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®				
Name of active ingredient: Dipyridamole / Acetylsalicylic Acid		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 14 September 2001	**Number:** U01-3042	**Study period (years):** 30 August 1999 to 23 September 1999		

Title of study:	Pharmacokinetics and safety of Asasantin extended release (RAD-SP) 200/25 mg capsules b.i.d. in randomised, double-blind, placebo-controlled study in Japanese healthy male volunteers
Investigator:	[redacted]
Study centre:	[redacted] Japan
Publication (reference):	Not yet published
Clinical phase:	I
Objectives:	Pharmacokinetics, pharmacodynamics and safety
Methodology:	Randomised, placebo-controlled, double blind
No. of subjects entered:	
total:	32
each treatment:	Asasantin® (RAD-SP): 24, Placebo: 8
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 20 - 35 years, body weight 50 - 80 kg, Broca-index: ± 20 %
Test product:	RAD-SP capsule
dose:	200/25 mg Asasantin® (DP/ASA) b.i.d. from Days 1 to 4, and one dose on Day 5
mode of admin.:	p.o.
batch no.:	99003
Duration of treatment:	5 days (b.i.d. from Days 1 to 4, and a morning dose on Day 5)
Reference therapy:	Matching placebo
dose:	not applicable
mode of admin.:	p.o.
batch no.:	99014

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Criteria for evaluation:

Efficacy:	Not applicable
Pharmacokinetics:	AUC_{ss}, $C_{max,ss}$, $C_{max,ss}/AUC_{ss}$, $C_{min,ss}$, t_{max}, $t_{1/2}$, MRT, %PTF
Pharmacodynamics:	Platelet parameter (platelet adenosine uptake inhibition rate, malondialdehyde production inhibition rate, thromboxane B_2 production inhibtion rate)
Safety:	Adverse events, vital signs, laboratory tests
Statistical methods:	Descriptive statistics

SUMMARY - CONCLUSIONS:

Pharmacokinetic results:
The Japanese plasma concentration profiles of DP, ASA and SA were higher than those of Caucasians in the trial 9.123 [U98-2379]. $AUC_{ss,t}$ and $C_{max,ss}$ of Japanese were slightly higher than those of Caucasians. It seemed to be due to the difference of body size, Japanese weight was 59.6 ± 8.2 kg (mean ± S.D.) and Caucasian weight was 76.8 ± 7.2 kg. Therefore, $AUC_{ss,t}$ and $C_{max,ss}$ were normalized to 70 kg weight and compared the normalized values between Japanese and Caucasians. The mean differences of each parameter were within ±20% against the corresponding mean values in Caucasians, and the 90% confidence intervals of both populations were overlapped each other.
These data indicate that there was no remarkable difference between Japanese and Caucasians when body weight was taken into account.

Pharmacokinetics/pharmacodynamics results:
Adenosine uptake inhibition rate (AUI)
In vitro
The Hill factor and IC_{50} were 1.06 and 164 ng/mL, respectively. The sigmoid E_{max} model described the good AUI – DP concentration relationship. This result was similar compared to that of Caucasians. These results showed that there was no racial difference in the response to DP between Japanese and Caucasian platelet.
Ex vivo
There was the good relationship between AUI and plasma concentration of DP *ex vivo*. The Hill factor and IC_{50} were 0.92 and 75.4 ng/mL, respectively.
Mean AUI at trough and at peak at steady state were 88.0 and 93.2%. The time-AUI profile at steady state was simulated using the sigmoid E_{max} model obtained above and the plasma concentration data of DP on Day 5. At steady state, mean AUI was over 80% at each time point during dosing interval on Day 5, and even the minimum value was over 69%.

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SUMMARY - CONCLUSIONS: (continued)

Malondialdehyde (MDA) production inhibition rate
The inhibition rates of MDA production of all samples were 100% before and at 2 hr after administration, excepting for one case.
Thromboxane B_2 (TXB_2) production inhibtion rate
The mean inhibition rate of TXB_2 was 94.9% before administration and 98.4% at 2 hr after administration.

The PK/PD analysis using surrogate markers indicated that the sufficient effect could be expected and sustained during dosing intervals at steady state after administration of RAD-SP capsule in Japanese as well as Caucasians.

Safety results:
Adverse events were reported by 95.8 % (23/24) and 25.0 % (2/8) of subjects in the RAD-SP group and the Placebo group, respectively. Significant reported adverse events consisted of headache (23/24, 95.8 %), nausea (15/24, 62.5 %) and vomiting (11/24, 45.8 %).
Five subjects were withdrawn due to headache, nausea and vomiting, which were only observed in the RAD-SP group. All of them fully recovered rapidly after discontinuation. These subjects discontinued the medication early (Day 1 or Day 2) in the trial. As to headache, which was the most significant adverse events, the reported symptom were mostly mild or moderate and transient. The cumulative products of intensity and duration were largest on Day 2 and diminished during the following days. Generally, since headache mainly occurred during the beginning of the treatment and disappeared late, it can be speculated that headache severity improves with time of treatment. Similar tendency was seen in the Caucasian healthy volunteer study (Trial No. 9.123).
There were no drug-related abnormal changes in laboratory measurement, vital signs and ECG finding throughout this study.

Conclusions:
It is confirmed that the results of pharmacokinetics and pharmacodynamics of RAD-SP capsules in this study are similar to those reported in Caucasian healthy volunteers (Trial No. 9.123).
Though the incidence of significant adverse events such as headache, nausea and vomiting in this study were slightly higher than that in Caucasians, it was concluded that there was no significant difference between the safety profile in Japanese healthy subjects and that in Caucasians from viewpoint of type, severity and course of adverse events.