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**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-004872-21	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 JUL 2013	**Trial No. / U No.:** 1220.65 / U13-1885-01	**Dates of trial:** 07 FEB 2013 – 15 MAR 2013	**Date of revision:** Not applicable

Title of trial:	Investigation of faldaprevir effect on steady state pharmacokinetics of raltegravir in healthy male and female volunteers (an open-label trial with two periods in a fixed sequence)
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data from this study have not been published.
Clinical phase:	I
Objectives:	The main objective was to investigate the effect of faldaprevir on the steady state pharmacokinetics of raltegravir. An additional objective was to assess the safety and tolerability of faldaprevir coadministered with raltegravir.
Methodology:	This was an open-label, 2-period, fixed-sequence study in healthy volunteers.
No. of subjects:	
planned:	entered: 24
actual:	entered: 25 Treatment A: raltegravir alone treated: 24 analysed (for primary endpoints): 24 Treatment B: raltegravir and faldaprevir treated: 23 analysed (for primary endpoints): 23
Diagnosis and main criteria for inclusion:	Healthy male and female subjects at the age of 18 to 50 years with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included in the study.
Test product 1:	Faldaprevir soft gelatin capsules
dose:	240 mg once daily given as two 120 mg capsules (loading dose of 240 mg twice daily on Day 1 of Treatment B)
mode of admin.:	Oral with 240 mL of water (fed conditions, fasted on Day 6 of Treatment B)
batch no.:	B113000194

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-004872-21	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 2 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 JUL 2013	**Trial No. / U No.:** 1220.65 / U13-1885-01	**Dates of trial:** 07 FEB 2013 – 15 MAR 2013	**Date of revision:** Not applicable

Test product 2:	Raltegravir coated tablets (Isentress® 400 mg Filmtabletten)
dose:	400 mg twice daily
mode of admin.:	Oral with 240 mL of water (fed conditions, fasted on Day 4 of Treatment A and Day 6 of Treatment B)
batch no.:	H015797 (MSD Sharp & Dohme GmbH, commercial product)
Duration of treatment:	Treatment A: Days 1 to 3: 400 mg raltegravir twice daily Day 4: 400 mg raltegravir once daily Treatment B: Day 1: 400 mg raltegravir twice daily and 240 mg faldaprevir twice daily (loading dose) Days 2 to 5: 400 mg raltegravir twice daily and 240 mg faldaprevir once daily Day 6: 400 mg raltegravir once daily and 240 mg faldaprevir once daily Treatments A and B were separated by a washout period of at least 7 days.
Criteria for evaluation:	
Pharmacokinetics:	Primary endpoints: $AUC_{\tau,ss}$ and $C_{max,ss}$ of raltegravir Other endpoints: further pharmacokinetic parameters of raltegravir, raltegravir-glucuronide, and faldaprevir
Safety:	Adverse events (AEs), clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse rate), and physical examination (occurrence of findings)
Statistical methods:	For the primary analyses, point estimates for the intrasubject ratio of the geometric means (for treatments Test and Reference) of the primary endpoints and their 2-sided 90% confidence intervals (CI) were calculated. Raltegravir coadministered with faldaprevir was the Test treatment and raltegravir given alone was the Reference treatment. The statistical model was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'subject' and 'treatment'. For the secondary analyses, descriptive statistics and tabular and graphical displays were used to summarise and evaluate the other endpoints.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-004872-21	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 3 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 JUL 2013	**Trial No. / U No.:** 1220.65 / U13-1885-01	**Dates of trial:** 07 FEB 2013 – 15 MAR 2013	**Date of revision:** Not applicable

SUMMARY – CONCLUSIONS:

Pharmacokinetics:

A total of 25 healthy subjects were entered into the study, 24 subjects (12 males and 12 females) were treated, and 23 subjects completed the trial according to protocol. One subject was not treated because she was not able to swallow the medication and 1 subject prematurely discontinued trial participation after Treatment A for personal reasons. The mean age of the treated subjects was 40.8 years, ranging from 22 to 50 years, and the mean BMI was 25.99 kg/m^2, ranging from 19.8 to 29.9 kg/m². There were no important protocol violations in this trial.

Geometric mean (gMean) $AUC_{\tau,ss}$ of raltegravir increased from 4070 ng·h/mL when raltegravir was administered alone to 11 100 ng·h/mL when raltegravir was coadministered with faldaprevir; gMean $C_{max,ss}$ of raltegravir increased from 1300 ng/mL when raltegravir was administered alone to 3220 ng/mL when raltegravir was coadministered with faldaprevir. Statistical comparison of $AUC_{\tau,ss}$ and $C_{max,ss}$ of raltegravir when raltegravir was administered with and without faldaprevir provided the results given in Table 1.

Table 1: Adjusted gMean ratio, 90% confidence interval, and intraindividual geometric coefficient of variation (gCV) for $AUC_{\tau,ss}$ and $C_{max,ss}$ of raltegravir

Raltegravir parameter	Adjusted gMean ratio (Test[1]/Reference[2]) [%]	Two-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
$AUC_{\tau,ss}$	272.1	199.7	370.7	67.9
$C_{max,ss}$	245.7	168.5	358.4	87.1

[1]Test: raltegravir with faldaprevir (N=23)
[2]Reference: raltegravir alone (N=24)

Thus, coadministration of raltegravir with faldaprevir led to an approximately 2.7-fold increase in gMean $AUC_{\tau,ss}$ of raltegravir and an approximately 2.5-fold increase in gMean $C_{max,ss}$ of raltegravir compared with raltegravir administered alone. Similar increases in gMean $AUC_{\tau,ss}$ and $C_{max,ss}$ were observed for the metabolite raltegravir-glucuronide.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-004872-21	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 4 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 JUL 2013	**Trial No. / U No.:** 1220.65 / U13-1885-01	**Dates of trial:** 07 FEB 2013 – 15 MAR 2013	**Date of revision:** Not applicable

Safety results:

Twenty-three subjects were administered all 7 doses of 240 mg faldaprevir (total dose: 1680 mg) and all 18 doses of 400 mg raltegravir (total dose: 7200 mg), while the subject who discontinued for personal reasons after Treatment A received 7 doses of 400 mg raltegravir (total dose: 2800 mg) and no faldaprevir.

Of the 24 treated subjects, 18 (75.0%) reported at least 1 AE during the treatment phase of the study. The incidence of AEs was higher during the combined treatment with raltegravir and faldaprevir than during treatment with raltegravir alone (17 subjects, 73.9% vs. 7 subjects, 29.2%), especially gastrointestinal disorders were more frequent during the combined treatment than during raltegravir alone (11 subjects, 47.8% vs. 3 subjects, 12.5%). On the preferred term level, AEs reported during treatment with raltegravir alone were headache (3 subjects, 12.5%), flatulence (2 subjects, 8.3%), dizziness (2 subjects, 8.3%), nausea, diarrhoea, abdominal pain, and feeling of relaxation (each reported for 1 subject, 4.2%); AEs reported during the combined treatment were nausea (6 subjects, 26.1%), headache (5 subjects, 21.7%), fatigue (5 subjects, 21.7%), diarrhoea (3 subjects, 13.0%), vomiting (2 subjects, 8.7%), flatulence, abdominal discomfort, upper abdominal pain, dry mouth, syncope, tremor, and chromaturia (each reported for 1 subject, 4.3%). All but 1 AE (mild vomiting) were assessed by the investigator as drug-related. The majority of AEs were of mild intensity, 1 AE was rated as moderate (flatulence), and no AE was rated as severe. No SAEs, protocol-specified significant AEs (hepatic injury), or other significant AEs according to ICH E3 occurred and no subject discontinued the trial due to an AE.

Reversible increases in bilirubin (primarily indirect bilirubin) were observed in nearly 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 vital signs or ECG recordings.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-004872-21	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 5 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 JUL 2013	**Trial No. / U No.:** 1220.65 / U13-1885-01	**Dates of trial:** 07 FEB 2013 – 15 MAR 2013	**Date of revision:** Not applicable

Conclusions:

Coadministration of 400 mg twice daily raltegravir with 240 mg once daily faldaprevir resulted in an approximately 2.7-fold increase in gMean $AUC_{\tau,ss}$ for raltegravir (adjusted gMean ratio 272.1%; 90% CI 199.7, 370.7) and an approximately 2.5-fold increase in gMean $C_{max,ss}$ for raltegravir (adjusted gMean ratio 245.7%; 90% CI 168.5, 358.4) compared with raltegravir administered alone.

Both treatments, raltegravir alone and raltegravir in combination with faldaprevir, were well tolerated by the healthy subjects.