Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.:** 2012-002941-39	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 July 2013	**Trial No. / U No.:** 1220.59 / U13-1884-01	**Dates of trial:** 28 SEP 2012 – 18 DEC 2012	**Date of revision:** Not applicable

Title of trial:	Investigation of the effect of food and of increased gastric pH on the relative bioavailability of a single oral dose of 240 mg faldaprevir in an open-label, randomised, three-way crossover trial in healthy subjects
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine, Human Pharmacology Centre, Birkendorfer Strasse 65, Biberach/Riss, Germany
Publication (reference):	Data from this study have not been published.
Clinical phase:	I
Objectives:	The objective was to investigate the effect of food and increased gastric pH (mediated by omeprazole) on the relative bioavailability of faldaprevir.
Methodology:	This was an open-label, randomised, single-dose (for faldaprevir), 3-way crossover study in healthy volunteers.
No. of subjects:	
planned:	entered: 15
actual:	entered: 15 Treatment A (faldaprevir in the fasted state) treated: 15 analysed (for primary endpoints): 14 Treatment B (faldaprevir in the fed state): treated: 14 analysed (for primary endpoints): 14 Treatment C (faldaprevir with omeprazole): treated: 15 analysed (for primary endpoints): 14
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 (two 120 mg capsules)
mode of admin.:	Oral with 240 mL water after an overnight fast of at least 10 h (Treatments A, C) Oral with 240 mL water after intake of a high-fat breakfast (Treatment B)
batch no.:	B113000118

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Test product 2:	Omeprazole gastro-resistant hard gelatin capsules (Omeprazol-ratiopharm®)
dose:	40 mg once daily
mode of admin.:	Oral with 240 ml water after an overnight fast of at least 10 h
batch no.:	E018 (ratiopharm)
Duration of treatment:	Faldaprevir was administered as a single dose in Treatments A, B, and C. Omeprazole was administered for 5 days in Treatment C (on Day 5 omeprazole and faldaprevir were coadministered). Faldaprevir administrations were separated by washout phases of at least 14 days.
Criteria for evaluation:	
Pharmacokinetic endpoints:	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of faldaprevir Secondary endpoint: AUC_{0-tz} of faldaprevir Other endpoints: t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, and V_z/F of faldaprevir, AUC_{0-24}, C_{max}, and t_{max} of omeprazole
Safety:	Adverse events (AEs), safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse rate), and physical examination
Statistical methods:	Point estimates for the intrasubject ratio of the geometric means (for treatments Test and Reference) of the primary and secondary endpoints and their 2-sided 90% confidence intervals were calculated. Faldaprevir given in the fed state was the Test treatment 1, faldaprevir coadministered with omeprazole (increased gastric pH conditions) was the Test treatment 2, and faldaprevir given in the fasted state was the Reference treatment in both comparisons. The statistical model was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. For all pharmacokinetic endpoints, descriptive statistics were calculated.
SUMMARY – CONCLUSIONS:	
Pharmacokinetic results:	A total of 15 healthy subjects (8 males and 7 females) were entered into the study and treated. The mean age was 34.7 years, ranging from 21 to 47 years, and the mean BMI was 23.51 kg/m^2, ranging from 19.1 to 28.3 kg/m^2. Thirteen subjects completed the trial according to protocol, while 2 subjects prematurely discontinued trial participation. One subject was withdrawn prior to drug administration in the third treatment period (faldaprevir under fed conditions)

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Pharmacokinetic results (cont.):

due to a positive drug screen result and 1 subject discontinued after the first dose of omeprazole in the third treatment period (faldaprevir and omeprazole) due to an AE.

Both geometric mean (gMean) $AUC_{0-\infty}$ and C_{max} values of faldaprevir were higher after administration of a single oral dose of 240 mg faldaprevir under fed conditions compared with the other 2 treatments. Geometric mean $AUC_{0-\infty}$ was 48 200 ng·h/mL for faldaprevir under fed conditions, while it was 37 900 and 36 000 ng·h/mL for faldaprevir under fasted and increased gastric pH conditions, respectively. Similarly, gMean C_{max} was 2600 g/mL for faldaprevir under fed conditions, while it was 2030 and 1920 ng/mL for faldaprevir under fasted and increased gastric pH conditions, respectively. Interindividual variability of $AUC_{0-\infty}$ and C_{max} of faldaprevir was high for all treatments with geometric coefficient of variation (gCV) values of 41.7 and 57.5% for faldaprevir under fed conditions, 67.2 and 140% for faldaprevir under fasted conditions, and 63.4 and 122% for faldaprevir under increased gastric pH conditions. Maximum plasma concentrations of faldaprevir were achieved at a median t_{max} of 4.0 h after administration of faldaprevir under fasted and increased gastric pH conditions, while median t_{max} was somewhat earlier for faldaprevir under fed conditions (3.0 h). Geometric mean $t_{1/2}$ was in the range of 30.3 to 31.5 h for all 3 treatments.

Statistical comparisons of the primary ($AUC_{0-\infty}$, C_{max}) and secondary (AUC_{0-tz}) endpoints of faldaprevir under fed vs. fasted conditions as well as under increased gastric pH vs. fasted conditions provided the following results.

Faldaprevir parameter	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Comparison faldaprevir fed (N=14) vs. faldaprevir fasted (N=14)				
$AUC_{0-\infty}$	120.4	102.1	141.9	23.2
AUC_{0-tz}	121.3	102.3	143.7	24.0
C_{max}	118.8	83.2	169.6	52.4
Comparison faldaprevir fasted with omeprazole (N=14) vs. faldaprevir fasted (N=14)				
$AUC_{0-\infty}$	94.3	76.2	116.8	30.8
AUC_{0-tz}	94.7	76.3	117.7	31.4
C_{max}	93.6	65.8	133.0	53.0

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Safety results:

Thirteen subjects were administered a total dose of 720 mg faldaprevir (3 single 240 mg doses) and a total dose of 200 mg omeprazole (40 mg once daily for 5 days), as planned, while 1 subject received 480 mg faldaprevir and 200 mg omeprazole and 1 subject received 480 mg faldaprevir and 40 mg omeprazole.

Of the 15 treated subjects, 10 (66.7%) reported at least 1 AE during the treatment phase of the study; 4 subjects each during treatment with faldaprevir (26.7%), faldaprevir in the fed state (28.6%), and during the combined treatment with faldaprevir and omeprazole (28.6%). No AEs occurred during the first 4 days of the combined treatment when omeprazole was administered without faldaprevir. The most frequently reported AEs in this study were gastrointestinal disorders (6 subjects, 40.0%) and headache (3 subjects, 20.0%). Other AEs were rhinitis, asthma, and arthritis, each reported for 1 subject. Gastrointestinal AEs were reported for 3 subjects each in the treatment periods with faldaprevir in the fasted state (vomiting and 2 cases of diarrhoea [investigator's reported term: loose stool]) and faldaprevir in combination with omeprazole (nausea and 2 cases of diarrhoea [investigator's reported term: loose stool]), and for 1 subject in the treatment period with faldaprevir in the fed state (upper abdominal pain). All gastrointestinal AEs were assessed by the investigator as drug-related. The majority of AEs were rated as mild, 2 AEs were rated as moderate (headache, arthritis). No severe or serious AEs occurred in this study. One AE (arthritis) led to discontinuation of trial drug and was classified as other significant AE according to ICH E3. This AE was not assessed as drug-related by the investigator.

No relevant changes in laboratory parameters were observed and there were no findings with respect to vital signs or ECG recordings.

Conclusions:

Administration of a single oral dose of 240 mg faldaprevir after a standardised high-fat breakfast led to a modest increase in faldaprevir exposure (gMean $AUC_{0-\infty}$ and C_{max} were increased by 20.4% and 18.8%, respectively), while an increase in gastric pH mediated by omeprazole did not appreciably influence faldaprevir exposure.

Single 240 mg doses of faldaprevir administered under fasted, fed, and increased gastric pH conditions were well tolerated by the healthy subjects.