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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Asasantin ER (Aggrenox)				
Name of active ingredient: Dipyridamole/ASA 200 mg / 25 mg		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 23 December 1999	**Number:** 9.136	**Study period (years):** 1999		

Title of study:	Impact of food on pharmacokinetics and pharmacodynamics of Asasantin extended release (ER) 200/25 mg capsules b.i.d. in a randomized, open, 2-way cross-over study in healthy subjects.
Investigator:	[redacted]
Study center(s):	[redacted] Germany
Publication (reference):	N.A.
Clinical phase:	I
Objectives:	Comparative pharmacokinetics and pharmacodynamics of Asasantin ER at fasted and fed state.
Methodology:	Two way cross-over, randomized, open.
No. of subjects entered: **total:** **each treatment:**	28, females and males 28 28
Diagnosis and main criteria for inclusion:	healthy female and male subjects
Test product: **dose:** **mode of admin.:** **batch no.:**	Asasantin ER (production batch) 200/25 mg Asasantin: b.i.d. from days 1 to 4, one dose on day 5 p.o. at fed state 907569
Duration of treatment:	b.i.d. from day 1 to 4 and a morning dose on day 5 for test and reference therapy
Reference therapy: **dose:** **mode of admin.:** **batch no.:**	Asasantin ER (production batch) 200/25 mg Asasantin: b.i.d. from days 1 to 4, one dose on day 5 p.o. at fasted state 907569
Criteria for evaluation: **Efficacy:**	**Pharmakokinetics**: primary endpoints: AUC_{ss}, $C_{max,ss}$ $C_{max,0\text{-}10h}$ of dipyridamole secondary endpoints: $AUC_{0\text{-}10h}$, $C_{max,ss}$ / AUC_{ss}, $t_{max,ss}$, %PTF, AUC_{fluct}, $t_{½}$ of dipyridamole, AUC_{ss}, $C_{max,ss}$, $C_{max,ss}$ /AUC_{ss} ,$t_{max,ss}$, $t_{½}$ of acetylsalicylic acid and salicylic acid (for ASA only when applicable) **Pharmacodynamics**: primary endpoint: inhibition of cyclo-oxygenase for ASA (analyte TXB_2) secondary endpoint: inhibition of cyclo-oxygenase for ASA (analyte malondialdehyde
Safety:	Pulse rate, systolic and diastolic blood pressure, laboratory, adverse events
Statistical methods:	Descriptive statistics, 90 % confidence intervals for pharmacokinetic and pharmacodynamic parameters.

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SUMMARY - CONCLUSIONS:

Efficacy results: Clinical efficacy was not established in this study.

Pharmacokinetic results: Summarized data for dipyridamole (DP) are given in FIGURE 2: 1 (day 1 only) and TABLE 2: 1, data for acetylsalicylic acid (ASA) and salicylic acid (SA) in FIGURE 2: 2 and TABLE 2: 2.

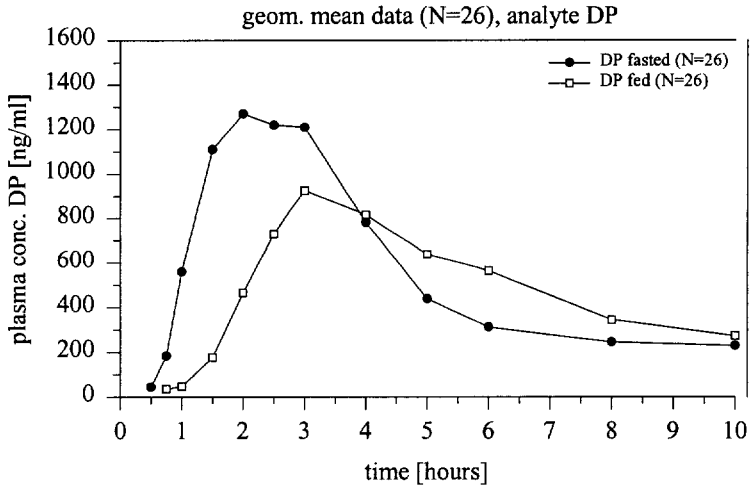

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FIGURE 2: 1 Comparison of geom. mean plasma concentration profiles for analyte DP at day 1 (N = 26). (source: FIGURE 16.3.2: 1)

TABLE 2: 1 Geometric Means and 90 % Confidence Intervals and Point Estimatiors for Pharmacokinetic Parameters; analyte Dipyridamole ($AUC_{ss\ 96\text{-}106\ h}$) (source: TABLES 16.3.2: 7, 8, 17)

IP 9.136 DP parameter	unit	gMean fasted	gMean fed	lower limit	point estimator	upper limit	intra-ind. CV %
$AUC_{0\text{-}10h}$	[ng·h/ml]	5560	4860	0.81	**0.88**	0.95	16.0
$C_{max,0\text{-}10h}$	[ng/ml]	1440	1010	0.64	**0.71**	0.78	21.1
AUC_{ss}	[ng·h/ml]	10800	8350	0.71	**0.77**	0.84	18.5
$C_{max,ss}$	[ng/ml]	1740	1330	0.69	**0.77**	0.85	21.7

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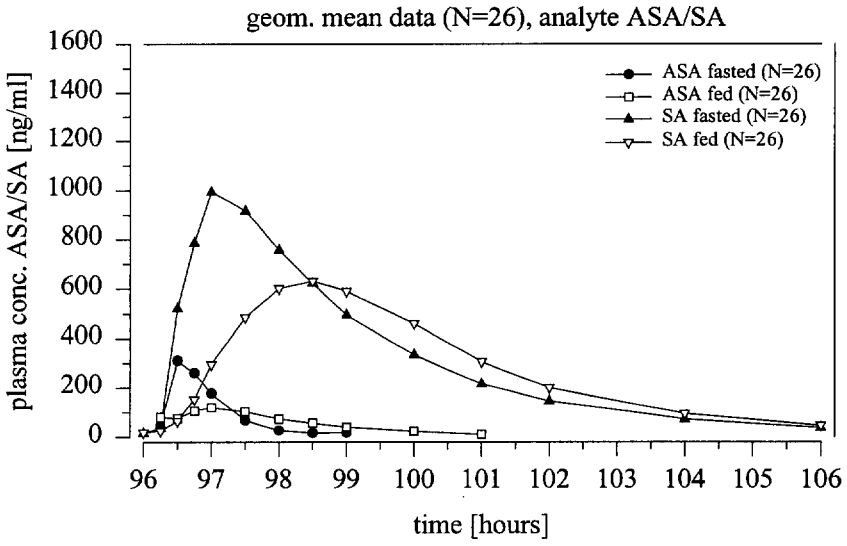

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FIGURE 2: 2 Comparison of geom. mean plasma concentration profiles for analytes ASA and SA at day 5 (N = 26). (source: FIGURE 16.3.2: 3)

TABLE 2: 2 Geometric Means and 90 % Confidence Intervals and Point Estimators for Pharmacokinetic Parameters; analyte Acetylsalicylicacid (calculation of AUC_{ss} individually) (source: TABLES 16.3.2: 9, 10, 18)

IP 9.136 ASA ind.		gMean	gMean	lower	point	upper	intra-ind.
Parameter	**unit**	**fasted**	**fed**	**limit**	**estimator**	**limit**	**CV %**
AUC_{ss}	[ng·h/ml]	292	284	0.90	**0.98**	1.06	17.2
$C_{max,ss}$	[ng/ml]	360	186	0.44	**0.52**	0.61	34.8

IP9_136bb.xls [summary tables]

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TABLE 2: 3 Geometric Means and 90 % Confidence Intervals and Point Estimators of Pharmacokinetic Parameters; analyte Salicylic acid (calculation of $AUC_{ss\ 96\text{-}106\ h}$) (source: TABLES 16.3.2: 13, 14, 20)

IP 9.136 SA parameter	unit	gMean fasted	gMean fed	lower limit	point estimator	upper limit	intra-ind. CV %
AUC_{ss}	[ng·h/ml]	3280	3000	0.85	**0.91**	0.99	16.6
$C_{max,ss}$	[ng/ml]	1140	788	0.62	**0.69**	0.78	25.2

IP9_136bb.xls [summary tables]

The graphs and tables indicate similar extent of absorption and confidence intervals within 0.8 – 1.25 for ASA, SA and dipyridamole on day1 but on day 5 AUC of dipyridamole is lower. Rate of absorption and thus C_{max} is consistently lower for all analytes at fed state.

Pharmacodynamic results:

Asasantin ER (Aggrenox) orally administered b.i.d. produced a sustained and profound inhibition of platelet cyclo-oxygenase. Subjects taking the study drug at fasted state showed a 29.3, 80.1, and 89.4 % inhibition of cyclo-oxygenase (analyte Thromboxane B2) at 4, 47.5 and 52 hours after the 1st intake of the study drug, respectively. At all further sampling times during intake of study drug cyclo-oxygenase inhibition was greater than 90 % (see also FIGURE 2: 3). Pre-dose levels were reached at day 19 which was 14 days after last study drug intake. Subjects taking the study drug with high fat meal showed a 24.8, 79.6 and 90.4 % inhibition of cyclo-oxygenase at 4, 47.5 and 52 hours after the 1st intake of the study drug, respectively. At all further sampling times cyclo-oxygenase inhibition was greater than 90 % and reached pre-dose levels at day 19. Platelet cyclo-oxygenase activity returned to pre-dose levels at day 19 which was 14 days after the last intake of the study drug. The geometric mean of the ratios 'high fat meal'/'fasted state intake' at the experimental times 71:30, 76:00, 95:30 and 100:00 hours after the first intake (steady state inhibition) is 1.0. Point estimator (confidence intervals) for summarized data (mean values of % inhibition for each subject and treatment) on days 4 and 5 were 1.002 (0.989 -1.015) for the primary endpoint inhibition of cyclo-oxygenase, analyte Thromboxane B2 and 0.997 (0.993 - 1.001) for the secondary endpoint inhibition of cyclo-oxygenase, analyte malondialdehyde. This shows that cyclo-oxygenase inhibition is independent of the mode of administration, intake at fasted state or with high fat meal. Measuring platelet cyclo-oxygenase inhibition via arachidonic acid-induced malondialdehyde synthesis seems to be a little bit more sensitive than measuring platelet cyclo-oxygenase inhibition via thromboxane synthesis in collagen (2 µg/ml)-stimulated platelets.

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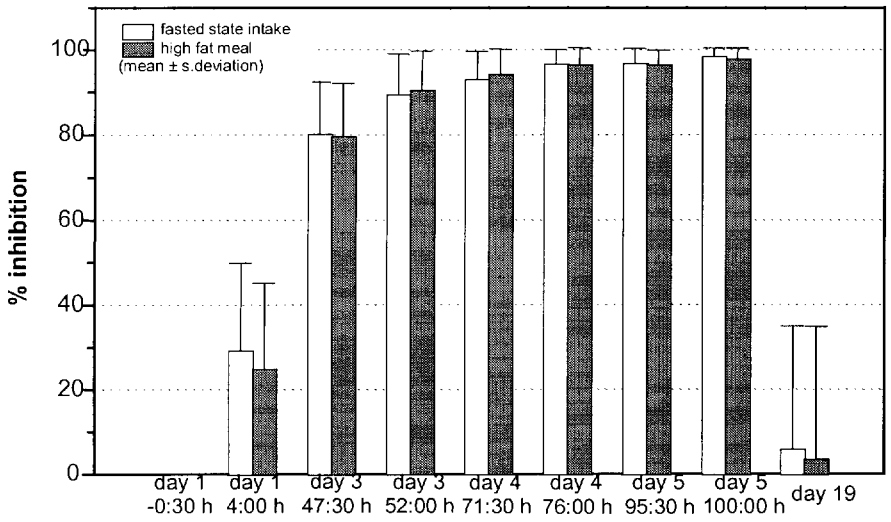

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FIGURE 2: 3 Mean %-cyclo-oxygenase inhibition values of the different treatment groups (analyte TXB_2; source data TABLE 11.4.1.1: 1)

Safety results: The majority of adverse events reported were headaches of mild and/or moderate intensity. One female subject withdrew from the 2nd treatment period due to nausea, vomiting and dizziness. In the first treatment period tolerability was assessed as good in 22 and satisfactory in 6 subjects; in the second treatment period tolerability was good in 25 and satisfactory and bad in one subject each.

Conclusions:

Pharmacokinetics:

Impact of a high fat meal taken immediately before drug intake on pharmacokinetics of ASA (and its main metabolite SA) was negligible with regard to extent of absorption. Due to the irreversible pharmacodynamic action of ASA the slower absorption rate resulting in lower peaks of ASA and SA does not interfere with efficacy as can be concluded from the complete inhibition of cyclo-oxygenase which was observed with both treatment modes.

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With dipyridamole kinetics, the expected lower peaks with intake at fed state were observed. There was no dose dumping at fed state.

The somewhat reduced extent of absorption at day 5 at fed state is probably due to the 4 hour fast with reference treatment.

An impact on efficacy of dipyridamole is unlikely as these extreme conditions with regard to composition of meals and timing are far from normal dietary behaviour. Furthermore trough levels are similar for both modes of administration that means there is no risk of inefficacy with lower trough concentrations. This and the absence of dose-dumping suggests that Aggrenox may reasonably taken by patients as they prefer, either before or with meals. Lack of impact of food can also be concluded from the well established safety and efficacy of the ESPS 2 study which had no limitations with regard to the relationship of food and drug intake.

Pharmacodynamics:

At days 3 to 5 cyclo-oxygenase inhibition was greater than 90 % for drug intake at fed and fasted state. Therefore pharmacodynamic efficacy of ASA at steady state is complete and independent from food intake. Time course is independent from plasma concentrations and thus confirms the irreversible action of ASA.

Safety:

Asasantin ER was well tolerated, with a slightly better tolerance in the second treatment period as compared to the first.