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.

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Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-003435-30	
BI Investigational Product: Faldaprevir (BI 201335)		**Page:** 1 of 8	
Report Date: 11 Dec 2014	**Trial No. / Doc. No.:** 1241.61 / c02420506-01	**Dates of Trial:** 12 Mar 2014 – 29 Apr 2014	**Date of Revision:** Not applicable

Title of Trial:	Investigation of potential drug-drug interactions between faldaprevir and immunosuppressants (cyclosporine and tacrolimus) in healthy male and female subjects (open-label, fixed-sequence trial)
Principal Investigator:	[redacted]
Trial Site:	[redacted] Germany
Publications:	Data from the trial had not been published at the time of CTR preparation
Clinical Phase:	I
Objectives:	To investigate the effect of multiple doses of faldaprevir (FDV) on the pharmacokinetics (PK) of a single dose of either cyclosporine or tacrolimus, and to investigate the effect of a single dose of either cyclosporine or tacrolimus on the PK of multiple dose FDV
Methodology:	Nonrandomised, open-label, fixed-sequence trial in 2 separate groups Group 1: Treatment A (reference) was to evaluate PK of cyclosporine alone, whereas Treatment B (test) was to evaluate the interaction of FDV and cyclosporine Group 2: Treatment C (reference) was to evaluate PK of tacrolimus alone, whereas Treatment D (test) was to evaluate the interaction of FDV and tacrolimus
No. of Subjects:	
Planned:	Entered: 32
Actual:	Entered: 32
	Group 1 (Treatments A and B) Entered: 16 Treated: 16 Analysed (for primary endpoint): 16
	Group 2 (Treatments C and D) Entered: 16 Treated: 15 Analysed (for primary endpoint): 15
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male or female subject, age 18 to 50 years with body mass index (BMI) of 18.5 to 29.9 kg/m^2

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BI Investigational Product:	FDV, 120 mg soft gelatine capsules
Dose:	Treatments B and D : Loading dose of 240 mg on first day and 120 mg per day thereafter
Mode of Admin.:	Oral, with 240 mL water after a meal
Batch No.:	B113000119
Comparator Product 1:	Cyclosporine (Neoral®), 25 mg soft capsules
Dose:	Treatments A and B: 50 mg single dose
Mode of Admin.:	Oral, with 240 mL water after a meal
Batch No.:	B131002967
Comparator Product 2:	Tacrolimus (Prograf®), 0.5 mg hard capsules
Dose:	Treatments C and D: 0.5 mg single dose
Mode of Admin.:	Oral, with 240 mL water after a meal
Batch No.:	B131002968
Duration of Treatment:	Group 1: Treatment A: single dose of 50 mg cyclosporine on Day 1 (reference treatment R1) Treatment B: loading dose of 240 mg FDV on Day -7 and 120 mg FDV on Days -6 to 7 (reference treatment R3); single dose of 50 mg cyclosporine on Day 1 (test treatment T1) A washout period of at least 14 days separated administration of cyclosporine in treatment periods A and B Group 2: Treatment C: single dose of 0.5 mg tacrolimus on Day 1 (reference treatment R2) Treatment D: loading dose of 240 mg FDV on Day -7 and 120 mg FDV on Days -6 to 7 (reference treatment R4); single dose of 0.5 mg tacrolimus on Day 1 (test treatment T2) A washout period of at least 14 days separated administration of tacrolimus in treatment periods C and D

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Criteria for Evaluation:

Clinical Pharmacology : Primary endpoints for cyclosporine and tacrolimus were $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max}. For FDV, primary endpoints were $AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{24,ss}$.

Safety: Safety was assessed by adverse events (AEs), safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse rate), and physical examination.

Statistical Methods: An analysis of variance (ANOVA) on the logarithmic scale including effects for 'subject' and 'treatment' was used to calculate geometric means (gMeans) of the primary endpoints. Relative bioavailability (BA) of cyclosporine, tacrolimus, or FDV for the test relative to the reference treatment was estimated by the ratios of the gMeans of the primary endpoints. Additionally, 2-sided 90% confidence intervals (CIs) were calculated based on the residual error from the ANOVA. Descriptive statistics were calculated for all endpoints. No interim analysis was planned or conducted.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol: A total of 32 male and female subjects was entered in the trial. In Group 1, 16 subjects were entered; 8 were male and 8 female. Mean age was 41.2±8.3 years and mean BMI was 25.20±2.64 kg/m^2. In Group 2, 16 subjects were entered and 15 were treated; of the treated subjects, 9 were male and 6 female. Mean age was 41.5±8.8 years and mean BMI was 24.95±2.79 kg/m^2. All trial subjects in both groups were of White race. In Group 1, of the 16 subjects, 13 (81.3%) completed the planned observation time. Two subjects withdrew informed consent for private reasons and 1 subject was removed from the trial due to an AE. In Group 2, of 16 subjects, 15 were treated; 1 subject withdrew consent prior to administration of trial medication for private reasons. Of the 15 treated subjects in Group 2, all completed the planned observation time. The data from all treated subjects were analysed for at least 1 primary endpoint.

One important protocol violation was reported: Subject No. 201 (Group 2) was inadvertently administered a second loading dose of 240 mg FDV on Day -6 rather than the scheduled 120 mg dose. No violations of trial inclusion or exclusion criteria were reported. Compliance with trial medication intake was assured by administration of trial medication under supervision of the investigating physician or his authorised designee.

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Clinical Pharmacology Results:

Group 1 (cyclosporine/FDV): Noncompartmental assessment of PK parameters was performed for treatment with cyclosporine coadministered with FDV (T1) and for treatment with cyclosporine alone (R1). Geometric $AUC_{0-\infty}$ values were 732 and 672 ng·h/mL, and gMean AUC_{0-tz} values were 685 and 635 ng·h/mL for T1 and R1, respectively. Interindividual gCV values for AUC parameters were between 16.2 and 25.2%. C_{max} values were also similar between treatments, at 164 ng/mL for T1 and 172 ng/mL for R1, with gCV values of 27.8 to 34.7%.

The relative BA of cyclosporine in whole blood was evaluated for T1 compared with R1. For $AUC_{0-\infty}$, the adjusted gMean ratio (T1/R1) was 108.20% (90% CI: 99.99%, 117.08%); for AUC_{0-tz}, the adjusted gMean ratio was 106.60% (90% CI: 98.36%, 115.53%); and for C_{max}, the adjusted gMean ratio was 90.14% (90% CI: 80.28%, 101.21%). Therefore, exposure to a single 50 mg dose of cyclosporine was similar whether or not multiple dose FDV was coadministered.

Noncompartmental assessment of steady state PK parameters was performed for multiple dose FDV coadministered with single dose cyclosporine (T1) and for multiple dose FDV alone (R3): values of gMean $AUC_{\tau,ss}$ were 30600 ng·h/mL for T1 and 24600 ng·h/mL for R3; for C_{max}, gMean values were 2470 ng/mL for T1 and 1740 ng/mL for R3; and for $C_{24,ss}$, gMean values were 723 ng/mL for T1 and 619 ng/mL for R3. The interindividual variability of the exposure parameters was high (gCVs of 196 to 331%), due largely to very low exposure observed in a single subject.

The relative BA of multiple dose FDV in plasma was assessed for R3 compared with T1. For $AUC_{\tau,ss}$, the adjusted gMean ratio (T1/R3) was 122.68% (90% CI: 104.80%, 143.60%); for $C_{max,ss}$, the adjusted gMean ratio was 140.98% (90% CI: 111.77%, 177.83%); and for $C_{24,ss}$, the adjusted gMean ratio was 116.92% (90% CI: 108.67%, 125.80%). These results indicate that exposure to FDV was slightly increased when FDV was coadminstered with single dose cyclosporine.

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Clinical Pharmacology Results (continued):

Group 2 (tacrolimus/FDV): Noncompartmental assessment of PK parameters was performed for coadministration of tacrolimus and FDV (T2) and for administration of tacrolimus alone (R2): gMean $AUC_{0-\infty}$ values were 20.4 and 16.0 ng·h/mL, and gMean AUC_{0-tz} values were 15.3 and 11.1 ng·h/mL, for T2 and R2, respectively. Interindividual gCV values for AUC parameters were between 57.6 and 66.2%. C_{max} values were similar between treatments, at 1.13 ng/mL for T2 and 1.14 ng/mL for R2, with gCV values of 35.5 to 48.9%.

The relative BA of tacrolimus in whole blood was evaluated for R2 compared with T2. For $AUC_{0-\infty}$, the adjusted gMean ratio (T2/R2) was 127.41% (90% CI: 114.45%, 141.83%); for AUC_{0-tz}, the adjusted gMean ratio was 136.85% (90% CI: 118.68%, 157.79%); and for C_{max}, the adjusted gMean ratio was 99.15% (90% CI: 82.86%, 118.64%). These results indicate that exposure to a single 0.5 mg dose of tacrolimus was slightly increased when tacrolimus was coadministered with multiple dose FDV

Noncompartmental assessment of steady state PK parameters was performed for multiple dose FDV coadministered with single dose tacrolimus (T2) and for multiple dose FDV alone (R4): values of gMean $AUC_{\tau,ss}$ were 38700 ng·h/mL for T2 and 40300 ng·h/mL for R4; for C_{max}, gMean values were 2930 ng/mL for T2 and 3120 ng/mL for R4; and for $C_{24,ss}$, gMean values were 900 ng/mL for T2 and 904 ng/mL for R4. The interindividual variability of the exposure parameters ranged from 35.7 to 56.1%.

The relative BA of FDV in plasma was assessed for R4 compared with T2. For $AUC_{\tau,ss}$, the adjusted gMean ratio (T2/R4) was 96.16% (90% CI: 88.53%, 104.45%); for $C_{max,ss}$, the adjusted gMean ratio was 93.85% (90% CI: 80.06%, 110.02%); and for $C_{24,ss}$, the adjusted gMean ratio was 99.54% (90% CI: 93.38%, 106.12%). Therefore, exposure to multiple dose FDV was similar whether or not FDV was coadministered with a single dose of tacrolimus.

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Safety Results:

Group 1: Of the 16 subjects receiving R1 (50 mg cyclosporine; Treatment A), 6 subjects (37.5%) reported AEs. In all 6 subjects, at least 1 AE was considered by the investigator to be related to trial medication. In 1 of 16 subjects (6.3%) an AE (mild anaemia, not considered by the investigator as related to trial medication) led to discontinuation of trial medication (an other significant AE according to ICH E3). The most frequent AEs by system organ class (SOC) were nervous system disorders, in 6 of 16 subjects (37.5%). The most frequent preferred term (PT) was headache, in 5 of 16 subjects (31.3%). Of the 15 subjects receiving R3 (7 days of FDV; Treatment B), 10 subjects (66.7%) reported AEs. In all 10 subjects, at least 1 AE was considered by the investigator to be related to trial medication. The most frequent AEs by SOC were gastrointestinal (GI) disorders, in 7 of 15 subjects (46.7%) and the most frequent PTs were dry mouth, nausea, and headache, each in 3 of 15 subjects (20.0%). Of the 14 subjects receiving T1 (50 mg cyclosporine+multiple dose FDV; Treatment B), 4 subjects (28.6%) reported AEs. In all 4 subjects, at least 1 AE was considered by the investigator to be related to trial medication (see table below). The most frequent AEs by SOC were GI disorders, in 4 of 14 subjects (28.6%), with the most common PTs diarrhoea and flatulence, each in 2 of 14 subjects (14.3%). For Group 1, there were no AEs of severe intensity, SAEs, or protocol-specified AEs of special interest (drug-induced liver injury, or grade 2 rash or photosensitivity related to trial medication).

Group 1: Adverse event overall summary, treated set

	R1 (cyclosporine) N (%)		R3 (FDV) N (%)		T1 (cyclo+FDV) N (%)	
Number of subjects	16	(100.0)	15	(100.0)	14	(100.0)
With any AE	6	(37.5)	10	(66.7)	4	(28.6)
With drug-related AEs[1]	6	(37.5)	10	(66.7)	4	(28.6)
With AEs leading to discontinuation	1	(6.3)	0	(0.0)	0	(0.0)
With other significant AEs[2]	1	(6.3)	0	(0.0)	0	(0.0)

[1]Investigator-defined
[2]According to ICH E3

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Safety Results (continued):

Group 2: Of the 15 subjects receiving R2 (0.5 mg tacrolimus; Treatment C), 5 subjects (33.3%) reported AEs. In 4 of 15 subjects (26.7%), at least 1 AE was considered by the investigator to be related to trial medication. The most frequent AEs by SOC were nervous system disorders, in 3 of 15 subjects (20.0%), and the most frequent PT was headache, in all 3 subjects (20.0%). Of the 15 subjects receiving R4 (7 days of FDV; Treatment D), 7 subjects (46.7%) reported AEs. In all 7 subjects, at least 1 AE was considered by the investigator to be related to trial medication. The most frequent AEs by SOC were nervous system disorders in 4 of 15 subjects (26.7%) and the most frequent PT was headache, also in 4 of 15 subjects (26.7%). Of the 15 subjects receiving T2 (0.5 mg tacrolimus+multiple dose FDV; Treatment D), 5 subjects (33.3%) reported AEs. In all 5 subjects, at least 1 AE was considered by the investigator to be related to trial medication. The most frequent AEs by SOC were GI disorders and eye disorders, each in 2 of 15 subjects (13.3%). The most common PT was ocular icterus in 2 of 15 subjects (13.3%). During treatment T2, an SAE was reported for 1 subject who had a mild road traffic accident with a mild ligament strain and who was therefore hospitalized (see table below). The event was not considered by the investigator to be related to trial medication. For Group 2, there were no AEs of severe intensity, AEs leading to trial discontinuation, protocol-specified AEs of special interest, or other significant AEs according to ICH E3.

Group 2: Adverse event overall summary, treated set

	R2 (tacrolimus) N (%)		R4 (FDV) N (%)		T2 (tacro+FDV) N (%)	
Number of subjects	15	(100.0)	15	(100.0)	15	(100.0)
With any AE	5	(33.3)	7	(46.7)	5	(33.3)
With drug-related AEs[1]	4	(26.7)	7	(46.7)	5	(33.3)
With serious AEs	0	(0.0)	0	(0.0)	1	(6.7)
Requiring hospitalisation	0	(0.0)	0	(0.0)	1	(6.7)

[1]Investigator-defined

Including all subjects treated in the trial, all AEs were of mild or moderate intensity and all had resolved by the end of follow-up.

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Safety Results (continued):

Safety laboratory assessments were performed on all trial subjects. In 1 subject, a laboratory assessment was reported as an AE (mild anaemia during treatment R1; see above). No other laboratory values were reported as AEs. As in previous trials with FDV, transient increases in bilirubin (primarily indirect bilirubin) were observed in most subjects, whether or not they showed overt signs of hyperbilirubinaemia. Two of 15 subjects had mild ocular icterus in treatment T2 (see above); however, only one of these subjects actually had increased total bilirubin levels. All increases in total bilirubin had resolved by the end of trial examination.

Descriptive assessments of blood pressure and heart rate indicated no relevant mean changes. For individual subjects, no vital signs assessment was reported as an AE. The investigator did not report any abnormal findings for physical examination of trial subjects.

Conclusions:

Assessment of relative BA indicated that exposure to a single 50 mg dose of cyclosporine was similar whether or not multiple dose FDV was coadministered. However, exposure to FDV was slightly increased when FDV was coadminstered with single dose cyclosporine. Exposure to a single 0.5 mg dose of tacrolimus was slightly increased when tacrolimus was coadministered with multiple dose FDV. In contrast, exposure to multiple dose FDV was similar whether or not FDV was coadministered with a single dose of tacrolimus.

During trial periods in which FDV was administered, AEs were similar to those reported in previous trials in healthy subjects; GI events were the most frequent AEs. During trial periods in which FDV was administered, laboratory assessments demonstrated transient, clinically irrelevant bilirubin increases (primarily in indirect bilirubin) similar to those observed in previous trials with FDV. Overall, the trial treatment (FDV alone or with single dose cyclosporine or tacrolimus) was safe and well-tolerated by the healthy subjects entered in the trial.