Boehringer Ingelheim

# 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**.

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| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:**<br>Not applicable | | **EudraCT No.:**<br>2012-005518-20 | |
| **Name of active ingredient:**<br>Faldaprevir (BI 201335 NA) | | **Page:**<br>1 of 6 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:**<br>23 JUL 2013 | **Trial No. / U No.:**<br>1220.61 /<br>U13-1365-01 | **Dates of trial:**<br>21 FEB 2013 – 27 MAY 2013 | **Date of revision:**<br>Not applicable |



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| **Title of trial:** | Investigation of interactions between faldaprevir, itraconazole, atorvastatin and rosuvastatin in healthy male and female subjects (open-label, fixed-sequence) |
| **Principal Investigator:** | [redacted] |
| **Trial site:** | Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine/Human Pharmacology Centre, Binger Str. 173, Ingelheim/Rhein, Germany |
| **Publication (reference):** | Data from this trial have not been published. |
| **Clinical phase:** | I |
| **Objectives:** | The objective of the itraconazole part of the trial (part 1), described in this clinical trial report, was to investigate the effect of multiple doses of itraconazole on the pharmacokinetics of steady state faldaprevir (BI 201335), in order to assess to which extent the pharmacokinetics of faldaprevir are influenced by co-administration of a drug that inhibits CYP3A4 and P-gp.<br><br>The objective of the statins part of the trial (part 2), described in a separate report [U13-1366-01], was to investigate the effect of steady state faldaprevir on the pharmacokinetics of single-dose atorvastatin as well as on the pharmacokinetics of single-dose rosuvastatin.<br><br>Please note that only the subjects, methods, treatments, and data of the itraconazole part of trial 1220.61 are described in this clinical trial report. Subjects, methods, treatments, and data of the statins part of trial 1220.61 are described in a separate report [U13-1366-01]. |
| **Methodology:** | The itraconazole part of this study was done open-label with a fixed-sequence, 2-period design (treatment A followed by treatment B). |

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| **No. of subjects:** | |
| **planned:** | entered: 18 subjects in the itraconazole part of this trial |
| **actual:** | entered: 18 subjects in the itraconazole part of this trial<br><br>Treatment A (faldaprevir alone):<br>entered and treated: 18 subjects<br>analysed (for primary endpoint): 17 subjects<br>Treatment B (faldaprevir + itraconazole):<br>entered and treated: 17 subjects<br>analysed (for primary endpoint): 17 subjects |
| **Diagnosis and main criteria for inclusion:** | Healthy male and female subjects in the age range of 18 to 50 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m$^2$ were included. |
| **Trial product 1:** | Faldaprevir, 120 mg soft gelatine capsules |
| **dose:** | Treatment A: 120 mg once daily with a 120 mg twice daily loading dose on Day -5<br>Treatment B: 120 mg once daily<br><br>(This faldaprevir dosing scheme is according to Protocol Amendment 1, dated 29 Jan 2013, which changed the originally planned '240 mg once daily with a loading dose of 480 mg' for faldaprevir into '120 mg once daily with a loading dose of 240 mg' in the itraconazole part of this trial.) |
| **mode of admin.:** | Oral administration with 240 mL water |
| **batch no.:** | B113000194 |
| **Trial product 2:** | Itraconazole (Sempera®), 100 mg capsules |
| **dose:** | Treatment B: 200 mg once daily with a 200 mg twice daily loading dose on Day -3<br><br>(This itraconazole dosing scheme is according to Protocol Amendment 1, dated 29 Jan 2013, which changed the originally planned '200 mg twice daily' for itraconazole into '200 mg once daily with a loading dose of 200 mg twice daily'.) |
| **mode of admin.:** | Oral administration with 240 mL water |
| **batch no.:** | CDL5C00 |

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| **Duration of treatment:** | *Treatment A (Reference):* | Faldaprevir (120 mg) was given twice daily on Day -5 and once daily from Day -4 to Day 1 (6 days in total). |
| | *Treatment B (Test):* | Faldaprevir (120 mg) was given once daily from Day -3 to Day 1 (4 days). In addition, itraconazole (200 mg) was given twice daily on Day -3 and once daily from Day -2 to Day 1 (4 days in total). |
| | Treatment A directly preceded treatment B, without an intermittent washout period. | |
| **Criteria for evaluation:** | | |
| **Clinical pharmacology:** | The following pharmacokinetic parameters were analysed as primary endpoints: $AUC_{\tau,ss}$ and $C_{max,ss}$ of faldaprevir. | |
| | In addition, other endpoints were calculated as appropriate. | |
| **Safety:** | Safety and tolerability were determined based on monitoring of adverse events, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), safety laboratory tests, and physical examination. | |
| **Statistical methods:** | Relative bioavailability was estimated based on the ratios (test to reference treatment) of the geometric means (gMeans) of the primary endpoints. Additionally, their 2-sided 90% confidence intervals (CIs) were provided. The statistical model used was an analysis of variance (ANOVA) on the logarithmic scale, including effects for 'subject' and 'treatment'. The 2-sided 90% CIs were calculated based on the t-distribution. | |
| | Descriptive statistics were calculated for all endpoints. | |

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**SUMMARY – CONCLUSIONS:**

**Clinical pharmacology results:**

In the itraconazole part of this trial, 18 subjects received trial medication and 17 subjects completed the trial according to the clinical trial protocol. The trial population consisted of healthy white male (55.6%) and female (44.4%) subjects. The mean age was 39.8 years, ranging from 23 to 50 years, and the mean BMI was 23.8 kg/m$^2$, ranging from 19.5 to 29.5 kg/m$^2$.

Pharmacokinetic parameters of faldaprevir after multiple oral administrations of faldaprevir without and with multiple doses of itraconazole are listed in Table 1. Compared with the administration of faldaprevir alone (reference treatment), co-administration with itraconazole (test treatment) resulted in increased exposure to faldaprevir.

Table 1 Pharmacokinetic parameters of faldaprevir after multiple oral once daily administrations of 120 mg faldaprevir alone or together with multiple oral once daily administrations of 200 mg itraconazole

| | Faldaprevir alone (reference) (N=17) | | Faldaprevir + itraconazole (test) (N=17) | |
|---|---|---|---|---|
| | gMean | gCV [%] | gMean | gCV [%] |
| $AUC_{\tau,ss}$ [ng·h/mL] | 29 900 | 62.8 | 59 500 | 53.8 |
| $C_{max,ss}$ [ng/mL] | 2 780 | 61.0 | 5 030 | 49.1 |

Statistical comparison of primary endpoints ($AUC_{\tau,ss}$ and $C_{max,ss}$ of faldaprevir) for the treatments showed that bioavailability of faldaprevir was higher when itraconazole was administered concomitantly than when faldaprevir was administered alone. The lower limit of the corresponding 90% CIs were well above 100% for both parameters (see Table 2).

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Table 2 Analysis of relative bioavailability of faldaprevir after multiple oral administration of faldaprevir alone or co-administration with mulitple doses of itraconazole

| Pharmacokinetic parameter | Adjusted gMean ratio of test to reference treatment[1] [%][1] | 90% CI of gMean ratio | | Intra-individual gCV [%] |
|---|---|---|---|---|
| | | Lower limit [%] | Upper limit [%] | |
| $AUC_{\tau,ss}$ | 198.6 | 182.4 | 216.1 | 14.2 |
| $C_{max,ss}$ | 180.6 | 165.7 | 196.9 | 14.5 |

[1] For the calculation of the adjusted gMean, the data of 17 subjects were used.

**Safety results:**

Seventeen of the 18 entered subjects received each a total dose of 1320 mg faldaprevir and 1000 mg itraconazole over the course of the trial, as planned. The remaining subject received a total of 360 mg faldaprevir and no itraconazole, before withdrawing his consent due to personal reasons.

A total of 13 out of the 18 subjects (72.2%) reported at least 1 adverse event during the treatment periods ('faldaprevir alone' and 'faldaprevir + itraconazole'). The most frequently reported on-treatment adverse events overall at the system organ class (SOC) level were 'nervous system disorders' (11 out of 18 subjects, 61.1%), followed by 'general disorders and administration site conditions (6 out of 18 subjects, 33.3%). The most frequent adverse event by preferred term was headache (10 out of 18 subjects, 55.6%). Fatigue was reported by 6 out of 18 subjects (33.3%), while all other adverse events were each reported by 2 subjects (11.1%) or less. All cases of adverse events classified as 'nervous system disorders' (10 cases of headache and 2 cases of dizziness) and all cases classified as 'general disorders and administration site conditions' (6 cases of fatigue) were reported during the treatment with faldaprevir alone (first treatment period), while no adverse events were reported in those SOCs during the combined treatment (second treatment period). Consequently, the overall frequency of adverse events was higher during the treatment period 'faldaprevir alone' (with 13 out of 18 subjects, 72.2%) than during the treatment period 'faldaprevir + itraconazole' (with 3 out of 17 subjects, 17.6%).

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| **Safety results (continued):** | The investigator classified adverse events in 12 subjects (66.7%) as possibly related to the trial medication. Due to the higher overall frequency of reported adverse events in the treatment period 'faldaprevir alone', the majority of the drug-related adverse events (10 cases of headache, 6 cases of fatigue, 2 cases each of dizziness and nausea, and 1 case each of ocular icterus, abdominal pain, diarrhoea, and vomiting) were reported under treatment with faldaprevir alone, compared with only a few (1 case each of dry mouth, nausea, and dry skin) under the combined treatment ('faldaprevir + itraconazole'). All other adverse events were judged as not drug-related. No death, no other serious or severe adverse events, no protocol-specified significant adverse events (no hepatic injury), no other significant adverse events (according to ICH E3), and no adverse events leading to discontinuation of trial drug occurred in the itraconazole part of the trial.<br><br>No increase from baseline to last value on treatment was observed for mean values of the liver enzymes AST/GOT, ALT/GPT, or GGT/γ-GT. Reversible increases of bilirubin were observed in a majority of all subjects, but were not considered clinically relevant as this is a known effect of faldaprevir treatment. Overall, no relevant changes in laboratory parameters were observed and there were no findings with respect to ECG recordings, physical examinations, and vital sign measurements. |
| **Conclusions:** | Co-administration with itraconazole, a strong CYP3A4 inhibitor and P-gp inhibitor, resulted in an approximately 2-fold increase in faldaprevir steady state exposure following administration of multiple oral doses of faldaprevir in the presence of multiple doses of itraconazole compared with administration of multiple oral doses of faldaprevir alone. The adjusted gMean test/reference ratios for $AUC_{\tau,ss}$ and $C_{max,ss}$ were 198.6% and 180.6%, respectively.<br><br>Administration of faldaprevir alone or in combination with itraconazole was generally safe and well tolerated by the healthy male and female subjects in this part of the trial. |