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 Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Aggrenox ®				
Name of active ingredient: Dipyridamole extended release		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 31 March 2001	**Number:**	**Study period (years):** July 2000 – Sept 2001		

Title of study:	Mechanism of dipyridamole action in platelets: in-vivo study with healthy volunteers
Investigator:	[redacted]
Study center(s):	[redacted]
Publication (reference):	In preparation
Clinical phase:	I
Objectives:	Dipyridamole is an established phosphodiesterase inhibitor and in particular for cGMP-specific phosphodiesterase PDE V, which is predominantly localized in platelets, vascular and viscular smooth muscle including corpus cavernosum [1,2]. The combination of low-dose acetylsalicylic acid (25 mg) with dipyridamole (200 mg) in extended release form has been demonstrated to be beneficial in secondary prevention of ischemic stroke [3,4]. These beneficial clinical effects strongly suggest an in-vivo antiplatelet effect which, however, has not been conclusively shown so far. VASP and VASP-phosphorylation have been proven to be involved in platelet inhibition [10-12]. Methods were developed to quantify both parameters which established tools to determine the extent of platelet inhibition in-vitro and in-vivo [5-9]. Recently, our group demonstrated by in-vitro studies that dipyridamole selectively enhances NO/cGMP-signalling cascade at therapeutically relevant concentrations (3.5µM) as measured by the phosphorylation of VASP. Using the methods and experiment conditions established by the previous in-vitro studies [in-vitro report-27.03.2000] we now investigated whether this dipyridamole potentiation of platelet inactivating mechanisms can be demonstrated in platelets obtained from volunteers with - acetylsalicylic acid alone (2 x 25 mg), - dipyridamole extended release (2 x 200 mg), and the - combination of acetylsalicylic acid / dipyridamole ext. release (2 x 25/200 mg)
Methodology:	• VASP-Ser239 / VASP-Ser157-phosphorylation induced by SNP 0.5µM or SNP 0.3µM and PG-E1 3nM (Western Blot) • Plasma level of dipyridamole by HPLC
No. of subjects entered:	15
total:	15
each treatment:	5

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Diagnosis and main criteria for inclusion:	Healthy female and male volunteers of age 20-50 years
Test product:	Dipyridamole extended release + ASA
dose:	Dipyridamole 200mg extended release plus Acetylsalicylic Acid 25mg
mode of admin.:	Per oral b.i.d. (at 8 and 18h) for 7 days
batch no.:	
Duration of treatment:	7 days
Reference therapy:	Dipyridamole extended release; Acetylsalicylic Acid
dose:	Dipyridamole 200mg extended release; Acetylsalicylic Acid 25mg
mode of admin.:	Per oral b.i.d. (at 8 and 18h) for 7 days
Criteria for evaluation:	VASP phosphorylation at serine 239 and serine 157
Efficacy:	Platelet inactivation
Safety:	adverse events assessed
Statistical methods:	Two-way-ANOVA

SUMMARY - CONCLUSIONS:

Efficacy results:

- 3-5.5-fold potentiation of VASP-Ser239 and VASP-Ser157-phosphorylation by dipyridamole 3 h after the first intake of DP ext.rel. + ASA or DP ext.rel.
- 2.5-4-fold potentiation of platelet VASP-Ser239-phosphorylation during steady-state of DP ext.rel. + ASA, DP ext.rel. and Acetylsalicylic Acid treated subjects
- 4-6-fold potentiation of platelet VASP-Ser239-phosphorylation 44 h after the last intake of DP ext.rel. + ASA, DP ext.rel. and Acetylsalicylic Acid
- Dipyridamole was detected in DP ext.rel. + ASA and DP ext.rel. treated subjects, however no correlation could be drawn between kinetics and VASP-phosphorylation.

Safety results: No serious adverse events were observed. Minor events were mainly headaches.

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Conclusions:

In the present study we could demonstrate for the first time that in-vivo dipyridamole treatment selectively enhances the NO/cGMP-signalling cascade analyzed ex-vivo. This agrees with our previous in-vitro findings. Surprisingly, the NO/cGMP-signalling cascade has been sensitized by acetylsalicylic acid treatment, which could represent an additional explanation for the benefit of aspirin in the prevention of chronic cardiovascular diseases. However, the biochemical mechanism underlying this observation needs further investigation. Our present data strongly support the concept that the enhancement of NO/cGMP signalling in vivo, most likely mediated by the PDE V, is an important component of the in-vivo mechanism of dipyridamole action.