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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
Name of active ingredient: dipyridamole/acetylsalicylic acid		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 15 November 2004	**Number:** U04-2005	**Study period (dates):** 20 JAN to 26 MAR 2004		

Title of study:	Bioequivalence of a new Asasantin capsule formulation (extended release combination 200 mg dipyridamole/25 mg ASA) compared to the commercially available Asasantin capsule formulation (Aggrenox® ; extended release combination 200 mg dipyridamole/25 mg ASA) following multiple oral administration at steady state after a run-in phase (Persantine ER BID for 2 days each: 25 mg, 50 mg, 100 mg; 150 mg [Persantine®]; 200 mg Dipyridamole/25 mg ASA [Asasantin ER])- an open label, randomized, multiple-dose, two-way crossover, change-over study in healthy male and female volunteers.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG, D-88397 Biberach/Riss
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	To establish the bioequivalence of a new formulation of Asasantin ER compared to the present commercially available Asasantin ER formulation (Aggrenox®).
Methodology:	open label, randomised, two-way cross-over, change-over trial with a run-in phase
No. of subjects:	
planned:	entered: 20
actual:	enrolled: 37 Treatment new formulation (Test): entered: 24, treated: 21, analysed for primary endpoint: 20 Treatment commercial formulation during main phase (Reference): entered: 24, treated: 20, analysed for primary endpoint: 20
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age≥21 and ≤65 years, BMI ≥18.5 and ≤29.9 kg/m^2
Product for run-in phase:	Persantine/ASA; Asasantin ER 200/25 mg, respectively.
dose:	Persantine/ASA: 25/0 mg, 50/0 mg, 100/0 mg, 150/0 mg; Asasantin ER 200/25 mg.
mode of admin.:	p.o.
batch no.:	25/0 mg: 307957; 150/0 mg: K031025 = 03H04 - 1 Boehringer Ingelheim; 200/25 mg: K031047 = 306780 Boehringer Ingelheim.
Test product:	Main phase: Asasantin ER capsules (new formulation), Test (T).
dose:	200 mg dipyridamole/25 mg ASA, BID

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mode of admin.:	p.o.
batch no.:	307873A = 307873
Reference therapy:	Main phase: Asasantin ER capsules (Aggrenox®; present commercial formulation), Reference (R)
dose:	200 mg dipyridamole/25 mg ASA, BID
mode of admin.:	p.o.
batch no.:	K031047 = 306780 Boehringer Ingelheim
Duration of treatment:	Three days per treatment (main phase) and 10 days in the run-in phase, total: 16 days
Criteria for evaluation:	
Efficacy:	Pharmacokinetics: *Primary Parameters:* $AUC_{\tau,ss}$, $C_{max,ss}$, (dipyridamole) *Secondary Parameters:* $C_{min,ss}$, C_{avg}, $t_{max,ss}$, PTF, (dipyridamole) $Ae_{0-10,ss}$, $Ae_{10-24,ss}$, $fe_{0-10,ss}$ and $fe_{10-24,ss}$ (dipyridamole and dipyridamole-glucuronide)
Safety:	Physical examination, vital signs (BP, PR), ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Two-sided 90% CIs for the intra-subject ratio (geometric mean) of each of $AUC_{\tau,ss}$ and $C_{max,ss}$ were calculated to determine whether the CIs are contained in the acceptance range of 80-125% for bioequivalence. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated.

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Efficacy results:

Pharmacokinetics

Pharmacokinetic results were derived from plasma concentration-time data of Dipyridamole at steady state conditions. PK parameters were evaluated for the last two days of the main phase for each treatment. Summarized results are shown in Table 2.1.

Table 2.1: Comparison of pharmacokinetic parameters by treatment (N=20)

Parameter	Unit	New formulation		Comm. formulation	
		gMean	gCV [%]	gMean	gCV [%]
$AUC_{\tau,ss}$	[ng·h/mL]	10300	49.0	10700	43.7
$C_{max,ss}$	[ng/mL]	1920	43.6	1890	43.6
$C_{min,ss}$	[ng/mL]	506	63.4	549	55.5
C_{avg}	[ng/mL]	1030	49.0	1070	43.7
$t_{max,ss}$ §	[h]	1.48-6.00	--	1.48-6.07	--
PTF	[%]	132	34.1	122	32.1

Source Data: Table 15.5.2.1: 2
§ range minimum to maximum

Extent of absorption was nearly identical between test and reference treatment. Similar results were observed for the rate of absorption as reflected by $C_{max,ss}$. Statistical evaluation is given in Table 2.2.

Table 2.2: Statistical evaluation of primary parameters (test formulation new, reference formulation commercial, N=20)

Parameter	intra-indiv. gCV	Adjusted Mean Ratio (Test/Ref.)	Two sided 90 % Confidence Interval	
			Lower limit	Upper limit
	[%]	[%]	[%]	[%]
$AUC_{\tau,ss}$ [ng·h/mL]	12.3	96.7	90.4	103.4
$C_{max,ss}$ [ng/mL]	18.0	101.7	92.2	112.2

Source Data: Table 15.5.3: 2

Confidence limits were within the acceptance limits of 80% to 125%. Thus the test treatment is bioequivalent to the reference formulation for both primary endpoints.

Safety results:

There were no SAEs. The AEs observed did not put subjects' health at risk. The most prominent AE were headaches of sometimes severe intensity leading to discontinuation in four subjects. The run-in phase could not prevent them. In accordance with other trials headaches of sometimes severe intensity may occur initially but will diminish when continuing medication. The headaches were similar in the commercial and new pharmaceutical form.

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Conclusions:	The new Asasantin capsule formulation is bioequivalent to the commercial Asasantin capsule formulation. Both products can be regarded as interchangeable.