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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-002741-11	
BI Investigational Product: Deleobuvir (BI 207127) Faldaprevir (BI 201335)		**Page:** 1 of 6	
Report Date: 26 Nov 2014	**Trial No. / Doc. No.:** 1241.40 / c02429515-01	**Dates of Trial:** 24 Oct 2013 - 20 Jan 2014	**Date of Revision:** Not applicable

Title of Trial:	Thorough QT study to evaluate the effects of BI 207127 (deleobuvir) combined with faldaprevir on cardiac safety parameters in healthy female and male subjects. Randomised, placebo-controlled, single-blind, three-period crossover Phase-I-study with moxifloxacin as positive control Boehringer Ingelheim decided to stop the further development of the interferon-free combination therapy for Hepatitis C and terminated the trial prematurely (trial interruption took place on 27 Dec 2013, trial termination on 20 Jan 2014).
Principal/Coordinating Investigator:	[redacted]
Trial Site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
Publications:	Data of this clinical trial have not been published at the time of this report.
Clinical Phase:	I
Objectives:	This thorough QT (TQT) clinical trial was planned to evaluate the effects of multiple doses of BI 207127 combined with faldaprevir on cardiac safety parameters in healthy subjects. These objectives could not be fully met as the sample size achieved until termination of the trial was too low compared to the planned sample size.
Methodology:	Randomised, placebo and positive-controlled (moxifloxacin open-label), single-blind, 3-period crossover in healthy subjects including the following 3 treatment periods (separated by wash-out periods of at least 8 days each): • BI 207127 and faldaprevir for 3 days (Days -2 to 1) • Placebo to BI 207127 plus placebo to faldaprevir for 3 days (Days -2 to 1) • Moxifloxacin 400 mg as single dose (Day 1) Intensive cardiac safety assessment was performed on Day 1 of each period (the number of completed periods per subject is given in the results section).

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-002741-11	
BI Investigational Product: Deleobuvir (BI 207127) Faldaprevir (BI 201335)		**Page:** 2 of 6	
Report Date: 26 Nov 2014	**Trial No. / Doc. No.:** 1241.40 / c02429515-01	**Dates of Trial:** 24 Oct 2013 - 20 Jan 2014	**Date of Revision:** Not applicable

No. of Subjects:	
Planned:	Entered: 60 (at least 52 to complete the trial per protocol)
Actual:	Entered: 48 (the trial was terminated prematurely) BI 207127 plus faldaprevir Entered: 48 Treated: 32 Analysed (for primary endpoint): 31 Placebo to BI 207127 plus placebo to faldaprevir Entered: 48 Treated: 32 Analysed (for primary endpoint): 32 Moxifloxacin Entered: 48 Treated: 31 Analysed (for primary endpoint): 31
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male and female volunteers in the age of ≥18 and ≤55 years and with a body mass index (BMI) between ≥18.5 and ≤29.9 kg/m^2 were included in this clinical trial.
BI Investigational Product 1:	BI 207127 tablets containing 200 mg BI 207127
Dose:	600 mg bid (bis in die, twice daily) on Days -2 and -1; 600 mg qd (quaque die, once daily) on Day 1
Mode of Admin.:	Oral with 240 mL of water
Batch No.:	B121001373
BI Investigational Product 2:	Faldaprevir soft gelatin capsules containing 120 mg faldaprevir
Dose:	240 mg (loading dose) on Day -2, 120 mg qd on Days -1 and 1
Mode of Admin.:	Oral with 240 mL of water
Batch No.:	B113000119
Comparator Product 1:	Moxifloxacin (Avalox®) tablets
Dose:	400 mg single dose on Day 1
Mode of Admin.:	Oral with 240 mL of water
Batch No.:	BXGALT1
Comparator Product 2:	Placebo tablets to BI 207127 and placebo capsules to faldaprevir
Dose:	Not applicable
Mode of Admin.:	Oral with 240 mL of water
Batch No.:	Placebo tablets to BI 207127: B121002148 Placebo capsules to faldaprevir: B113000117

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-002741-11	
BI Investigational Product: Deleobuvir (BI 207127) Faldaprevir (BI 201335)		**Page:** 3 of 6	
Report Date: 26 Nov 2014	**Trial No. / Doc. No.:** 1241.40 / c02429515-01	**Dates of Trial:** 24 Oct 2013 - 20 Jan 2014	**Date of Revision:** Not applicable

Duration of Treatment:	• For 3 days BI 207127 (bid on Days -2 and -1, qd on Day 1) plus faldaprevir (qd on Days -2 to 1) • For 3 days placebo to BI 207127 (bid on Days -2 and -1, qd on Day 1) plus placebo to faldaprevir (qd on Days -2 to 1) • Moxifloxacin single dose • Wash-out of at least 8 days between treatment periods
Criteria for Evaluation:	
Clinical Pharmacology:	The primary endpoint was a safety endpoint. No primary or secondary pharmacokinetic (PK) endpoints were planned to be analysed regarding BI 207127 and its metabolites (BI 208333, CD 6168 and CD 6168 acylglucuronide) as well as faldaprevir (exploratory PK endpoints were planned as further endpoints).
Safety:	The primary safety endpoint was defined as the largest mean placebo-corrected QTcN change from baseline on Day 1 between 1 to 24 h after dosing of BI 207127 plus faldaprevir (QTcN = length of the QT interval in the electrocardiogram [ECG] corrected for heart rate [HR] according to a parabolic population-based model). The secondary safety endpoints were defined as (i) the largest mean placebo-corrected QTcN change from baseline on Day 1 between 1 to 6 h after dosing of moxifloxacin (assessment of assay sensitivity) and (ii) the maximum and minimum mean placebo-corrected changes from baseline in HR on Day 1 between 1 to 24 h after dosing of BI 207127 plus faldaprevir. Further safety endpoints derived from the centrally assessed ECGs comprised QTcF interval, uncorrected QT interval, HR, RR interval, QRS complex, PR interval, and cardiologic assessments. Further safety endpoints included physical examinations and assessments of vital signs (blood pressure [BP], pulse rate [PR]), locally assessed 12-lead ECGs, clinical laboratory tests as well as monitoring of adverse events (AEs).
Statistical Methods:	The planned formal hypothesis testing was not done, because the achieved sample size at the time of trial termination was insufficient to allow meaningful statistical conclusions. A repeated measurements analysis was performed on the primary and secondary safety endpoints. For the subsequent comparisons to placebo, two-sided 90% confidence intervals (CIs) for the mean differences per time point and corresponding point estimators adjusted for baseline were computed. All further ECG endpoints were analysed descriptively. An interim analysis was not planned and not conducted.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-002741-11	
BI Investigational Product: Deleobuvir (BI 207127) Faldaprevir (BI 201335)		**Page:** 4 of 6	
Report Date: 26 Nov 2014	**Trial No. / Doc. No.:** 1241.40 / c02429515-01	**Dates of Trial:** 24 Oct 2013 - 20 Jan 2014	**Date of Revision:** Not applicable

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

Based on the sample size calculation, at least 52 subjects were to complete the trial according to protocol. Until early termination, 48 subjects had entered the trial. Out of these, only 12 subjects completed all 3 treatment periods, while 23 subjects completed 2 periods, and 12 subjects completed 1 period; 1 subject discontinued the trial due to AEs after the first period. As fewer subjects than the calculated sample size were available for the analyses, the trial objectives could not be fully met.

All 24 male and 24 female subjects were healthy and of White race. Subjects' mean (SD) age was 37.5 (8.8) years, ranging from 22 to 53 years, and their mean (SD) BMI was 25.06 (2.28) kg/m^2, ranging from 20.3 to 29.7 kg/m^2.

Clinical Pharmacology Results:

The planned PK exploratory endpoints were not analysed because the trial was terminated prematurely.

Safety Results:

All safety data available until trial termination were analysed.

Adverse events

Overall, 27/48 healthy subjects (56.3%) reported AE(s) and 20/48 subjects (41.7%) developed drug-related AEs. More subjects experienced at least one AE on BI 207127 plus faldaprevir (56.3%; N = 18) compared with placebo (31.3%; N = 10). In addition, 16.1% of subjects (N = 5) developed AE(s) on moxifloxacin.

Mainly gastrointestinal (34.4%) and nervous system disorders (31.3%) were reported on the combination therapy. Evaluating the most frequent AEs (incidence >5% on the PT level) that were assessed as related to trial drugs by the investigator, revealed that headache (28.1% on combination therapy vs. 9.4% on placebo), diarrhoea (12.5% vs. 3.1%), nausea (12.5% vs. 0.0%), abdominal distension (9.4% vs. 3.1%), and abdominal pain (6.3% vs. 0.0%) occurred more often with the combination therapy than with placebo.

All AEs were of mild to moderate intensity and their outcome was reported as resolved at the end of the trial. Deaths, other severe AEs, SAEs, and protocol-specified significant AEs were not observed. One subject discontinued the trial due to AEs (gastroenteritis, nausea, headache, and fatigue; all categorised as other significant AEs according to ICH E3) following the co-administration of BI 207127 plus faldaprevir.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-002741-11	
BI Investigational Product: Deleobuvir (BI 207127) Faldaprevir (BI 201335)		**Page:** 5 of 6	
Report Date: 26 Nov 2014	**Trial No. / Doc. No.:** 1241.40 / c02429515-01	**Dates of Trial:** 24 Oct 2013 - 20 Jan 2014	**Date of Revision:** Not applicable

Safety Results (cont.):

Laboratory parameters

Safety laboratory parameters remained largely unaffected by the trial medication. During co-administration of BI 207127 plus faldaprevir, several subjects had increases in total bilirubin (10 subjects >1.5-fold ULN, 4 subjects >2-fold ULN) that were not associated with any clinical symptoms and not documented as AEs by the investigator.

Vital signs

Blood pressure and PR did not reveal any clinically relevant treatment-induced effects.

ECG analyses

In general, QTcN, QTcF, and the uncorrected QT interval on Day 1 (adjusted mean changes from baseline) were prolonged following the combination therapy as compared with placebo. At least partly, these observations reflect time-matched decreases in HR (the placebo-corrected adjusted mean changes from baseline ranged between -4.42 bpm at 5 h and +0.17 bpm at 1 h after dosing).

After dosing of BI 207127 plus faldaprevir, the largest placebo-corrected adjusted mean change from baseline in QTcN was 7.90 ms observed at 6 h with a 90% upper confidence limit of 10.43 ms. At all other time points from 1 to 24 h after dosing, the corresponding 90% upper confidence limits remained below the pre-defined non-inferiority margin of 10 ms. The sensitivity analysis largely confirmed the analysis of the primary endpoint. All 90% confidence limits of the placebo-corrected adjusted mean changes from baseline in QTcF between 1 and 24 h after dosing were below 10 ms.

Assay sensitivity was confirmed; the QTcN effects observed following the administration of 400 mg moxifloxacin as compared with placebo fell within the range expected for this compound. The largest placebo-corrected adjusted mean change from baseline in QTcN was 12.70 ms (90% CI: 9.32, 16.08) at 4 h.

Overall, the analyses of the ECG endpoints are of limited relevance as the required sample size was not achieved due to premature trial termination.

Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-002741-11	
BI Investigational Product: Deleobuvir (BI 207127) Faldaprevir (BI 201335)		**Page:** 6 of 6	
Report Date: 26 Nov 2014	**Trial No. / Doc. No.:** 1241.40 / c02429515-01	**Dates of Trial:** 24 Oct 2013 - 20 Jan 2014	**Date of Revision:** Not applicable

Conclusions:	The objectives of this clinical trial could not be fully met as it was terminated prematurely due to BI's decision not to continue the further development of the interferon-free combination therapy for Hepatitis C. Fewer than the planned number of 52 subjects were available for analyses, resulting in some loss of precision in the ECG results. The data available until trial termination did not indicate any new safety issues for the combination of BI 207127 plus faldaprevir administered over 3 days to 48 healthy male and female subjects.