Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-003697-10	
Name of active ingredients: Deleobuvir (BI 207127) and faldaprevir (BI 201335)		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 25 JUL 2014	**Trial No. / Doc. No.:** 1241.35 / c02098814-02	**Dates of trial:** 29 NOV 2012 – 26 MAR 2013	**Date of revision:** Not applicable

Title of trial:	An open-label, multiple dose study to assess safety, tolerability, and pharmacokinetics of different multiple doses of BI 207127 BID administered orally for 9 days (Part 1) and multiple doses of BI 207127 combined with faldaprevir administered orally for 16 days (Part 2) in healthy male and female subjects
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data from this study have not been published at the time of this clinical trial report.
Clinical phase:	I
Objectives:	Part 1: To investigate the safety, tolerability, and pharmacokinetics of 2 different doses of deleobuvir (400 and 600 mg) administered twice daily for 9 days to healthy male and female subjects Part 2: To investigate the safety, tolerability, and pharmacokinetics of the combination of 600 mg twice daily deleobuvir and 120 mg once daily faldaprevir administered for 16 days to healthy male and female subjects
Methodology:	Part 1: Open-label, non-randomised, multiple rising dose design with 2 dose groups Part 2: Open-label, non-randomised, multiple dose design with 1 treatment group
No. of subjects:	
planned:	entered: 32 (Part 1: 16, Part 2: 16)
actual:	entered: 32 Part 1: Treatment A: 400 mg deleobuvir: entered: 8 treated: 8 analysed (for primary endpoint): 8 Treatment B: 600 mg deleobuvir: entered: 8 treated: 8 analysed (for primary endpoint): 8 Part 2: Treatment C: Deleobuvir and faldaprevir in combination: entered: 16 treated: 16 analysed (for primary endpoints): 14

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Diagnosis and main criteria for inclusion:	Healthy male and female subjects at the age of 18 to 50 years with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 and a minimum body weight of 50 kg were included in the study.
Test product 1:	Deleobuvir film-coated tablet
dose:	400 mg (given as two 200 mg tablets) twice daily in Treatment A 600 mg (given as three 200 mg tablets) twice daily in Treatments B and C
mode of admin.:	Oral administration with 240 mL of water under fed conditions
batch no.:	B101004474
Test product 2:	Faldaprevir soft gelatin capsule
dose:	120 mg once daily (loading dose of 240 mg on the first treatment day) in Treatment C
mode of admin.:	Oral administration with 240 mL of water under fed conditions
batch no.:	B113000118
Duration of treatment:	In Part 1, deleobuvir was administered for 9 days at a dose of 400 or 600 mg twice daily. A single morning dose was administered on Days 1 and 9. In Part 2, deleobuvir 600 mg twice daily and faldaprevir 120 mg once daily were administered together for 16 days. A loading dose of 240 mg faldaprevir was administered on Day 1 and a single morning dose of deleobuvir was administered on Day 16.
Criteria for evaluation:	
Pharmacokinetics:	Part 1: The primary endpoint of Part 1 was a safety endpoint and is described in the safety section below; no primary pharmacokinetic endpoints were defined for this trial part. Secondary endpoints: $AUC_{0\text{-}tz}$ ($AUC_{0\text{-}12}$) and C_{max} of deleobuvir and metabolites after the first dose on Day 1; $AUC_{\tau,ss}$ ($AUC_{0\text{-}12,ss}$) and $C_{max,ss}$ of deleobuvir and metabolites after the last dose on Day 9 Part 2: Primary endpoints: AUC_{τ} ($AUC_{0\text{-}12}$), C_{max}, C_{τ} (C_{12}) of deleobuvir and metabolites, and AUC_{τ} ($AUC_{0\text{-}24}$) and C_{max} of faldaprevir after the first dose on Day 1; $AUC_{\tau,ss}$ ($AUC_{0\text{-}12,ss}$), $C_{max,ss}$, $C_{\tau,ss}$ ($C_{12,ss}$) of deleobuvir and its metabolites, and $AUC_{\tau,ss}$ ($AUC_{0\text{-}24,ss}$) and $C_{max,ss}$ of faldaprevir after the last dose on Day 16. No secondary endpoints were defined for this trial part.

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Safety:	The evaluation of safety was based on adverse events (AEs), safety laboratory tests, 12-lead electrocardiograms (ECG), vital signs (blood pressure and pulse rate), and physical examinations (occurrence of findings). In Part 1, the number (percentage) of subjects with AEs was the primary endpoint, all other safety parameters were considered to be other endpoints. In Part 2, all safety parameters were considered to be other endpoints.
Statistical methods:	Descriptive statistics were calculated for all endpoints. Part 1: Dose proportionality was explored using a regression model; a 95% confidence interval (CI) for the slope β was computed. Linearity with respect to multiple administration using $AUC_{0-\infty}$ and $AUC_{\tau,ss}$ was addressed using a linear model on the logarithmic scale including 'subject' and 'order' as fixed effects. Attainment of steady state was explored by using a repeated measures linear model for trough concentrations. Part 2: Attainment of steady state was explored by using a repeated measures linear model for trough concentrations.

SUMMARY – CONCLUSIONS:

Pharmacokinetics:

A total of 32 healthy subjects were entered into the trial and treated, and 29 subjects completed the trial according to protocol. Three subjects prematurely discontinued trial participation: 2 subjects (1 allocated to 600 mg deleobuvir, 1 allocated to the combined treatment) discontinued due to AEs and 1 subject (allocated to the combined treatment) withdrew her consent. Of the 32 entered subjects, 19 subjects (59.4%) were male and 13 subjects (40.6%) were female. One subject was Black; the other subjects were White. The age (mean and standard deviation [SD]) of the treated subjects was 38.3 (9.3) years, and the BMI (mean and SD) was 25.10 (2.44) kg/m^2. Generally, the treatment groups were comparable with respect to sex, age, and BMI. No important protocol violations were reported.

Pharmacokinetics of deleobuvir and deleobuvir metabolites

The pharmacokinetics of deleobuvir and metabolites (CD 6168, BI 208333, and CD 6168 acylglucuronide) for subjects administered deleobuvir 400 and 600 mg twice daily, and 600 mg twice daily combined with 120 mg once daily faldaprevir, are summarised in the table below; geometric means (gMean) and geometric coefficients of variation (gCV%) for the primary and secondary pharmacokinetic parameters are given.

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Pharmacokinetics (continued):

Primary and secondary pharmacokinetic parameters of deleobuvir and metabolites

Analyte Parameter[1]	Deleobuvir 400 mg twice daily (N=8) gMean (gCV%)	Deleobuvir 600 mg twice daily (N=7) gMean (gCV%)	Deleobuvir 600 mg twice daily + faldaprevir 120 mg once daily (N=14) gMean (gCV%)
Deleobuvir			
AUC_{0-12} [nmol·h/L]	8210 (45.5)	18 000 (77.6)	37 500 (49.4)
C_{max} [nmol/L]	2010 (41.5)	3740 (79.4)	6930 (47.9)
C_{12} [nmol/L]			1090 (69.3)
$AUC_{0-12,ss}$ [nmol·h/L]	6160 (45.2)	18 500 (93.3)	51 400 (57.2)
$C_{max,ss}$ [nmol/L]	1380 (48.3)	3650 (91.6)	9710 (43.3)
$C_{12,ss}$ [nmol/L]			1000 (85.9)
CD 6168			
AUC_{0-12} [nmol·h/L]	1690 (56.0)	2920 (88.3)	6080 (55.0)
C_{max} [nmol/L]	329 (60.5)	516 (92.7)	902 (49.2)
C_{12} [nmol/L]			488 (67.5)
$AUC_{0-12,ss}$ [nmol·h/L]	2810 (63.1)	6960 (106)	38 100 (76.0)
$C_{max,ss}$ [nmol/L]	451 (66.3)	1130 (90.9)	4860 (60.5)
$C_{12,ss}$ [nmol/L]			1650 (102)
BI 208333			
AUC_{0-12} [nmol·h/L]	3940 (38.7)	6060 (57.1)	9130 (46.9)
C_{max} [nmol/L]	766 (41.5)	1050 (54.2)	1450 (40.0)
C_{12} [nmol/L]			520 (80.8)
$AUC_{0-12,ss}$ [nmol·h/L]	2840 (51.7)	5270 (102)	13 600 (71.1)
$C_{max,ss}$ [nmol/L]	576 (44.4)	983 (82.4)	2060 (57.6)
$C_{12,ss}$ [nmol/L]			447 (101)
CD 6168 acylglucuronide			
AUC_{0-12} [nmol·h/L]	155 (27.2)	342 (66.0)	511 (69.9)
C_{max} [nmol/L]	27.3 (36.8)	57.9 (61.0)	83.9 (63.7)
C_{12} [nmol/L]			56.4 (67.1)
$AUC_{0-12,ss}$ [nmol·h/L]	256 (42.7)	701 (94.0)	3560 (120)
$C_{max,ss}$ [nmol/L]	33.3 (61.3)	116 (80.6)	457 (106)
$C_{12,ss}$ [nmol/L]			178 (122)

[1] AUC_{0-12}, C_{max}, C_{12} after the first dose on Day 1; $AUC_{0-12,ss}$, $C_{max,ss}$, $C_{12,ss}$ after the last dose on Day 9 (Part 1) or Day 16 (Part 2)

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Pharmacokinetics (continued):

When deleobuvir dose was increased from 400 to 600 mg (that is, a 50% increase in dose), 2.2- and 1.9-fold increases in AUC_{0-12} and C_{max} were observed on Day 1 after the first dose, and 3.0- and 2.6-fold increases in $AUC_{0-12,ss}$ and $C_{max,ss}$ were observed on Day 9 after multiple days of dosing. When faldaprevir was added to the 600 mg deleobuvir dosing regimen, 2.1- and 1.9-fold increases in AUC_{0-12} and C_{max} relative to 600 mg deleobuvir alone were observed on Day 1 after the first dose, and 2.8- and 2.7-fold increases in $AUC_{0-12,ss}$ and $C_{max,ss}$ were observed after multiple days of dosing (Day 16 compared with Day 9).

Assessment of dose proportionality, linearity index, and steady state for deleobuvir

For C_{max}, AUC_{0-12}, $C_{max,ss}$, and $AUC_{0-12,ss}$ of deleobuvir, the point estimates for the slope β were much larger than 1.00 (1.52, 2.01, 2.40, and 2.71, respectively), and the corresponding 95% CIs were very wide. Thus, dose proportionality for deleobuvir cannot be assumed. However, there was a tendency towards a greater than dose proportional increase in exposure.

Assessment of the linearity index for deleobuvir indicated no linearity for deleobuvir at a dose of 400 mg twice daily. For deleobuvir at a dose of 600 mg twice daily, however, there appears to be linearity.

For deleobuvir administered alone at 400 and 600 mg twice daily, steady state may be indicated at approximately Days 7 to 8. When deleobuvir was combined with faldaprevir, steady state was indicated at approximately Day 14.

Faldaprevir pharmacokinetics

On Day 1 of the combined treatment, gMean AUC_{0-24} and C_{max} of faldaprevir were 44 800 ng·h/mL (23.6 gCV%) and 4060 ng/mL (25.0 gCV%), respectively. On Day 16 gMean $AUC_{0-24,ss}$ and $C_{max,ss}$ of faldaprevir were 66 200 ng·h/mL (46.1 gCV%) and 5940 ng/mL (32.3 gCV%), respectively.

Safety results:

In Treatment A, 8 subjects were administered 16 doses of 400 mg deleobuvir (total dose 6400 mg) over 9 days as planned. In Treatment B, 7 subjects were administered 16 doses of 600 mg deleobuvir (total dose 9600 mg) over 9 days, while 1 subject only received the first 2 doses. In Treatment C, 14 subjects were administered 31 doses of 600 mg deleobuvir (total dose 18 600 mg) and 16 doses of faldaprevir (total dose 2040 mg) over 16 days, 1 subject was administered 23 doses of deleobuvir and 12 doses of faldaprevir over 12 days, and 1 subject was administered 1 dose of 600 mg deleobuvir and 1 dose of 240 mg faldaprevir.

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Safety results (continued):

Serious or severe AEs did not occur in this study. Two subjects prematurely discontinued the trial due to AEs: 1 subject who was allocated to 600 mg deleobuvir discontinued due to dizziness, nausea, and vomiting; 1 subject who was allocated to the combined treatment with deleobuvir and faldaprevir, discontinued due to increased transaminase values. These AEs were categorised as other significant AEs according to ICH E3. They were assessed by the investigator as related to the trial medication.

Of the 32 treated subjects, 20 (62.5%) reported at least 1 AE during the study. Nineteen subjects (59.4%) reported AEs that were assessed by the investigator as drug-related. All AEs reported in this study were of mild or moderate intensity. All subjects had recovered from their AEs by the end of the study.

Part 1: AEs were reported for 6 subjects (75.0%) in the 400 mg group and for 5 subjects (62.5%) in the 600 mg group. In both dose groups, the most frequently reported AEs by system organ class were gastrointestinal disorders (3 subjects, 37.5%). AEs that occurred in the 400 mg dose group were nausea (reported for 2 subjects), folliculitis, diarrhoea, upper abdominal pain, cheilitis, dry skin, pruritus, skin fissures, back pain, and fatigue (each reported for 1 subject); AEs that occurred in the 600 mg dose group were nausea (reported for 3 subjects), rhinitis, headache, dizziness, vomiting (each reported for 1 subject). With the exception of back pain and rhinitis, all AEs in Part 1 were assessed as drug-related.

Part 2: In the combined treatment group, AEs were reported for 9 of 16 subjects (56.3%). The most frequently reported AEs were diarrhoea (5 subjects, 31.3%), nausea (4 subjects, 25.0%), headache (3 subjects, 18.8%), pruritus (2 subjects, 12.5%), and fatigue (2 subjects, 12.5%). Dizziness, dry skin, haemoptysis, upper abdominal pain, vomiting, flatulence, polymenorrhoea, and transaminases increased were reported for 1 subject each. With the exception of haemoptysis, all AEs in Part 2 were assessed as drug-related.

The evaluation of laboratory parameters revealed no trends that were considered to be of clinical relevance. Except for an increase in alanine transaminase up to 107 U/L in 1 subject in the combined treatment group (reported as an AE), no clinically significant abnormal laboratory values were observed. There were no clinically relevant findings with respect to vital signs or ECG.

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Conclusions:

Multiple doses of 400 or 600 mg twice daily deleobuvir administered orally for 9 days were safe and well tolerated in healthy volunteers. Multiple doses of 600 mg twice daily deleobuvir combined with 120 mg once daily faldaprevir administered orally for 16 days were in general well tolerated, however, in several subjects an increase in liver transaminase and bilirubin values was observed which was not considered clinically meaningful as the subjects were asymptomatic.

Deleobuvir exposure appeared to increase more than proportionally between the groups of subjects receiving deleobuvir 400 mg twice daily and 600 mg twice daily. When 600 mg twice daily deleobuvir was combined with 120 mg once daily faldaprevir, an increase in deleobuvir, deleobuvir metabolite, and faldaprevir concentrations occurred, which is consistent with the drug interaction previously observed in HCV-infected patients.