Clinical Study Synopsis for Public Disclosure

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### Name of company:
Boehringer Ingelheim

### Name of finished product:

### Name of active ingredient:
Dabigatran etexilate

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<tr>
<th>Report date:</th>
<th>Number:</th>
<th>Study period (dates):</th>
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<tr>
<td>06 JUL 2004</td>
<td>U04-1459-01</td>
<td>7 Aug - 26 Sep 2003</td>
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### Title of study:
Bioavailability of BIBR 953 ZW after 150 mg of BIBR 1048 (oral pro-drug of BIBR 953 ZW) administered as HPMC capsule relative to a gelatine capsule, and bioavailability of the HPMC capsule under the influence of food in healthy subjects. A three-way crossover, randomised, open trial

### Investigator:

### Study centre:
Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach

### Publication (reference):
-

### Clinical phase:
I

### Objectives:
To investigate the relative bioavailability of BIBR 953 ZW after administration of a 150 mg BIBR 1048 HPMC capsule versus BIBR 953 ZW after administration of a 150 mg BIBR 1048 gelatine capsule, and to investigate the relative bioavailability of BIBR 953 ZW given as BIBR 1048 MS HPMC capsule with food versus without food

### Methodology:
Treatment with 150 mg BIBR 1048 HPMC capsule 1.5 hours before and immediately after breakfast and 150 mg BIBR 1048 gelatine capsule 1.5 hours before breakfast was assessed in an open-label, randomised three-way crossover trial

### No. of subjects:
- planned: 12
- actual: 12

### Diagnosis and main criteria for inclusion:
Healthy male subjects, age \( \geq 18 \) to \( \leq 55 \) years, BMI \( \geq 18.5 \) and \( \leq 29.9 \) kg/m\(^2\)

### Test product:
BIBR 1048 MS HPMC capsule

#### dose:
150 mg

#### mode of admin.:
p.o.

#### batch no.:
9030066

### Duration of treatment:
3 x 1 day

### Reference therapy:
BIBR 1048 MS gelatine capsule
**Name of company:**
Boehringer Ingelheim

**Name of finished product:**
SUPPLEMENTARY SHEET

**Name of active ingredient:**
Dabigatran etexilate

**Ref. to Documentation:**
Volume: I
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**Report date:**
06 JUL 2004

**Study period (dates):**
7 Aug - 26 Sep 2003

**Date of Revision:**
01 SEP 2005

**dose:**
150 mg

**mode of admin.:**
p.o.

**batch no.:**
9030042

**Criteria for evaluation:**

**Efficacy:**
Primary variables: AUC\textsubscript{0-\infty} and AUC\textsubscript{0-tz}, C\textsubscript{\text{max}}, t\textsubscript{\text{max}}
Secondary variables: MRT, CL/F, t\textsubscript{1/2}, Vz/F

**Safety:**
ECG, systolic and diastolic blood pressure, routine lab., adverse events

**Statistical methods:**
Descriptive statistics, test/reference ratios and 90 % confidence intervals
SUMMARY – CONCLUSIONS:

The bioavailabilities of BIBR 953 ZW after oral administration of 150 mg BIBR 1048 either as gelatine capsule or HPMC capsule were similar. The AUC_{0-\infty} of BIBR 953 ZW of the HPMC capsule was on average 9% lower than the AUC_{0-\infty} observed with the gelatine capsule. The wide 90% confidence intervals of the AUC_{0-\infty} treatment ratios of 64% - 130% indicated high intraindividual variability. The average 9% decrease of AUC_{0-\infty} for the HPMC capsule was not considered clinically relevant. Test/reference ratios of AUC_{0-\infty} and C_{max} and their 90% confidence intervals are shown in the table below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference</th>
<th>Test</th>
<th>Point estimator</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-\infty}</td>
<td>Gelatine caps. fasted</td>
<td>HPMC caps. fasted</td>
<td>91.0</td>
<td>63.59</td>
<td>130.36</td>
</tr>
<tr>
<td>C_{max}</td>
<td>Gelatine caps. fasted</td>
<td>HPMC caps. fasted</td>
<td>94.6</td>
<td>62.11</td>
<td>144.17</td>
</tr>
</tbody>
</table>

Upon administration of the BIBR 1048 HPMC capsules together with a high fat, high caloric breakfast, the average AUC_{0-\infty} of BIBR 953 ZW increased by 27%. The test(fed)/reference(fasted) ratios and 90% confidence intervals are shown in the table below:

<table>
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<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-\infty}</td>
<td>HPMC caps. fasted</td>
<td>HPMC caps. fed</td>
<td>127.4</td>
<td>99.96</td>
<td>162.35</td>
</tr>
<tr>
<td>C_{max}</td>
<td>HPMC caps. fasted</td>
<td>HPMC caps. fed</td>
<td>108.5</td>
<td>75.95</td>
<td>154.87</td>
</tr>
</tbody>
</table>

The interindividual variability of AUC_{0-\infty} in the fasted state was 51% gCV compared to 32% gCV in the fed state.
# Safety results:
In this study no serious adverse events and no deaths occurred. In total, 8 subjects experienced adverse events during the study. During screening, 1 subject reported headache. During washout after period 1 or 2, 2 subjects reported influenza or flu like symptoms. During the treatment periods, 6 subjects reported adverse events (headache n=3, dyspepsia n=2, vomiting n=1, epistaxis n=1). One subject reported pharyngolaryngeal pain at post-examination. All adverse events had fully recovered after the end of the study.

# Conclusions:
Repeated single administrations of 150 mg BIBR 1048 given as gelatine or HPMC capsule were well tolerated. The HPMC capsule formulation of BIBR 1048 MS is considered suitable for use in Phase III clinical trials.