment 3 (N=23)	Treatment 2 (N=23)	16.57	128.80	118.50	139.99

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Safety results:

Twenty-one (21) of the 24 subjects reported at least one AE. There were 91 AEs reported, 76 of these were assessed to be treatment related.

The most frequent disorders involved were nervous system disorders (20 subjects reported 46 AEs) followed by gastrointestinal disorders (13 subjects with 27 AEs) and general disorders and administration site conditions (4 subjects with 4 AEs). The most frequently reported events were headache (20/44); nausea (10/14), vomiting (6/10) and influenza like illness (4/4).

There were no serious AEs. Most AE records were of mild (65/91) or moderate (18/91) intensity. Eight AEs were reported to be severe (8/91) due to gastrointestinal disorders like nausea (2) and vomiting (3) or nerval disorders like headache (2) and dizziness (1). All severe AEs were associated with medication of ASA/ER-DP alone or in combination with telmisartan.

One drop out occurred after the first treatment period (ASA/ER-DP alone) of subject [redacted], who withdrew her consent after suffering from headache, vomiting and tachycardia related to drug intake.

Those events which were judged to be not related to the trial medication (9 subjects reported 15 events) included influenza like illness, pharyngolaryngeal pain, headache, dizziness, haematoma. Most of these episodes reflect infection dependent illnesses.

No relevant safety problems concerning vital signs, ECG, physical examination and clinical laboratory safety test results related to the intake of the study drugs occurred.

Conclusions:

There was an effect especially of telmisartan on the bioavailability of dipyridamole which was even more pronounced when telmisartan was given 30 minutes before dipyridamole. The magnitude of the increase in exposure of dipyridamole was, however, moderate (mean AUC and Cmax increased by 29 % and 36 %, respectively) and is most probably of minor clinical relevance.

In conclusion concerning safety, the tolerability of the combined treatment with single doses of telmisartan and ASA/ER-DP was reduced by headache, nausea and vomiting which is already known to be mainly the side effect profile of ASA/ER-DP intake.