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.:** Not applicable	
Name of active ingredient: BI 201335		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 DEC 2011	**Trial No. / U No.:** 1220.50 / U11-2785-01	**Dates of trial:** 19 APR 2011 – 06 JUN 2011	**Date of revision:** Not applicable

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Title of trial:	Effect of multiple dosing with 240 mg BID BI 201335 on the steady state pharmacokinetics of 300mg QD Tenofovir and effect of multiple dosing with 300mg QD Tenofovir on steady state BI 201335 pharmacokinetics in healthy male and female volunteers
Principal Investigator:	[redacted]
Trial site:	[redacted] USA
Publication (reference):	Data from this trial have not been published
Clinical phase:	I
Objectives:	1) To evaluate the effect on tenofovir pharmacokinetics of 8 days of codosing tenofovir disoproxil fumarate (TDF; 300 mg per day) with BI 201335 (240 mg twice daily) compared to 7 days of dosing with TDF alone (300 mg per day) and 2) To evaluate the effect on BI 201335 pharmacokinetics of 8 days of codosing tenofovir disoproxil fumarate (TDF; 300 mg per day) with BI 201335 (240 mg twice daily) compared to 7 days of dosing with BI 201335 alone
Methodology:	Nonrandomised, noncontrolled, open label, 2-way interaction study. Single treatment sequence in a single group of subjects.
No. of subjects:	
planned:	entered: 16
actual:	entered: 16 Treatment: TDF alone (Days 1 to 7): entered: 16 treated: 16 analysed (for primary endpoint): 16 Treatment: TDF+BI 201335 (Days 8 to 15) entered: 16 treated: 16 analysed (for primary endpoint): 16 Treatment: BI 201335 alone (Days 16 to 22) entered: 16 treated: 16 analysed (for primary endpoint): 14

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Diagnosis and main criteria for inclusion:	Healthy male or female volunteers, age ≥18 and ≤55 years, body mass index (BMI) ≥18.5 and ≤29.9 kg/m^2
Test product 1:	BI 201335, 120 mg soft gelatin capsule
dose:	Day 8: Loading dose of 480 mg (4 capsules) in the morning and 240 mg (2 capsules) in the evening; Days 9 to 21: 240 mg (2 capsules) every morning and 240 mg (2 capsules) every evening; Day 22: single dose of 240 mg (2 capsules) in the morning
mode of admin.:	Oral
batch no.:	B103000075
Test product 2:	Tenofovir disoproxil fumarate (Viread®), 300 mg tablet
dose:	Days 1 to 15: 300 mg (1 tablet) every morning
mode of admin.:	Oral
batch no.:	02008486 (manufacturer's lot number), expiration date 07/2014
Duration of treatment:	22 days total (Days 1 to 15 with TDF, and Days 8 to 22 with BI 201335)
Criteria for evaluation:	
Clinical pharmacology:	Primary pharmacokinetic (PK) endpoints were comparison of $AUC_{0-24,ss}$, $C_{max,ss}$, and $C_{24,ss}$ of tenofovir after dosing with TDF alone (Day 7) with $AUC_{0-24,ss}$, $C_{max,ss}$ and $C_{24,ss}$ of tenofovir after co-dosing of TDF with BI 201335 (Day 15); and comparison of $AUC_{0-12,ss}$, $C_{max,ss}$, and $C_{12,ss}$ of BI 201335 alone (Day 22) with $AUC_{0-12,ss}$, $C_{max,ss}$ and $C_{12,ss}$ of BI 201335 after co-dosing with TDF (Day 15).
Safety:	Safety was evaluated by monitoring vial signs (blood pressure and pulse rate), 12-lead ECG, laboratory tests, and adverse events (AEs).
Statistical methods:	For the PK evaluation, point estimators (geometric means [gMeans]) and 2-sided 90% confidence intervals (CIs) of the intra-subject ratios of $AUC_{0-\tau,ss}$, $C_{max,ss}$ and $C_{\tau,ss}$ were calculated (where τ was the dosing interval of 24 h for TDF and 12 h for BI 201335). The statistical model employed was analysis of variance (ANOVA) on log-transformed parameters, and included effects for 'subject' and 'treatment'. Descriptive statistics were used for analysis of safety.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Of the 16 subjects entered in the trial, 14 completed the assigned treatment and observation time. Of the 16 subjects, 13 (81.3%) were male and 3 (18.8%) were female. Eight subjects (50.0%) were of black/African American race and 8 (50.0%) were of white race. Mean age was 37 years and mean BMI was 25.7 kg/m^2.

PK assessment indicated that steady-state conditions were achieved for tenofovir during dosing with TDF alone and for codosing with BI 201335, and steady-state conditions were achieved for BI 201335 during dosing with BI 201335 alone and for codosing with BI 201335 and TDF.

For tenofovir, noncompartmental PK analysis demonstrated that $t_{max,ss}$ and gMean $C_{max,ss}$ values were similar for treatment with TDF alone and for combination treatment. Values of $AUC_{0-24,ss}$ and $C_{24,ss}$, however, were increased for codosing: $AUC_{0-24,ss}$ was 3290 ng·h/mL for TDF+BI 201335 and 2700 ng·h/mL for TDF alone; $C_{24;ss}$ was 79.4 ng/mL for TDF+BI 201335 and 54.0 ng/mL for TDF alone. Apparent oral clearance was somewhat less for tenofovir after dosing with TDF+BI 201335 when compared with TDF alone.

For BI 201335, values of $t_{max,ss}$ were similar for treatment with BI 201335 alone and for combination treatment. Geometric mean values of $C_{max,ss}$ were decreased for codosing, at 41700 ng/mL for BI 201335+TDF and 50400 ng/mL for BI 201335 alone. Values of $AUC_{0-12,ss}$ and $C_{12,ss}$, were also decreased for codosing: $AUC_{0-12,ss}$ was 418000 ng·h/mL for BI 201335+TDF and 523000 ng·h/mL for BI 201335 alone; $C_{12;ss}$ was 31000 ng/mL for BI 201335+TDF and 40000 ng/mL for BI 201335 alone. Apparent oral clearance was somewhat higher for BI 201335+TDF when compared with BI 201335 alone.

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Clinical pharmacology results:

Statistical analysis indicated differences in exposure parameters of tenofovir and BI 201335 for codosing compared with administration of the individual drugs. On codosing, for tenofovir, adjusted gMean AUC_{0-24ss} and $C_{24,ss}$ were increased by 22% and 47%; for BI 201335, adjusted gMean $AUC_{0-12,ss}$, $C_{max,ss}$, and $C_{12,ss}$ were decreased by 22%, 18%, and 25%, respectively (see table below).

		TDF+BI 201335 gMean (N=16)	TDF gMean (N=16)	gMean ratio[a]	90% CI (%)
$AUC_{0-24,ss}$	[ng·h/mL]	3292	2701	121.9	111.7-133.0
$C_{max,ss}$	[ng/mL]	284.5	300.3	94.7	85.2-105.3
$C_{24,ss}$	[ng/mL]	79.43	53.99	147.1	134.5-160.9
		TDF+BI 201335 gMean (N=16)	BI 201335 gMean (N=14)	gMean ratio[a]	90% CI (%)
$AUC_{0-12,ss}$	[ng·h/mL]	417600	536200	77.9	71.2-85.2
$C_{max,ss}$	[ng/mL]	41700	51030	81.7	71.6-93.3
$C_{12,ss}$	[ng/mL]	30980	41160	75.2	68.7-82.5

[a]Adjusted

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Safety results:

All subjects received all planned doses of TDF (15 doses, 4500 mg total). For BI 201335, all doses were administered (30 doses, 7200 mg total) except for 2 subjects who discontinued treatment early due to AEs.

There were no deaths, other SAEs, or AEs of severe intensity reported for the trial. During treatment with TDF alone, an AE (presyncope), not considered to be treatment-related by the investigator, was reported for 1 subject (6.3%). During codosing with BI 201335 and TDF, AEs were reported for all 16 subjects (100.0%). AEs considered to be treatment-related by the investigator were reported for 15 subjects (93.8%). The most frequently reported AEs, both overall and treatment-related, were gastrointestinal (GI) disorders, in 13 subjects (81.3%) and nervous system disorders, primarily headache, in 10 subjects (62.5%). During treatment with BI 201335 alone, 10 subjects (62.5%) reported AEs, and in 9 subjects (56.3%) AEs were assessed as treatment-related by the investigator. The most common AEs, both overall and treatment-related, were GI disorders, in 3 subjects (18.8%) and musculoskeletal and connective tissue disorders, in 3 subjects (18.8%). For 2 subjects (12.5%), treatment-related AEs (moderate myalgia or mild rash) during BI 201335 treatment led to premature discontinuation of trial participation. All AEs resolved by the end of the trial.

Laboratory assessments indicated a minor mean decrease in haematocrit, and mean decreases in reticulocyte count and cholesterol. Total mean bilirubin increased substantially, largely due to increased indirect bilirubin. Transitions from normal values at baseline to values above the normal reference range (last value on treatment) were observed for all 16 subjects for direct bilirubin and 14 subjects for total bilirubin. Evaluation of the ratio of direct to total bilirubin indicated that indirect bilirubin levels rose much higher, proportionally, than did direct bilirubin levels. Bilirubin elevations were not accompanied by increases in hepatic enzyme levels. Transitions to values below the reference range were observed for 9 subjects for haematocrit, 7 subjects for cholesterol, and 6 subjects for reticulocyte count. Increases in bilirubin were associated with AEs of ocular icterus or jaundice in 5 subjects each. No other laboratory abnormalities were considered clinically significant by the investigator or were reported as AEs. No notable mean changes in vital signs were observed during the trial, and no clinically significant abnormalities in vital signs or ECGs were reported.

Treatment with BI 201335, alone or in combination with TDF, appeared to be safe for the healthy subjects included in the trial.

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Conclusions:

Co-administration of TDF and BI201335 led to increases of 22% and 47% in steady state adjusted gMean ratios of tenofovir for $AUC_{0\text{-}24,ss}$ and $C_{24,ss}$, respectively, compared with TDF alone. For tenofovir, adjusted gMean values of $C_{max,ss}$ were similar for treatment with TDF alone and for codosing with BI 201335. For BI 201335, adjusted gMean values of C_{max}, $AUC_{0\text{-}12,ss}$, and $C_{12,ss}$ were decreased 18 to 25% for codosing with TDF. The increase in tenofovir exposure and the decrease in BI 201335 exposure are not considered clinically relevant and do not require dosage adjustment.

Safety analysis suggested that co-administration of BI 201335 and TDF was safe in the subjects treated in this trial, which along with the clinical non-relevance of the drug-drug interaction, supports co-administration of these agents in patients infected with both HCV and HIV.