# 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:** 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:** November 28, 2000 | **Number:** | **Study period (years):** 04/00 - 05/00 | | |

| | |
|---|---|
| **Title of study:** | Comparison of pharmacokinetics of dipyridamole in Asasantin extended release (ER) 200/25 mg capsules bid and in a combination of Persantin immediate release tablets (100 mg qid) and ASA tablets (25 mg bid) in an open, randomized, 2-way crossover study in healthy subjects. |
| **Investigator:** | [redacted] |
| **Study center (s):** | [redacted] Germany |
| **Publication (reference):** | Not applicable |
| **Clinical phase:** | I |
| **Objectives:** | Comparative pharmacokinetics of Asasantin ER and of immediate release Persantin tablets combined with ASA tablets |
| **Methodology:** | Two way crossover, randomized, open |
| **No. of subjects entered:** | |
| **total:** | 20 |
| **each treatment:** | 20 |
| **Diagnosis and main criteria for inclusion:** | Healthy female and male subjects of 18 - 55 years old, Broca Index ≥-20%, ≤+20% |
| **Test Product:** | Asasantin ER (production batch) |
| **dose:** | 200/25 mg Asasantin bid |
| **mode of admin.:** | p.o. |
| **batch no.:** | 006357 |
| **Duration of treatment:** | bid from day 1 to 4 and a morning dose on day 5 |
| **Reference therapy 1:** | Persantin + ASA immediate release tablets |
| **dose:** | 100 mg Persantin qid from days 1 to 4, two doses on day 5<br>25 mg ASA bid from days 1 to 4, one dose on day 5 |
| **mode of admin.:** | p.o. |
| **batch no.:** | 854624, 006806 |

| | | | | |
|---|---|---|---|---|
| **Name of company:** Boehringer Ingelheim Pharma KG | | **Tabulated Study Report** | | **(For National Authority Use only)** |
| **Name of finished product:** Asasantin ER (Aggrenox) | | **SUPPLEMENTARY SHEET** | | |
| **Name of active ingredient:** Dipyridamole/ASA 200 mg/25 mg | | **Page:** | **Number:** | |
| **Ref. to Documentation:** | **Volume:** | **Page:** | **To:** | **Addendum No.:** |
| **Report date:** November 28, 2000 | **Number:** | **Study period (years):** 04/00 - 05/00 | | |

**Criteria for evaluation:**

**Efficacy:** Pharmacokinetics

Primary endpoints: $AUC_{ss}$, %PTF of dipyridamole

Secondary endpoints: $C_{max,ss}$ / $AUC_{ss}$, $C_{max,ss}$, $T_{max,ss}$, $AUC_{fluct}$, $t_{½}$, Ae% of dipyridamole (dp), its glucuronide (dp-gluc) and of salicylic acid

**Safety:** Laboratory, adverse events

**Statistical methods:** Descriptive statistics, 90% confidence intervals

**SUMMARY CONCLUSIONS:**

**Efficacy results:** Not applicable.

**Pharmacokinetic results:**

Summarized pharmacokinetic results of primary parameters are shown in Table 2: 1, point estimators and confidence intervals for primary and secondary parameters derived from plasma concentrations in TABLE 2: 2, point estimators and confidence intervals for secondary parameters derived from urinary excretion in TABLE 2: 3. FIGURE 2: 1 displays geometric means of both treatments.

TABLE 2: 1 Short summary statistics of primary PK parameters (source TABLES 14.4: 3 and 14.4: 4)

| primary PK parameters | Aggrenox $AUC_{ss}$ [ng·h/mL] | tablet $AUC_{ss}$ [ng·h/mL] | Aggrenox PTF (%) | tablet PTF (%) |
|---|---|---|---|---|
| N | 19 | 19 | 19 | 19 |
| gMean | 12600 | 12600 | 151 | 178 |
| gCV (%) | 27.6 | 30.0 | 27.5 | 27.0 |

bb\persantin\9_138\bb_b1537.xls[tables]

| | | | | |
|---|---|---|---|---|
| **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:** November 28, 2000 | **Number:** | **Study period (years):** 04/00 - 05/00 | | |

TABLE 2: 2 Test/reference ratios, 90 % confidence intervals and intra-individual CV (%) of primary and secondary PK parameters derived from SAS procedure ANOVA
(source TABLES 14.4: 6 and 14.4: 7)

| parameter | lower limit | point estimator | upper limit | intra-ind. CV% |
|---|---|---|---|---|
| $AUC_{ss}$ | 0.91 | 1.00 | 1.11 | 17.2 |
| PTF | 0.73 | 0.85 | 0.98 | 26.5 |
| $C_{max,ss}$ | 0.84 | 0.92 | 1.02 | 17.3 |
| $C_{min,ss}$ | 1.01 | 1.23 | 1.49 | 35.7 |
| $C_{max,ss}/AUC_{ss}$ | 0.85 | 0.92 | 1.00 | 14.4 |
| $AUC_{fluc,ss}$ | 0.84 | 0.99 | 1.15 | 28.1 |
| $t_{½}$ | 0.84 | 0.96 | 1.09 | 23.3 |

bb\persantin\9_138\bb_b1537.xls[sas_results]

TABLE 2: 3 Test/reference ratios, 90 % confidence intervals and intra-individual CV (%) of parameter Ae (% of dose) derived from SAS procedure ANOVA (source TABLE 14.4: 10)

| parameter | analyte | lower limit | point estim. | upper limit | intra-ind. CV (%) |
|---|---|---|---|---|---|
| $A_e$ (% of dose) | RA-8 | 0.89 | 1.05 | 1.23 | 27.7 |
| $A_e$ (% of dose) | RA-8 gluc | 0.93 | 1.06 | 1.21 | 23.7 |
| $A_e$ (% of dose) | SA | 0.92 | 1.00 | 1.09 | 13.4 |
| $A_e$ (% of dose) | HHA | 0.90 | 0.99 | 1.09 | 17.1 |

bb\persantin\9_138\bb_b1537_urine.xls[sas]

| | | | | |
|---|---|---|---|---|
| **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:** November 28, 2000 | **Number:** | **Study period (years):** 04/00 - 05/00 | | |

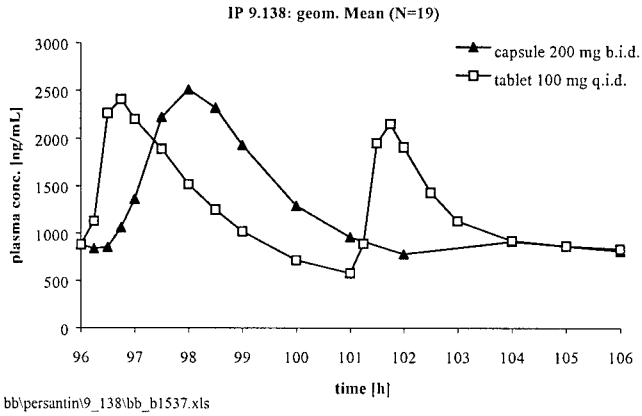


FIGURE 2: 1 Geometric means of analyte dipyridamole at steady-state interval (96 - 106 h) after administration of Asasantin extended release (ER) 200/25 mg capsules bid and Persantin tablets 2 • 50 mg qid (N = 19) (source TABLES 14.4: 1 and 14.4:2)

The results indicate clearly that pharmacokinetics of the dipyridamole component of Aggrenox given bid compared to tablets given qid is bioequivalent with regard to extent of absorption and superior with regard to rate and maintenance of absorption as peak trough fluctuation is reduced and trough concentrations are higher. Therefore, the extended release properties of Aggrenox could be confirmed. Urinary excretion showed bioequivalence with regard to extent of absorption for dipyridamole as well as acetylsalicylic acid.

**Safety results:**
Headache was the most frequently reported adverse event in this trial (3 subjects during Asasantin bid, 6 subjects during Persantin qid plus ASA bid and 1 subject in both treatment periods); it was considered study drug related in all but one cases. Gastrointestinal symptoms as abdominal pain, nausea, were reported from 6 subjects, of mild to moderate intensity and are considered study drug related. Constipation, diarrhea, heartburn, appetite loss, dyspepsia, retching and vomiting, paraesthesia, hot flushes, herpes simplex, somnolence, toothache, shivering, and dizziness occurred in 1 subject each. All those adverse events were of mild to severe intensity and were considered study drug related. except for herpes simplex, toothache and constipation.

**Conclusions:**
The safety profile of multiple oral doses of 400 mg dipyridamole plus 50 mg ASA per day given as Asasantin bid or Persantin qid plus ASA bid over 5 days was satisfactory. Tolerance in the second treatment period was slightly better than during first period. This is probably due to the stress conditions of the subjects during the study. In the second trial period subjects were already used to the trial conditions.