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: Aggrenox®				
Name of active ingredient: Dipyridamole, ASA		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 12 MAR 2004	**Number:** U04-1182	**Study period (dates):** 14 JAN 03 – 28 FEB 03		

Title of study:	Bioavailability of dipyridamole of Asasantin p.o. (extended release 200 mg dipyridamole/25 mg ASA) in three experimental formulations (given BID over 3 days each) relative to the standard formulation after a run-in phase (Persantine ER BID for 2 days each: 25 mg, 50 mg, 100 mg; 150 mg [Persantine®]; 200 mg Persantine/25 mg ASA [Asasantin ER] in healthy male subjects. Four-way, change-over, randomised, open.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG D-88397 Biberach an der Riss, Germany
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	Comparative pharmacokinetics of dipyridamole in three new formulations of Asasantin ER compared to the present commercial formulation
Methodology:	Randomised, open label, 4-way cross-over, change-over trial with a run-in phase
No. of subjects: **planned:** **actual:**	 entered: 20 entered: 19 discontinued: 1 completed: 18
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥50 years, BMI ≥18.5 and ≤29.9 kg/m^2
Test product: **dose:** **mode of admin.:**	Asasantin ER capsules (three new formulations with altered production) Run-in phase: Persantine/ASA: 25/0 mg, 50/0 mg, 100/0 mg, 150/0 mg; Asasantin ER 200/25 mg, BID Main phase: Asasantin ER capsules (three new formulations with altered production), 200 mg dipyridamole/25 mg ASA, BID p.o.

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batch no.:	25/0 mg Persantine/ASA: 207868; 150/0 mg Persantine/ASA: 02H15-1; Asasantin ER (present commercial formulation, reference): 203293; Asasantin ER (new formulation I "low"): 203240; Asasantin ER (new formulation II "high"): 203232; Asasantin ER (new formulation III "medium"): 203237
Duration of treatment:	Three days per treatment (main phase) and two days per treatment (run-in phase); total: 22 days
Reference therapy:	Asasantin ER capsules (present commercial formulation)
dose:	200 mg dipyridamole/25 mg ASA BID over 3 days each
mode of admin.:	p.o.
batch no.:	
Criteria for evaluation:	
Efficacy:	Pharmacokinetics:
	Primary endpoints: %Ae of dipyridamole over the two last treatment days of each treatment
	Secondary endpoints: $\%Ae_{1\text{-}3h}$, $\%Ae_{8\text{-}10h}$, $(\%Ae_{1\text{-}3h}\text{-}\%Ae_{8\text{-}10h}) / \%Ae_{0\text{-}10h}$
Safety:	Adverse events, laboratory tests
Statistical methods:	Two-sided 90 % confidence intervals for test/reference ratios for Ae, descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics:

Pharmacokinetic results are derived from urinary excretion over the last two days for each treatment. Summarized results are shown in Table 2.1.

Table 2. 1: Comparison of pharmacokinetic parameters by treatment (in percent of dose/2 h, parameter $fe_{Ae,d2\&3}$ given in [mg]); low, high and medium represent in-vitro-release of test products, comm is the commercial formulation)

	LOW (N=18)		**HIGH** (N=17)		**MEDIUM** (N=18)		**COMM.** (N=18)	
	gMean	gCV (%)	gMean	gCV (%)	gMean	gCV (%)	gMean	gCV (%)
fe_{max}	1.00	35.2	1.05	28.4	0.965	26.9	1.01	35.8
fe_{min}	0.374	40.2	0.364	46.2	0.373	43.5	0.367	35.9
fe_{avg}	0.631	24.7	0.616	22.8	0.610	25.6	0.615	30.1
$fe_{Ae,d2\&3}$	3.18	22.0	$ 3.17	$ 26.0	3.16	28.3	3.25	26.4
fe_{PTF}	91.5	48.2	102	50.7	91.9	33.4	101	28.8

BI Trial No.: 0009.0163
Source data: Table 15.5.3: 1
$ N=18

Overall urinary excretion of the four treatments was nearly identical. Similar results were observed for all parameters indicating rate of absorption.

Interindividual variability for rate and extent of absorption was within the normal range.

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Statistical evaluation is given in Tables 2.2 and 2.3.

Table 2. 2: Statistical evaluation of primary parameter $fe_{Ae,d2\&3}$ [mg] comparing all test batches to the commercial form.

Test	Ref.	intra-ind. gCV (%)	Point Estim. (Test/Ref.)	Two sided 90 % Confidence Interval	
				Lower Limit	Upper Limit
low	comm.	8.4	0.98	0.93	1.03
medium	comm.	7.7	0.97	0.93	1.02
high	comm.	11.0	0.97	0.91	1.03

BI Trial No.: 0009.0163
Source data: Table 15.5.2.1:1 and 15.5.3:2

Confidence intervals were within the limits for the primary endpoint which indicates bioequivalence of all three test batches versus the commercial formulation.

Table 2. 3: Statistical evaluation of primary parameter $fe_{Ae,d2\&3}$ [mg] comparing the different test batches to each other.

Test	Ref.	intra-ind. gCV (%)	Point Estim. (Test/Ref.)	Two sided 90 % Confidence Interval	
				Lower Limit	Upper Limit
high	low	10.8	0.99	0.93	1.05
high	medium	11.2	1.00	0.94	1.07
low	medium	8.4	1.01	0.96	1.06

BI Trial No.: 0009.0163
Source data: Table 15.5.2.1:1 and 15.5.3:2

Confidence intervals for the primary endpoint were also within the limits for the comparison between the different test batches.

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Safety results:	The run-in phase in this trial reduced incidence and severity of headaches and associated symptoms although even the low starting doses caused headaches of sometimes severe intensity (starting at dose level of 4x25 mg BID). In general incidence and severity decreased with continuation of treatment, no subject discontinued due to headaches. Severe headaches were not observed in the main phase. This indicates that gradual increase of the dose might solve the problem of severe headaches leading to discontinuation in patients who might benefit from treatment.
Conclusions:	As all test treatments were bioequivalent to the commercial product, change of production is feasible. There were no SAEs. The AEs observed did not put subjects' health at risk. The run-in phase reduced incidence and severity of headaches and associated symptoms. It can be concluded that gradual increase of the dose might avoid intolerable headaches.