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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-003967-74	
BI Investigational Product: Deleobuvir (BI 207127)		**Page:** 1 of 5	
Report Date: 26 Nov 2014	**Trial No. / Doc. No.:** 1241.44 / c02327040-01	**Dates of Trial:** 12 NOV 2013- 15 JAN 2014	**Date of Revision:** Not applicable

Title of Trial:	Investigation of the effect of food and of increased gastric pH on the relative bioavailability of deleobuvir following single oral administration in healthy Caucasian and Japanese subjects (an open-label, randomised, 4-way crossover study) This trial was prematurely discontinued due to termination of the clinical development of deleobuvir.
Principal Investigator:	[redacted]
Trial Site:	[redacted] Germany
Publications:	Data from this trial have not been published at the time of this clinical report.
Clinical Phase:	I
Objectives:	The primary objective of this trial was to investigate the effect of food with different fat content and of gastric pH increase (mediated by multiple dosing of omeprazole [OMP]) on the bioavailability of deleobuvir and its major metabolites following single dose administration of 600 mg deleobuvir. The assessment of safety and tolerability was an additional objective of this trial.
Methodology:	This was a randomised, open-label, 4-way crossover trial consisting of 4 treatment periods of 4 days in treatments A, B, and C, and 7 days in treatment D (A: 600 mg deleobuvir fasted, B: 600 mg deleobuvir following a high-fat, high-calorie meal, C: 600 mg deleobuvir, following a low-fat meal, and D: 600 mg deleobuvir following 4 days pre-treatment with OMP). Subjects were randomly allocated to 1 of the 4 treatment sequences: A-B-D-C, B-C-A-D, C-D-B-A, and D-A-C-B.
No. of Subjects:	
Planned:	Entered: 32 subjects (16 Caucasian and 16 Japanese, both males and females, at least one third of each sex).
Actual:	Entered: 16 Caucasian Treatment A (600 mg deleobuvir fasted) Treated: 11 Analysed (for primary endpoint): 11 Treatment B (600 mg deleobuvir following a high-fat, high-calorie meal) Treated: 10 Analysed (for primary endpoint): 10

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No. of Subjects (cont'd):	Treatment C (600 mg deleobuvir following low-fat meal)
Actual (cont'd):	Treated: 12 Analysed (for primary endpoint): 12 Treatment D (600 mg deleobuvir following pre-treatment with OMP) Treated: 10 Analysed (for primary endpoint):10
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male or female subjects at the age of 20 to 35 years and with a body mass index (BMI) of 18.5 to 25 kg/m^2.
BI Investigational Product:	Deleobuvir film-coated tablet
Dose:	600 mg single dose, unit strength 200 mg, posology 3-0-0
Mode of Admin.:	Oral with 240 mL of water
Batch No.:	B121001373
Trial Product:	Omeprazole (OMP) gastro-resistant hard capsule
Dose:	40 mg once daily for 4 days, unit strength 40 mg, posology 0-0-1
Mode of Admin.:	Oral with 240 mL of water
Batch No.:	B131002676/H002
Duration of Treatment:	Treatment A: Each subject received a single dose of deleobuvir after an overnight fast of at least 10 h. Treatment B: Each subject received a single dose of deleobuvir after a standardised high-fat, high-calorie meal after an overnight fast of at least 10 h. Treatment C: Each subject received a single dose of deleobuvir after a standardised low-fat meal after an overnight fast of at least 10 h. Treatment D: Each subject received a single dose of deleobuvir after an overnight fast of at least 10 h after 4 days of pre-treatment with 40 mg OMP once daily. Deleobuvir administrations were separated by washout phases of at least 6 days.

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Criteria for Evaluation:

Clinical Pharmacology

The following pharmacokinetic (PK) parameters of deleobuvir were analysed as primary endpoints: C_{max} and AUC_{0-tz}.

$AUC_{0-\infty}$ of deleobuvir was analysed as secondary endpoint.

Safety:

The evaluation of safety was based on monitoring for adverse events (AEs), clinical laboratory assessments (haematology, clinical chemistry, and urinalysis), vital signs, 12-lead electrocardiograms (ECG), and physical examination.

Statistical Methods:

To assess relative bioavailability, the ratios of the geometric means (test/reference) for the primary and secondary endpoints and their 2-sided 90% confidence intervals (CIs) were calculated. Test 1 was deleobuvir after a standardised high-fat, high-calorie meal, test 2 was deleobuvir after a low-fat meal, and test 3 was deleobuvir after pre-treatment with OMP. The reference was deleobuvir in fasting state. For comparison of tests 1 and 2, test 2 was regarded as reference. The statistical model used was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects nested within sequences', 'period', and 'treatment'. Confidence intervals were calculated based on the residual error from ANOVA.

Descriptive statistics were calculated for all safety and clinical pharmacology parameters. No interim analyses were planned or performed.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

None of the 16 entered subjects completed the trial according to protocol due to premature discontinuation of the trial. All subjects completed the first 2 treatment periods according to the randomisation scheme. Treatment period 3 was started and completed by 11 subjects, and none of the subjects started treatment period 4. All 16 subjects (9 males [56.3%]; 7 females [43.8%]) were White. The mean age (standard deviation) was 28.6 years (3.5) and the mean BMI (standard deviation) was 22.01 kg/m^2 (1.67). Of the 16 entered subjects, 11 subjects received 600 mg deleobuvir in the fasting state (A). Ten subjects received 600 mg deleobuvir following a high-fat, high-calorie meal (B). Twelve subjects received 600 mg deleobuvir following a low-fat meal (C). Ten subjects received 600 mg deleobuvir after 160 mg (4 days, 40 mg daily) pre-treatment with OMP (D).

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Clinical Pharmacology Results:	This relative bioavailability trial was performed to investigate the effect of food with different fat content and of gastric pH increase (mediated by multiple dosing of OMP) on the bioavailability of deleobuvir and its major metabolites following single dose administration of 600 mg deleobuvir. This study was discontinued prematurely and included only half of the planned number of subjects because the clinical development of deleobuvir was stopped. Therefore, only the primary endpoints (C_{max} and AUC_{0-tz} of deleobuvir) were analysed and only part of the planned statistical analyses could be performed. Deleobuvir gMean C_{max} and AUC_{0-tz} were lower in the fasting state (A) than for either of the fed treatments (B and C) or following pre-treatment with OMP (D). However, inter-individual variability for deleobuvir C_{max} and AUC_{0-tz} values was moderately high in the fasting state (A) and following a low-fat meal (C), and very high following a high-fat, high-calorie meal (B) and following pre-treatment with OMP (D). Inferential statistics results were obtained only for deleobuvir following a low-fat meal (C) compared with the fasting state (A). Relative bioavailability of deleobuvir appeared to be slightly higher following a low-fat meal (C) as compared with the fasting state (A). The adjusted gMean ratio (C/A) was 114.83% (90% CI 74.8%, 176.3%) for C_{max} and 115.80% (90% CI 63.5%, 211.1%) for AUC_{0-tz}. Relative bioavailability estimated with all terms as fixed effects included data from fewer subjects and resulted in slightly lower ratios. The adjusted gMean ratio (C/A) with all terms as fixed effects was 108.5% (90% CI 68.0%, 172.9%) for C_{max} and 109.7% (90% CI 71.1%, 169.3%) for AUC_{0-tz}. Because of the low number of subjects, no conclusions can be drawn from these results.
Safety Results:	No deaths, SAEs, other significant AEs according to ICH E3, AEs of special interest, or severe AEs were observed in this study. There were no subjects with AEs leading to trial discontinuation. A total of 10 subjects (62.5%) reported at least 1 AE during the on-treatment phase of the study: 2 subjects (18.2%) in the period of treatment in the fasting state (A), 1 subject (10.0%) in the period of treatment following a high-fat, high-calorie meal (B), 4 subjects (33.3%) in the period of treatment following a low-fat meal (C), and 7 subjects (70.0%) in the period of treatment following pre-treatment with OMP (D). Adverse events were separately analysed for the 4 days when OMP was administered without deleobuvir. No AEs were reported during this period. Overall, the most frequently reported treatment-emergent AEs on

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Safety Results (cont'd):	system organ class level were gastrointestinal disorders (8 subjects, 50.0%) and nervous system disorders (4 subjects, 25.0%). Ten subjects (62.5%) were reported with AEs that were considered as drug-related by the investigator. These concerned gastrointestinal disorders (8 subjects [50.0%]; nausea, 7 subjects [43.8%], diarrhoea, 1 subject [6.3%], and upper abdominal pain, 1 subject [6.3%]), nervous system disorders (4 subjects [25.0%]; headache, 3 subjects [18.8%], and dizziness, 1 subject [6.3%]), and general disorders and administration site conditions (fatigue, 1 subject [6.3%]). All AEs were of mild or moderate intensity, and they had all resolved at the end of the trial. There were no clinically relevant findings with respect to laboratory parameters, vital signs, physical examination, and 12-lead ECGs.
Conclusions:	Deleobuvir gMean C_{max} and AUC_{0-tz} were lower in the fasting state (A) than for either of the fed treatments (B and C) or following pre-treatment with OMP (D). However, inter-individual variability for deleobuvir C_{max} and AUC_{0-tz} values was moderately high in the fasting state (A) and following a low-fat meal (C) and very high following a high-fat, high-calorie meal (B) and following pre-treatment with OMP (D). Administration of 600 mg deleobuvir as single dose in the fasting state (A), following a high-fat, high-calorie meal (B), following a low-fat meal (C), and following pre-treatment with OMP (D) was safe and generally well tolerated by the healthy subjects entered in the trial.