Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.:** 2011-006061-17	
Name of active ingredient: Faldaprevir (BI 201335)		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 FEB 2013	**Trial No. / U No.:** 1220.56 / U13-1189-01	**Dates of trial:** 03 APR 2012 – 06 AUG 2012	**Date of revision:** Not applicable

Title of trial:	An open-label, two-period, fixed-sequence, phase I trial to evaluate the effect of multiple doses of 240 mg BI 201335 QD on the multiple-dose pharmacokinetics of a combination of ethinylestradiol and levonorgestrel in healthy premenopausal female volunteers
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre Birkendorfer Strasse 65 Biberach/Riss, Germany
Publication (reference):	Data from this trial have not been published
Clinical phase:	I
Objectives:	To investigate the effect of multiple oral doses of faldaprevir on the multiple dose pharmacokinetics (PK) of a combination oral tablet of ethinylestradiol (EE) and levonorgestrel (LNG)
Methodology:	Open-label, 2-period fixed-sequence trial. A run-in period was employed prior to the first trial period. No washout period separated the 2 trial periods
No. of subjects:	
planned:	entered: 16
actual:	Treatment EE+LNG (period 1) and EE+LNG with faldaprevir (period 2): entered: 16 treated: 16 analysed (for primary endpoint): 16
Diagnosis and main criteria for inclusion:	Healthy female premenopausal subjects, age 18 to 35 years, body mass index (BMI) 18.5 to 27 kg/m²

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Test therapy:	EE+LNG (Microgynon®) tablets and faldaprevir soft gelatine capsules (Period 2)
dose:	EE+LNG: 30 µg EE+150 µg LNG once daily in the morning faldaprevir: loading dose of 480 mg (morning and evening doses of 240 mg on Day 1 of Period 2), on subsequent days 240 mg once daily in the morning
mode of admin.:	Oral. On Day 8 of Period 2 (PK profiling), medication was administered with 240 mL water after an overnight fast. On other days, fasting was not required
batch no.:	faldaprevir: B103000064 EE+LNG: 02858CY Bayer
Reference therapy:	EE+LNG (Microgynon®) tablets (Period 1)
dose:	30 µg EE+150 µg LNG once daily in the morning
mode of admin.:	Oral. On Day 13 of Period 1 (PK profiling), medication was administered with 240 mL water after an overnight fast. On other days, fasting was not required
batch nos.:	02858CY Bayer (Periods 1 and 2); 12851B Bayer (run-in phase)
Duration of treatment:	Run-in period: 30 µg EE+150 µg LNG once daily for 21 to 49 days, depending on duration of menstrual cycle Reference treatment (Period 1): On Days 1 to 13, 30 µg EE+150 µg LNG once daily Test treatment (Period 2): On Day 1, 30 µg EE+150 µg LNG and 480 mg faldaprevir; on Days 2 to 8, 30 µg EE+150 µg LNG and 240 mg faldaprevir once daily
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints: $AUC_{\tau,ss}$, $C_{max,ss,}$ and $C_{24,ss}$ of both EE and LNG for test treatment (EE+LNG with faldaprevir) compared with reference treatment (EE+LNG alone). Other parameters of interest: $t_{max,ss}$, $MRT_{po,ss}$, V_z/F_{ss}, CL/F_{ss}, $\lambda_{z,ss}$, $t_{1/2,ss}$ of both EE and LNG; trough levels of EE, LNG, and faldaprevir (to demonstrate attainment of steady state)
Safety:	Vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), physical examination, clinical laboratory tests (haematology, clinical chemistry, urinalysis), adverse events

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Statistical methods: For primary endpoints ($AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{24,ss}$ of EE and LNG), the statistical model was a mixed-effects ANOVA on log-transformed parameters including effects for 'subjects' and 'treatment'. Point estimates of the ratio for the geometric means (gMeans) of test and reference treatments and the corresponding 2-sided 90% confidence intervals were calculated. Confidence intervals were based on the residual error from the ANOVA. Steady state of faldaprevir, EE, and LNG were investigated by fitting trough concentrations of each analyte to a repeated-measures ANOVA model on the logarithmic scale including 'time' as a repeated effect. For all other parameters, descriptive statistics were calculated.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Sixteen white female subjects were entered in the trial and were treated. Fifteen of 16 subjects (93.8%) received all doses of trial medication and completed the planned observation time; 1 subject prematurely discontinued trial participation. Mean subject age was 28.4 years (range 18 to 35 years) and mean BMI was 23.4 kg/m^2 (range 19.3 kg/m^2 to 26.3 kg/m^2). No subject reported relevant medical history or baseline conditions.

Overall, gMean exposures (peak and total) to ethinylestradiol and levonorgestrel were higher for steady-state coadministration with faldaprevir (Period 2) than for steady-state administration alone (Period 1). For ethinylestradiol, gMean values of $AUC_{\tau,ss}$ increased from 1010 pg·h/mL in Period 1 to 1450 pg·h/mL in Period 2, whereas gMean values of $C_{max,ss}$ increased from 108 pg/mL in Period 1 to 127 pg/mL in Period 2. Similarly, for levonorgestrel, gMean values of $AUC_{\tau,ss}$ increased from 83.3 ng·h/mL in Period 1 to 120 ng·h/mL in Period 2, whereas gMean values of $C_{max,ss}$ increased from 7.57 ng/mL in Period 1 to 8.95 ng/mL in Period 2. Trough levels of both ethinylestradiol and levonorgestrel were also higher when coadministered with faldaprevir: for ethinylestradiol, $C_{24,ss}$ was 19.1 pg/mL in Period 1 and 33.2 pg/mL in Period 2, and for levonorgestrel, $C_{24,ss}$ was 2.43 ng/mL in Period 1 and 3.85 ng/mL in Period 2. Values of t_{max} (median and range) for ethinylestradiol and levonorgestrel did not change substantially upon coadministration with faldaprevir. However, values of $t_{1/2,ss}$ were longer for both substances when coadministerered with faldaprevir, with gMean values increasing by 3.0 h for ethinylestradiol and by 10.8 h for levonorgestrel.

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Clinical pharmacology results (continued):

Statistical analysis of steady state demonstrated that steady state was achieved for ethinylestradiol and levonorgestrel in Period 1, and for ethinylestradiol, levonorgestrel, and faldaprevir in Period 2.

Statistical comparison of peak and total exposure of ethinylestradiol in Period 2 (T) with Period 1 (R) provided adjusted gMean ratios of 141.0% for $AUC_{\tau,ss}$, 114.8% for $C_{max,ss,}$ and 171.4% for $C_{24,ss}$. Similarly, for levonorgestrel, statistical comparison of peak and total exposure in Period 2 with Period 1 provided adjusted gMean ratios of 140.5% for $AUC_{\tau,ss}$, 115.3% for $C_{max,ss}$, and 153.9% for $C_{24,ss}$. None of the 90% CIs included 100%. Intra-individual gCV values were very low for both ethinylestradiol and levonorgestrel, at 13.2% or less (see table below).

Relative bioavailability of EE and LNG in Period 2 compared with Period 1

Parameter	EE+LNG and faldaprevir (T)[1] Adj. gMean	EE+LNG (R)[2] Adj. gMean	gMean ratio T/R [%]	Intra-indiv gCV [%]	90% CI [%]
EE $AUC_{\tau,ss}$ [pg·h/mL]	1421	1008	141.0	8.1	133.8 to 148.5
EE $C_{max,ss}$ [pg/mL]	123.7	107.7	114.8	13.2	105.5 to 125.0
EE $C_{24,ss}$ [pg/mL]	32.72	19.09	171.4	10.5	160.2 to 183.3
LNG $AUC_{\tau,ss}$ [ng·h/mL]	117.0	83.28	140.5	4.6	136.4 to 144.8
LNG $C_{max,ss}$ [ng/mL]	8.721	7.565	115.3	6.1	110.8 to 119.9
LNG $C_{24,ss}$ [ng/mL]	3.737	2.429	153.9	8.2	146.0 to 162.1

[1]N=15
[2]N=16

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Safety results:

Overall, 15 of 16 subjects received all planned doses trial medication. One subject discontinued trial treatment in Period 2 because of an adverse event. For the trial as a whole, there were no deaths, other serious adverse events, or significant (prespecified) adverse events (hepatic injury).

During treatment with ethinylestradiol and levonorgestrel alone (Period 1), 12 of 16 subjects (75.0%) reported adverse events. The most frequently reported adverse events by system organ class (SOC) were nervous system disorders, reported for 7 of 16 subjects (43.8%); the most frequent PT was headache, reported for 5 of 16 subjects (31.3%). The next most frequent SOCs were gastrointestinal disorders, infections and infestations, and musculoskeletal and connective tissue disorders, each reported for 2 of 16 subjects (12.5%). Intensity of all adverse events was mild or moderate, except for nontreatment related severe orthostatic intolerance in 1 of 16 subjects (6.3%). Investigator-defined drug-related adverse events were reported for 2 of 16 subjects (12.5%), and included metrorrhagia (investigator's term: menstrual spotting) and swelling (feeling swollen), each in 1 subject. All adverse events resolved within 21 h after onset, except for nontreatment related mild arthralgia in 1 subject, which was considered sufficiently characterised by the investigator.

During treatment with ethinylestradiol and levonorgestrel plus faldaprevir (Period 2), 16 of 16 subjects reported adverse events (100%). As in previous trials with faldaprevir, the most frequently reported adverse events by SOC were gastrointestinal (GI) disorders, reported for 12 of 16 subjects (75.0%); PTs were nausea (in 8 of 16 subjects, or 50.0%), abdominal discomfort or vomiting (each in 4 of 16 subjects, or 25.0%), diarrhoea (in 2 of 16 subjects, or 12.5%), and upper abdominal pain, stomatitis, or flatulence (each in 1 of 16 subjects, or 6.3%).The second most frequent SOC was nervous system disorders, reported for 8 of 16 subjects (50%), with the most frequent PTs headache, in 6 of 16 subjects (37.5%) and dizziness, in 3 of 16 subjects (18.8%). All adverse events were mild or moderate in intensity, except for treatment-related severe diarrhoea and severe nausea in 1 subject, and treatment-related severe nausea in 3 additional subjects, for a total of 4 of 16 subjects (25.0%).

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Safety results (continued):

Recurrent nausea after faldaprevir administration led to 1 of 16 subjects (6.3%) discontinuing treatment with trial medication, and was therefore an other significant adverse event according to ICH E3. Investigator-defined drug-related adverse events were reported for 15 of 16 subjects (93.8%), and included all GI disorders, as well as increased or decreased appetite in 7 of 16 subjects (43.8%), ocular icterus in 6 of 16 subjects (37.5%), dizziness and hot flush, each in 3 of 16 subjects (18.8%), apathy in 2 of 16 subjects (12.5%), and paraesthesia, dysgeusia, tachycardia, hyperhidrosis, pruritus, papular rash, muscle tightness, myalgia, aesthenia, fatigue and peripheral oedema, each in 1 of 16 subjects (6.3%). All adverse events resolved by the end of the trial, with the exception of mild treatment-related papular rash in 1 subject and mild pain (investigator's terms: pain in ankle and mediastinal pain), not related to treatment, in 2 subjects. These adverse events were considered sufficiently characterised by the investigator. No signs of phototoxicity were observed in any subject.

Safety laboratory evaluation demonstrated that during Period 2, bilirubin concentrations outside of the reference range were observed for 15 of 16 subjects (93.8%), and were associated with the adverse event ocular icterus in 6 subjects (see above). In all cases, total bilirubin elevations were <5 times the upper limit of normal (ULN). For 4 subjects, bilirubin concentrations had not yet resolved into the normal range at the end of the trial, but were decreasing. It is known that faldaprevir administration results in clinically irrelevant, transient elevations in bilirubin (primarily in indirect bilirubin) due to inhibition of UDP-glucuronosyltransferase 1A1. For 2 of 16 subjects (12.5%), values of ALT and/or AST during the trial increased to >2 times ULN. For both subjects, later control measurements demonstrated complete resolution of the enzyme levels.

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Conclusions:

When compared with steady-state administration of ethinylestradiol and levonorgestrel alone, steady-state coadministration of ethinylestradiol and levonorgestrel with faldaprevir resulted in ethinylestradiol gMean ratios of 141.0% for $AUC_{\tau,ss}$, 114.8% for $C_{max,ss}$, and 171.4% for $C_{24,ss}$ and levonorgestrel gMean ratios of 140.5% for $AUC_{\tau,ss,}$ 115.3% for $C_{max,ss}$, and 153.9% for $C_{24,ss}$. None of the 90% CIs included 100%. Therefore, coadministration of faldaprevir resulted in a modest increase in peak, total, and trough exposure to both ethinylestradiol and levonorgestrel.

The adverse events observed in this trial were consistent with the expected adverse event profiles of levonorgestrel+ethinylestradiol and for faldaprevir. Administration of ethinylestradiol and levonorgestrel with or without faldaprevir was safe for healthy female subjects who participated in the trial.