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***.

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Title of trial:	Evaluation of the effects of single oral dose and multiple oral doses of BI 201335 NA on Cytochrome P_{450} and P-glycoprotein activity using a probe drug cocktail. An open-label, single-arm Phase I study in healthy human volunteers
Coordinating Investigator:	[redacted]
Trial sites:	[redacted]
Publication (reference):	Data from this study have not been published.
Clinical phase:	I
Objectives:	The objective of this trial was to quantify the effect of oral single-dose (480 mg) and steady-state BI 201335 NA (240 mg BID) on intestinal and hepatic cytochrome P450 (CYP) and P-glycoprotein (P-gp) probe drugs as a means of predicting drug interactions. The AUCs for the probe drugs caffeine, warfarin, omeprazole, dextromethorphan, midazolam, and digoxin were assessed.
Methodology:	Open-label, within-group comparison study of overall 38 days duration.
No. of subjects:	
planned:	entered: 24 healthy volunteers
actual:	Enrolled: 47 Entered: 24 treated: 23 analysed (for primary endpoint):
Diagnosis and main criteria for inclusion:	Healthy subjects age ≥18 to ≤55 and weighing at least 50 kg with BMI 18.5-29.9 kg/m2, and negative HIV ELISA, and negative for Hepatitis A, B, and C infection.
Test product:	Probe drugs caffeine, warfarin (with vitamin K), dextromethorphan, omeprazole, intravenous and oral midazolam, and oral digoxin without and co-administered with BI 201335 NA.

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dose:	BI 201335 NA 480 mg loading dose, followed by 240 mg BID for 14 days. Probe drug cocktail, containing caffeine 200 mg, dextromethorphan 30 mg, omeprazole 40 mg, warfarin 10 mg (with vitamin K 10 mg), and midazolam 5 mg. Digoxin, 0.25 mg Midazolam 2 mg intravenously
mode of admin.:	PO: Probe drug cocktail, including caffeine, midazolam, dextromethorphan, warfarin, vitamin K, omeprazole; digoxin, and BI 201335 NA IV: midazolam
batch no.:	Caffeine: Lot# 10043209 Warfarin: Lot# 7C26844A Vitamin K: Lot# 7G773 Dextromethorphan: Lot# (L)480271 Digoxin: Lot# 53422 Omeprazole: Lot# X1712 Midazolam (PO): Lot# H070356A Midazolam (IV): Lot# 107110 BI 201335 NA: B083000212
Reference therapy:	N/A
Duration of treatment:	BI 201335 NA was administered for 14 days on study Days 10 through 23. Probe drug cocktail was administered once each on study Days 1, 10, and 19. Digoxin, was administered on study Days 2 and 20, and IV Midazolam was administered on study Days 3 and 21.

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Criteria for evaluation:

Efficacy / clinical pharmacology:

Efficacy evaluation was not applicable for this study.

Primary pharmacokinetic endpoints:

The effect of multiple doses of BI 201335 NA on systemic probe drug exposures (AUC) utilizing the oral probe drugs caffeine, warfarin (+ vitamin K), omeprazole, dextromethorphan, midazolam (and IV midazolam), and digoxin to predict BI201335 interaction with CYP enzymes 1A2, 2C9, 2C19, 2D6, 3A4/5 (3A), and the P-glycoprotein transporter.

Secondary pharmacokinetic endpoints:

The effect of single dose BI 201335 NA on systemic probe drug exposures (AUC) utilizing the oral probe drugs caffeine, warfarin (+ vitamin K), omeprazole, dextromethorphan and midazolam to predict BI201335 interaction with CYP enzymes 1A2, 2C9, 2C19, 2D6 and 3A4/5.

The effect of single dose compared with that of multiple doses of BI 201335 NA systemic probe drug exposures (AUC) utilizing the oral probe drugs caffeine, warfarin (+ vitamin K), omeprazole and dextromethorphan to predict BI201335 interaction with CYP enzymes 1A2, 2C9, 2C19, 2D6 and 3A4/5.

Other secondary pharmacokinetic endpoints:

The effect of single dose and multiple doses of BI 201335 NA on caffeine-, caffeine metabolites AUC, and dextromethorphan-, dextrophan AUC to predict BI201335 interaction with CYP 1A2, N-acetyltransferase-2 (NAT-2) and xanthine oxidase (XO) and CYP 2D6 activity by comparing parent compound/metabolite ratios in urine before, after one dose, and multiple dosing with BI 201335 NA.

Similar endpoints as listed above for secondary pharmacokinetic parameters C_t, C_{max}, t_{max}, CL/F and $t_{1/2}$.

Determination of BI 201335 NA pharmacokinetic parameters following single dose (e.g., on study day 10) and multiple dosing (e.g., on study Day 19), including: $AUC_{\tau,N}$, $C_{max,N}$, $t_{max,N}$ and $C_{min,N}$ Day 19 (steady state): $C_{max,ss,N}$, $t_{max,ss,N}$, $C_{min,ss,N}$, $AUC_{\tau,ss,N}$, $CL/F_{,ss,N}$

Safety:

Physical examination, vital signs (blood pressure, pulse rate, temperature, respiratory rate), laboratory tests, 12-lead EKG, adverse events, and tolerability

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Statistical methods:

Safety and tolerability:

Descriptive statistics were used to summarize and evaluate safety

Pharmacokinetics: The area under the plasma concentration time curve (AUC, trapezoidal rule, linear up/log down) for caffeine, warfarin, omeprazole, dextromethorphan, midazolam, digoxin and BI 201335 NA was derived using noncompartmental pharmacokinetic analysis. To assess the degree of interaction, two-sided 90% confidence intervals for the geometric mean ratios were provided for all PK parameters and comparisons. No formal statistical hypothesis was tested as the objective of the study was to quantify the effect of BI 201335 NA on probe drug pharmacokinetics.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Results showed no relevant inhibition or induction of CYP1A2, and CYP2D6. A 1.29-fold increase in S-warfarin AUC (geometric means ratio, GMR) was observed with multiple dosing of BI 201335 NA, suggesting mild inhibition of CYP2C9.

Mild inhibition of hepatic CYP3A4/5 (IV midazolam) and moderate inhibition of hepatic and intestinal CYP3A4/5 (oral midazolam) was observed with multiple dosing of BI 201335 NA (e.g., 1.56-fold increase of IV midazolam AUC GMR, and 2.92-fold increase of oral midazolam AUC GMR).

A 1.58-fold and 1.54-fold increase in omeprazole and 5-OH-omeprazole of AUC GMR respectively, was observed with multiple dosing of BI 201335 NA. This similar increase in parent compound (omeprazole) and its CYP2C19 metabolite (5-OH-omeprazole) cannot be explained by inhibition of CYP2C19, but is consistent with BI 201335 inhibiting the CYP3A4/5-dependent minor pathway of omeprazole metabolism, and CYP3A4/5-dependent 5-OH omeprazole metabolism. We therefore conclude that BI 201335 NA did not inhibit nor induce CYP2C19.

A 2.19-fold increase in the digoxin AUC GMR was observed with multiple dosing of BI 201335 NA, suggestive of possible P-glycoprotein inhibition.

CYP genotypes and MDR1 genotypes were not informative in predicting changes in probe drug exposures when BI 201335 NA was administered. No correlation was observed between CYP genotype and baseline BI 201335 AUC, and MDR1 genotype and baseline BI 201335 AUC. With the exception of CYP2C19, no genotypes were associated with the steady-state accumulation of BI 201335. CYP2C19 wild type homozygotes had a 2-fold greater accumulation ratio for the BI 201335 AUC when compared to CYP2C19 heterozygotes.

Steady-state BI 201335 median AUC_{0-12h} for the population of Black/African American subjects with Gilbert's Syndrome (N=6) was approximately 25% lower when compared to the population of White subjects (N=11) and approximately 17% lower when compared to the population of Black/African American subjects without Gilbert's Syndrome (N=5). These differences were not observed with the first (loading) dose of BI 201335 NA. The relevance of this observation in this small population of healthy volunteers to an HCV-infected patient population is not known.

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Safety results:

Twenty-three (96%) of 24 total subjects experienced at least one AE, regardless of causality to study drugs. Diarrhoea, headache, nausea, and jaundice were the most common adverse events occurring in 78%, 78%, 48%, and 74% of these subjects, respectively. There were no deaths, serious, or significant (pre-specified) AEs. The majority of AEs were of mild intensity with only few subjects reporting AEs of moderate intensity. Six of 23 subjects with study drug-related AEs had dyspepsia which was judged to be related to BI201335 NA and resolved after completion of BI201335 NA dosing. One subject discontinued prematurely from the study for protocol violation. All 23 subjects who received BI201335 completed the study and all experienced increases in total bilirubin above the upper limit of the reference range. In 22 of 23 subjects (96%) highest total bilirubin values (range 3.1 to 11.9 mg/dL) were measured on the last day of BI201335 administration (Day 23). These reversible increases in bilirubin were due to increases in indirect bilirubin levels and declined rapidly after completion of BI201335 dosing. The magnitude of indirect hyperbilirubinemia might have been associated with the predicted UGT1A1 activity based on UGT1A1 genotype of the subjects. Subjects with Gilbert's UGT1A1 polymorphism (*28/*28) or (*60/*60) had higher elevations of indirect bilirubin when compared to subjects with wild type or heterozygous UGT1A1 genotype. One of 23 subjects developed an asymptomatic 2.5-fold elevation of ALT liver enzyme that spontaneously reversed. Observed adverse events and laboratory findings are consistent with the known profile of BI 201335 NA.

Conclusions:

A phenotypic cocktail study was conducted with normal volunteers to quantify the effect of 14 days of BI 201335 NA administration on the activity of hepatic CYP1A2 (caffeine), 2C9 (warfarin), 2C19 (omeprazole), 2D6 (dextromethorphan) and the activity of intestinal and hepatic CYP3A4/5 (CYP3A) (midazolam) and P-gp (digoxin). This study determined the first-dose and steady-state effects of BI 201335 NA oral capsules administered as a 480 mg loading dose, followed by 240mg twice-daily, and BI 201335 NA was well tolerated.

No relevant net effects were observed on CYP1A2-, 2D6-, and 2C19. Based on the observed weak inhibition of CYP2C9 with multiple dosing of BI 201335 NA using a loading dose of 480 mg followed by 240 mg twice daily dosing of BI 201335 NA, dose adjustments for CYP2C9 substrates with narrow therapeutic range (NTR), such as warfarin and phenytoin, may be necessary and should be followed with therapeutic monitoring.

With the loading dose of 480 mg followed by twice daily dosing with 240 mg, BI 201335 is a moderate CYP3A inhibitor. Dose adjustment should be

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considered for concomitant medications that meet one or more of the following criteria:

sensitive CYP3A substrate,

major CYP3A metabolism ± CYP3A inhibition,

CYP3A substrate with narrow therapeutic range (NTR)

CYP3A substrates with NTR, whose exposure response indicates that increases in their exposure levels by the concomitant use of BI 201335 NA may lead to serious safety concerns (e.g., Torsades de Pointes) should not be used concurrently with the BI 201335 NA dosing and schedule used in this study.

A loading dose of 480 mg followed by 240 mg twice daily dosing of BI 201335 NA increased digoxin AUC geometric mean ratio by ~2-fold, which is suggestive but not proof of P-gp inhibition, and results may not be extrapolated to other P-gp substrates. Dose reduction and careful monitoring of digoxin levels is recommended with concomitant BI 201335 NA therapy using the described dosing and schedule.

It is currently not known, whether the magnitude of effect on CYP2C9, CYP3A and P-gp observed is dependent on the dose and schedule of BI 201335 NA. It is possible that multiple dosing with 120mg or 240mg once daily BI 201335 NA may show a lesser effect on the respective CYP enzymes and P-gp.

CYP and MDR1 genotype were not observed to be predictive of changes in probe drug exposures when BI 201335 NA was administered.

Steady-state BI 201335 AUC was more variable in the population of African American subjects when compared to Caucasians. The relevance of this observation in this small population of healthy volunteers to an HCV-infected patient population is not known.