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			
Name of active ingredient: Faldaprevir, BI 201335 NA		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 MAY 2013	**Trial No. / U No.:** 1220.53 / U13-1793-01	**Date of trial:** 10 OCT 2012 – 09 JAN 2013	**Date of revision:** Not applicable

Title of trial:	Assessment of bioequivalence between two different formulations of BI 201335 NA soft gelatine capsules in healthy male volunteers. (an open-label, randomised, single-dose, four-period replicated crossover study)
Principal/Coordinating Investigator:	[redacted]
Trial site:	1 site [redacted] Japan)
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objective:	To investigate the bioequivalence of 2 dose-strengths of 40 mg and 120 mg faldaprevir (BI 201335 NA) soft gelatine capsules
Methodology:	Open-label, randomised, single-dose, two-sequence, four-period replicated crossover design
No. of subjects:	
planned:	To be entered: 60 subjects (30 per group)
actual:	Treatment sequence 1: (In the order of 'test treatment,' 'reference treatment,' 'reference treatment,' and 'test treatment') entered: 30 treated: 30 analysed (for primary endpoint): 30 Treatment sequence 2: (In the order of 'reference treatment,' 'test treatment,' 'test treatment,' and 'reference treatment') entered: 30 treated: 30 analysed (for primary endpoint): 30
Diagnosis and main criteria for inclusion:	Healthy male subjects age ≥20 and ≤45 years; body mass index range: ≥18.0 and ≤25.0 kg/m^2
Test product:	Faldaprevir 40 mg soft gelatine capsule
dose:	120 mg (40 mg x 3 capsules)
mode of admin.:	Oral administration with 150 mL water after an overnight fast
batch no.:	B121001927

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Reference therapy:	Faldaprevir 120 mg soft gelatine capsule
dose:	120 mg (120 mg x 1 capsule)
mode of admin.:	Oral administration with 150 mL water after an overnight fast
batch no.:	B121001926
Duration of treatment:	One day treatment (single oral dose) for each treatment period Screening period within 4 weeks Four treatment periods (Periods 1 to 4) of 6 days each (Days -1 to 5) Washout period of at least 14 days between treatments
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters: Primary endpoints: AUC_{0-tz} and C_{max} Secondary endpoints: $AUC_{0-\infty}$, t_{max}, λ_z, $t_{1/2}$, and MRT_{po}
Safety:	Physical examination, vital signs (blood pressure, pulse rate, and body temperature), 12-lead electrocardiography, laboratory tests, and adverse events
Statistical methods:	Two-sided 90% confidence intervals for the intra-subject ratio (as estimated by the geometric mean of the ratio) of each of AUC_{0-tz} and C_{max} were calculated to determine whether the confidence intervals were contained in the acceptance range of 80-125% for bioequivalence. Additionally, the corresponding point estimators (geometric means) for the median intra-subject ratios were provided. The statistical model based on a four-period replicated crossover design was an analysis of variance (ANOVA) on log transformed parameters including "sequence," "period," and "treatment" as fixed effect and "subjects within sequence" as random effect. Confidence intervals were based on the residual error from ANOVA. Descriptive statistics were calculated for all other parameters.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

In total, 60 healthy male subjects, ranging in age from 20 to 44 years, were entered and treated in this trial: 59 subjects completed the trial as planned and 1 subject prematurely discontinued the trial because of withdrawal of consent for personal reasons during the washout period after Period 1. All the 60 subjects were included in the pharmacokinetics set.

The adjusted geometric mean ratio (90% confidence interval) of the test treatment (faldaprevir 40 mg x 3 capsules) to the reference treatment (faldaprevir 120 mg x 1 capsule) was 103.0% (95.6% to 111.0%) for C_{max} and 100.5% (95.9% to 105.3%) for AUC_{0-tz}. The 90% confidence intervals for C_{max} and AUC_{0-tz} were within the acceptance range for bioequivalence (80% to 125%). The 90% confidence intervals of the secondary parameters were all within the criteria.

Safety results:

No death or serious adverse event was reported in this trial. The frequency of adverse events was similar after treatment with faldaprevir 40 mg x 3 capsules (13.6% [8/59 subjects]) and faldaprevir 120 mg x 1 capsule (13.3% [8/60 subjects]). All the adverse events were equally distributed to the 2 treatments and no difference in adverse event profiles was observed. The most frequently reported drug-related adverse events were diarrhoea, reported in 3 (5.1%) subjects after treatment with faldaprevir 40 mg x 3 capsules and in 3 (5.0%) subjects after faldaprevir 120 mg x 1 capsule.

No clinically significant changes were observed in clinical laboratory values, vital signs, or electrocardiograms. No apparent increases in liver parameters including bilirubin were seen and no hepatic injury was reported throughout the trial.

Overall, single oral administrations of faldaprevir 40 mg x 3 capsules (test treatment) were safe and well tolerated in healthy Japanese male subjects and no difference in safety profiles was observed in comparison with faldaprevir 120 mg x 1 capsule (reference treatment).

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Conclusions:

The 90% confidence intervals of the adjusted geometric mean ratio for C_{max} and AUC_{0-tz} of faldaprevir were within the acceptance range for bioequivalence (80% to 125%). Therefore, the 40 mg and 120 mg soft gelatine capsule formulation strengths of faldaprevir are considered bioequivalent.

Single oral administration of 120 mg faldaprevir, whether given as 40 mg soft gelatine capsules or 120 mg soft gelatine capsule, was safe and well tolerated in healthy male subjects. No differences were observed in safety profiles between the 2 dose-strength formulations.