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 study:	A study to evaluate the effect of multiple doses of 500 mg of BIRT 2584 XX tablets on the pharmacokinetic parameters of warfarin, omeprazole, caffeine, and dextromethorphan dosed orally and midazolam dosed IV, in healthy male volunteers
Investigator:	[redacted]
Study center:	[redacted] Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The study aimed to investigate the effect of BIRT 2584 XX and its metabolite BI 610100 on the PK of five probe substrates for cytochrome P450 isozymes. The substrates used to monitor enzyme activity were oral warfarin (for CYP2C9), oral omeprazole (for CYP2C19), oral dextromethorphan (for CYP2D6), oral caffeine (for CYP1A2) and intravenous midazolam (for hepatic CYP3A).
Methodology:	Open-label, single-group, multiple-dose, fixed sequential treatment design in healthy male volunteers
No. of subjects: **planned:** **actual:**	20 entered: 20 enrolled: 35 <u>BIRT 2584 XX:</u> entered: 20 treated: 19 analysed: 19 <u>PK-cocktail:</u> Warfarin entered: 20 treated: 20 analysed (for primary endpoint): 20 Caffeine entered: 20 treated: 20 analysed (for primary endpoint): 20 Dextromethorphan entered: 20 treated: 20 analysed (for primary endpoint): 20 Omeprazole entered: 20 treated: 20 analysed (for primary endpoint): 20 Midazolam IV entered: 20 treated: 20 analysed (for primary endpoint): 20 Vitamin K_1 entered: 20 treated: 20

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Diagnosis and main criteria for inclusion:	Healthy; male; ≥ 18 and ≤ 55 years old; BMI ≥ 18.5 and ≤ 29.9 kg/m^2; signed written informed consent; non-smoker
Test product:	BIRT 2584 XX tablets
dose:	500 mg qd (dosing on days 1 and 2 was bid)
mode of admin.:	Oral
batch no.:	PD-2522
Duration of treatment:	16 days
Reference therapy:	PK-cocktail (single doses on days -4, 1, and 15)
	Warfarin
dose:	10 mg
mode of admin.:	Oral
batch no.:	5D08
	Vitamin K_1
dose:	10 mg
mode of admin.:	Oral
batch no.:	F003901
	Caffeine
dose:	200 mg
mode of admin.:	Oral
batch no.:	76104A
	Dextromethorphan
dose:	30 mg
mode of admin.:	Oral
batch no.:	E36289

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	Omeprazole
dose:	40 mg
mode of admin.:	Oral
batch no.:	E16913
	Midazolam
dose:	0.025 mg/kg
mode of admin.:	Intravenous
batch no.:	F009701

Criteria for evaluation:

Efficacy:

Pharmacokinetic parameters of S-warfarin, midazolam IV, omeprazole and its metabolite 5-hydroxyomeprazole, dextromethorphan and its metabolite dextrophan, and the N-demethylated metabolites of caffeine were determined before dosing of BIRT 2584 XX (day -4), after a single dose of BIRT 2584 XX (on day 1), and after repeated doses of BIRT 2584 XX (on day 15).

Primary endpoints:
$AUC_{0\text{-}inf}$ of S-warfarin and midazolam IV;
AUC ratio of omeprazole to 5-hydroxyomeprazole;
0-12 hr urinary molar caffeine metabolite ratio (1X+1U+AFMU)/17U;
0-12 hr urinary dextromethorphan/dextrorphan ratio

Secondary endpoints:
$AUC_{0\text{-}tz}$, C_{max}, t_{max}, λ_Z, $t_{1/2}$, MRT, CL/F, V_Z/F of S-warfarin, omeprazole, and intravenous midazolam; $AUC_{0\text{-}inf}$ of omeprazole; trough levels and approximate peak levels of BIRT 2584 XX and BI 610100

Safety:

Physical examination, vital signs (systolic and diastolic blood pressure and pulse rate), ECG, laboratory measurements, adverse events, and tolerability

Statistical methods:

Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0\text{-}inf}$ and C_{max} and their two-sided 90% confidence intervals (CIs) were calculated for comparisons:

before BIRT 2584 XX dosing on day -4,
after a single dose of BIRT 2584 XX on day 1,
and after repeated doses of BIRT 2584 XX on day 15.

The statistical model was ANOVA on log transformed parameters. CIs were based on the residual error from ANOVA. Descriptive statistics were calculated for all other parameters.

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SUMMARY – CONCLUSIONS:

Efficacy results:

The study investigated the effect of BIRT 2584 XX and its metabolite BI 610100 on the cytochrome P450 isozymes CYP2C9, CYP2C19, CYP2D6, CYP1A2, and hepatic CYP3A using the probe substrates of the Cooperstown 5+1 cocktail.

Hepatic CYP3A:

On the first day, a small increase in plasma $AUC_{0\text{-}inf}$ of 11% compared to baseline was observed for midazolam with a 90% CI of 105-115%. On day 15, midazolam $AUC_{0\text{-}inf}$ decreased to 52% of the baseline value with a 90% CI of 48-56%. This demonstrated an irrelevant inhibition of hepatic CYP3A by BIRT 2584 XX and BI 610100 after a single dose combined with a substantial induction of hepatic CYP3A manifesting after multiple doses of BIRT 2584 XX.

CYP2C19:

A statistically significant increase of the plasma ratio of omeprazole $AUC_{0\text{-}tz}$ to 5-hydroxyomeprazole $AUC_{0\text{-}tz}$ (30% compared to baseline, 90% CI 119-143%) was seen after a single dose of BIRT 2584 XX; the ratio remained at this higher level after multiple doses as determined on day 15 (90% CI 114-148%). The increase in the ratio of omeprazole to its metabolite 5-hydroxyomeprazole could indicate a slight inhibition of CYP2C19. However, there was substantial inter-subject variability and an inconsistent pattern of increase in individual subjects, suggesting that inhibition was not important.

CYP2C9:

The plasma S-warfarin $AUC_{0\text{-}inf}$ increased 52% on the first day of BIRT 2584 XX dosing compared to baseline (90% CI 143-163%) and was 3.3-fold higher than baseline on day 15 of dosing (90% CI 286-381%). These data demonstrated that BIRT 2584 XX and or BI 610100 exhibit substantial inhibition but no apparent induction of CYP2C9.

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CYP2D6:

There was a 58% increase in the mean urinary dextromethorphan/dextrophan molar ratio after a single dose of BIRT 2584 XX (90% CI 122-206%) compared to the pre-BIRT 2584 XX ratio at baseline; after multiple doses on day 15, the mean ratio had returned to the baseline value (90% CI 69-126%). A very high inter-subject variability was observed. Because of the substantial inter-subject variability, one could not conclude that there was inhibition of CYP2D6 by BIRT 2584 XX or BI 6010100. CYP2D6 is not an inducible enzyme and therefore, the decrease in ratio from day 1 to day 15, which also had high inter-subject variability, was not due to induction by BIRT 2584 XX or BI 610100.

CYP1A2:

The caffeine N-demethylated metabolite urinary molar concentration ratio [(AFMU+1U+1X)/17U] was calculated based on the data of all subjects and additionally for only those subjects who had no pre-dose 17U in their urine. Both analyses did not relevantly differ from each other, therefore the conclusions are made only for all the subjects together. For all subjects, the 90% CI for the comparison of baseline (pre-BIRT 2584 XX, day -4) to day 1 (single dose of BIRT 2584 XX) was 98-133%; the 90% CI for the comparison of baseline to day 15 was 91-121%. Furthermore, the change in urinary metabolite concentration ratio for each day was variable and not consistent among the subjects. These data indicate that no inhibition or induction of CYP1A2 by BIRT 2584 XX or BI 610100 occurs.

BIRT 2584 XX / BI 610100:

Geometric mean plasma concentrations were 1320 ng/ml for BIRT 2584 XX and 202 ng/mL for BI 610100 on day 1; on day 15, plasma concentrations were 822 ng/mL for BIRT 2584 XX and 1370 ng/mL for BI 610100. These plasma concentrations were slightly higher than in a recently completed multiple rising dose study (BI 1206.2, U06-1059) and were considered adequate to assess enzyme inhibition or induction.

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Safety results:

There were no serious adverse events and no discontinuations due to adverse events (AEs). A total of 18 subjects experienced an AE during the trial. The adverse event profile was consistent with that seen in previous trials on BIRT 2584 XX in healthy volunteers and with drug-drug interaction (DDI) studies using the Cooperstown 5+1 cocktail. The most common adverse events observed were (by number of subjects and preferred term) fatigue (13 subjects), diarrhoea (8 subjects, investigator's reported term: loose stools), abdominal distension (5 subjects), abdominal pain (3 subjects), and headache (6 subjects). Two subjects developed exanthema during the study. Drug related AEs were observed in 18 out of 20 subjects. The most frequently observed drug-related AE was fatigue which occurred predominantly following administration of the Cooperstown 5+1 cocktail and is a known side effect of midazolam. As loose stools, abdominal pain, and exanthema were already observed in preceding studies with BIRT 2584 XX in healthy subjects, a causal relation of these AEs with the investigational drug was assumed by the investigator. All subjects who experienced an AE recovered fully.

During this study, an increase of ALT to 5.1 times the ULN accompanied by a less pronounced increase in AST was observed in one subject. The increase was recorded as an AE related to BIRT 2584 XX. As already seen in the previous phase I studies, lymphocyte counts increased on treatment with BIRT 2584 XX. The increase is of no concern; it is considered a mechanism-related effect caused by decreased margination and transmigration of lymphocytes from the blood stream and consistent with publications reporting that the approved LFA-1 antibody efalizumab exhibits a similar effect (R04-2288). No adverse effects were revealed upon evaluation of the vital signs and physical examination. The administration of BIRT 2584 XX and the Cooperstown 5+1 cocktail was well tolerated in the majority of subjects; however, due to the multitude of substances given, the attribution of AEs to treatments remains unclear and definitive conclusions are difficult.

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Conclusions:

The midazolam $AUC_{0\text{-}inf}$ data indicated that the overall effect of BIRT 2584 XX or its metabolite BI 610100 on hepatic CYP3A at steady-state was induction. The weak inhibition of hepatic CYP3A observed before the induction appeared was considered minor. The omeprazole/5-hydroxyomeprazole ratio data suggested that there was no relevant inhibition or induction of CYP2C19. The S-warfarin $AUC_{0\text{-}inf}$ data demonstrated a strong and consistent inhibition of CYP2C9 by BIRT 2584 XX or BI 610100. The dextromethorphan/metabolite urinary concentration ratio data did not show consistent inhibition of CYP2D6; the inter-subject variability was high. The caffeine metabolite urinary concentration ratio data indicated that there is no inhibition or induction of CYP1A2 by BIRT 2584 XX or BI 610100.

BIRT 2584 XX was safe and well tolerated in the majority of subjects at a daily dose of 500 mg.