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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2011-000505-41	
Name of active ingredient: BI 201335, darunavir, ritonavir		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 FEB 2012	**Trial No. / U No.:** 1220.49 / U12-1162-01	**Dates of trial:** 07 JUN 2011 – 11 JUL 2011	**Date of revision:** Not applicable

Title of trial:	Effect of multiple dosing with 240 mg QD BI 201335 on the steady-state pharmacokinetics of 800 mg QD darunavir coadministered with 100 mg QD ritonavir (DRV/r) in healthy male and female volunteers (an open-label, multiple-dose, single group, single fixed sequence phase I study)
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The objective was to investigate the effect of multiple dosing with BI 201335 240 mg once daily on the steady-state pharmacokinetics of darunavir 800 mg coadministered with ritonavir 100 mg once daily (DRV/r).
Methodology:	This was an open-label, multiple-dose, single-group, fixed-sequence study in healthy volunteers.
No. of subjects:	
planned:	entered: 14
actual:	entered: 14
	DRV/r alone: treated: 14 analysed (for primary endpoints): 14
	DRV/r and BI 201335: treated: 14 analysed (for primary endpoints): 14
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers at the age of 18 to 55 years with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included in the study.
Test product:	BI 201335 capsule
dose:	240 mg once daily (given as two 120 mg capsules) on Days 10 to 16 480 mg loading dose on Day 9
mode of admin.:	Oral
batch no.:	B103000064

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Reference product 1:	Darunavir tablet (Prezista®)
dose:	800 mg once daily (given as two 400 mg tablets)
mode of admin.:	Oral
batch no.:	BBZ0000 (Janssen-Cilag)
Reference product 2:	Ritonavir tablet (Norvir®)
dose:	100 mg once daily
mode of admin.:	Oral
batch no.:	923428D (Abbott)
Duration of treatment:	DRV/r alone was administered on Days 1 to 8, DRV/r and BI 201335 were administered together on Days 9 to 16.
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints: $AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{\tau,ss}$ of darunavir on Days 8 and 16 Secondary endpoint: $t_{max,ss}$ of darunavir
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), clinical laboratory tests, analysis of adverse events (AEs), assessment of tolerability by investigator
Statistical methods:	The point estimates for the intrasubject ratio of the geometric means (for treatments Test and Reference) of the primary pharmacokinetic parameters and their 2-sided 90% confidence intervals (CIs) were calculated. DRV/r administered together with BI 201335 was regarded as the Test treatment, DRV/r alone was regarded as the Reference treatment. The statistical model was an analysis of variance (ANOVA) model on log-transformed parameters including effects for 'subject' and 'treatment'. For all other parameters, descriptive statistics were calculated.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	A total of 14 healthy subjects (12 males and 2 females) were entered into the study and treated. The mean age was 40.4 years, ranging from 20 to 55 years, and the mean BMI was 23.47 kg/m^2, ranging from 19.3 to 29.3 kg/m^2. All subjects completed the planned observation time.

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Clinical pharmacology results (cont.):

The steady-state pharmacokinetics of darunavir when coadministered with ritonavir and BI 201335 and when administered with ritonavir alone are summarised in Table 1 and the results of the statistical analysis are summarised in Table 2.

Table 1: Steady-state pharmacokinetic parameters of darunavir

Darunavir parameter	DRV/r + BI 201335 (Test)		DRV/r alone (Reference)	
	gMean (N=14)	gCV [%]	gMean (N=14)	gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	66000	39.9	57200	29.5
$C_{max,ss}$ [ng/mL]	6330	26.5	4930	23.9
$C_{24,ss}$ [ng/mL]	1170	90.3	1330	49.5
$t_{max,ss}$ [h]	2.06	37.3	1.73	33.9

Table 2: Adjusted gMean ratio, 90% confidence interval, and intraindividual geometric coefficient of variation (gCV) for the primary parameters of darunavir

Darunavir parameter (N=14)	Adjusted gMean ratio Test/Reference [%]	Two-sided 90% CI		gCV [%]
		Lower limit [%]	Upper limit [%]	
$AUC_{\tau,ss}$	115.3	101.4	131.1	19.4
$C_{max,ss}$	128.4	115.7	142.5	15.6
$C_{24,ss}$	87.9	68.6	112.6	38.3

When DRV/r was coadministered with BI 201335, darunavir gMean $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased by 15% and 28%, respectively, and gMean $C_{24,ss}$ was decreased by 12% compared with DRV/r alone.

In this study, BI 201335 was not administered without DRV/r, thus the effect of DRV/r on the pharmacokinetics of BI 201335 can only be estimated. Geometric mean $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 201335 in the presence of DRV/r were 115000 ng·h/mL and 8780 ng/mL, respectively. Compared to exposure data obtained in a previous study for BI 201335 alone (study 1220.6: gMean $AUC_{\tau,ss}$ 50100 ng·h/mL and $C_{max,ss}$ 5360 ng/mL), this means an increase of approximately 2.3-fold and 1.6-fold, respectively, when BI 201335 is coadministered with DRV/r.

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Safety results:

Each subject was administered a total dose of 2160 mg BI 201335 (1 dose of 480 mg and 7 doses of 240 mg), 12800 mg darunavir (16 doses of 800 mg), and 1600 mg ritonavir (16 doses of 100 mg) as planned.

Serious or severe AEs did not occur and no subject discontinued due to an AE. Of the 14 treated subjects, 11 (78.6%) reported at least 1 AE during the study; 7 subjects (50.0%) during treatment with DRV/r and 11 subjects (78.6%) during the combined treatment. The majority of AEs was assessed as treatment-related. Six subjects (42.9%) reported drug-related AEs during treatment with DRV/r and 11 subjects (78.6%) reported drug-related AEs during the combined treatment. The most frequently reported AEs in this study were gastrointestinal disorders; they occurred more often during treatment with DRV/r + BI 201335 (10 subjects, 71.4%) than during treatment with DRV/r alone (2 subjects, 14.3%). Diarrhoea was the most frequently reported AE on the preferred term level, followed by abdominal distension, headache, fatigue, and nausea. Diarrhoea was reported for 1 subject (7.1%) during treatment with DRV/r alone and for 6 subjects (42.9%) during the combined treatment. Abdominal distension only occurred during the combined treatment (4 subjects, 28.6%).
During the study, mean values for total bilirubin increased from 8.5 µmol/L at baseline to 19.1 µmol/L at the end-of-study visit and mean values for direct bilirubin increased from 3.0 µmol/L to 4.5 µmol/L. No other relevant changes in laboratory parameters were observed and there were no findings with respect to vital signs or ECG recordings. The assessment of tolerability was good for all subjects and both treatments.

Conclusions:

Coadministration of 240 mg once daily BI 201335 with DRV/r resulted in an increase in $AUC_{\tau,ss}$ and $C_{max,ss}$ of darunavir by 15% and 28%, respectively, and a decrease in $C_{24,ss}$ by 12%. These changes are not considered clinically important. However, $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 201335 were 2.3-fold and 1.6-fold higher, respectively, than what was seen in a previous trial (1220.6), suggesting a clinically meaningful increase in BI 201335 exposure when BI 201335 and DRV/r are coadministered. Therefore, it is recommended that a dose of 120 mg once daily BI 201335 be coadministered with 800 mg/100 mg once daily DRV/r, as part of antiretroviral therapy, in the treatment of HIV/HCV co-infected patients.

Both treatments, DRV/r alone and DRV/r coadministered with BI 201335, were well tolerated by all subjects.