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.

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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 Study Report**		
Name of finished product:				
Name of active ingredient: BIRT 2584 XX		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 24 JAN 2006	**Number:** U06-1059	**Study period (dates):** 23 JUN 05 - 16 AUG 05		

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 midazolam in healthy male volunteers
Investigator:	[redacted]
Study centers:	Human Pharmacology Centre, Biberach
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The objective of the study was to investigate the effect of BIRT 2584 XX and its metabolite BI 610100 when BIRT 2584 XX is administered as a tablet to near steady state in estimated high therapeutic dose on the pharmacokinetics (PK) of midazolam, a probe substrate for CYP3A4. The PK of midazolam was measured before dosing of BIRT 2584 XX, after a single dose of BIRT 2584 XX and after repeated doses of BIRT 2584 XX for 3 and 12 days.
Methodology:	Open-label, randomized fixed sequence, multiple dose study
No. of subjects:	20
planned:	entered: 20
actual:	enrolled: 20
	BIRT 2584 XX: entered: 20 treated: 20 analysed (for primary endpoint): 20 Midazolam (probe substrate): entered: 20 treated: 20 analysed (for primary endpoint): 20
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
Test product:	BIRT 2584 XX as a tablet formulation with the excipients lactose, povidone K30, avicel PH 102, sodium starch glycolate, and magnesium stearate
dose:	500 mg qd with a bid regimen on the first two days of BIRT 2584 XX administration
mode of admin.:	Oral
batch no.:	PD-2522
Duration of treatment:	14 days

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Reference therapy:	Midazolam (as a probe substrate)
dose:	7.5 mg as a single dose on days -2, 1, 3, and 12
mode of admin.:	Oral
batch no.:	B155811
Criteria for evaluation:	
Efficacy:	Pharmacokinetic parameters of midazolam and 1'-hydroxymidazolam were determined before and during treatment with BIRT 2584 XX. Primary endpoints: $AUC_{0-\infty}$ and C_{max} for midazolam and 1'-hydroxymidazolam, and $AUC_{0-\infty}$ ratio of 1'-hydroxymidazolam/midazolam Secondary endpoints: AUC_{0-tz}, t_{max}, λ_Z, $t_{1/2}$, MRT_{po}, CL/F, and V_Z/F for midazolam and 1'-hydroxymidazolam, and pre-dose levels of BIRT 2584 XX and its metabolite BI 610100 on days 1, 3, and 12
Safety:	Physical examination, vital signs (BP, PR), ECG, laboratory measurements, adverse events, and tolerability
Statistical methods:	Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-\infty}$ and C_{max} and their two-sided 90% confidence intervals (CIs) were calculated. The statistical model was ANOVA (analysis of variance) on log transformed parameters. CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Following the administration of a single dose of BIRT 2584 XX, the geometric mean plasma $AUC_{0\text{-}tz}$ of the probe substrate midazolam increased from 94.9 hr•ng/mL (baseline) to 140 hr•ng/mL. The $AUC_{0\text{-}tz}$ of the metabolite 1'-hydroxymidazolam also increased. As a consequence, the 1'-hydroxymidazolam/midazolam AUC ratio did not differ significantly from baseline. The increase in mean plasma $AUC_{0\text{-}tz}$ indicated weak inhibition of CYP3A4 metabolism by BIRT 2584 XX and/ or its metabolite BI 610100.

After 3 days of BIRT 2584 XX dosing, plasma concentrations of midazolam had decreased, while plasma concentrations of 1'-hydroxymidazolam had further increased. After 12 days of BIRT 2584 XX dosing, the mean midazolam $AUC_{0\text{-}tz}$ was 23.4 hr•ng/mL (or 25% of the baseline value) and the mean 1'-hydroxymidazolam $AUC_{0\text{-}tz}$ was 89.9 hr•ng/mL (or 306% of the baseline value). The calculated AUC ratio for 1'-hydroxymidazolam/midazolam was 3.84. Thus, after multiple dosing, BIRT 2584 XX and/or BI 610100 substantially induced CYP3A4 metabolism.

A similar pattern as for $AUC_{0\text{-}tz}$ was observed for the mean C_{max} values of midazolam and 1'-hydroxymidazolam. However, intersubject variability was much higher for C_{max} than for $AUC_{0\text{-}tz}$.

Exposures to BIRT 2584 XX and BI 610100 were comparable to exposures seen in a previous study (BI 1206.2) after multiple dosing and thus adequate for assessing inhibition and induction of midazolam metabolism by these compounds.

Overall, the PK data indicated that BIRT 2584 XX/BI 610100 exhibits both a weak inhibition and a significant induction of the metabolising enzyme CYP3A4. The net effect at steady state was substantial induction as the observed inductive effect was much stronger than the inhibitory effect.

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Safety results:

BIRT 2584 XX administered as a tablet formulation was generally well tolerated at the dose administered (500 mg qd with a bid regimen on the first two days).

No deaths and no serious adverse events (SAE) occurred in this study. A total of 11 subjects (55.0%) experienced adverse events (AE). All AEs observed during the study were classified as mild with the exception of one AE, which was moderate in intensity. Loose/watery stools mapped to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term 'diarrhoea' was the AE with the highest incidence (6 subjects). This AE did not occur on the days when subjects were treated with 500 mg BIRT 2584 XX qd. Two subjects experienced loose/watery stools when they had not received BIRT 2584 XX yet (during the wash-out period and on day -2, respectively). Three subjects had loose or watery stools after they had been administered a daily dose of 1000 mg of BIRT 2584 XX (500 mg bid). In 1 subject, the onset of watery stools was post-treatment. One subject experienced diarrhoea (investigator's reported term) in the post-treatment period. Other AEs within the system organ class 'gastrointestinal disorders' included nausea (3 subjects), flatulence (2 subjects), abdominal pain (1 subject), and upper abdominal pain (1 subject). Skin and subcutaneous tissue disorders affected a total of 3 subjects. Of those, 2 subjects reported exanthema. One subject had alopecia and hyperkeratosis. One subject developed acne and rash. The nervous system disorders observed were headache (2 subjects) and dizziness (1 subject). One subject experienced myalgia during the study. One subject had a folliculitis. Loose/watery stools and flatulence were judged as related to BIRT 2584 XX in 5 subjects and 1 subject, respectively.

The laboratory evaluation revealed no clinically relevant abnormalities. An increase of WBCs mainly attributable to rising lymphocyte and neutrophils counts was noted. This is considered a mechanism-related effect caused by a decrease of margination and transmigration of lymphocytes from the blood stream and not regarded as a safety concern. No clinically relevant effects of BIRT 2584 XX on vital signs and electrocardiograms (ECGs) were observed. The physical examination did not reveal any abnormalities.

The global tolerability was good in all subjects.

Conclusions:

At or near steady state, a net induction of CYP3A4 metabolism by BIRT 2584 XX and/or its metabolite BI 610100 was found. Single-dose data indicated BIRT 2584 XX and/or BI 610100 are weak CYP3A4 inhibitors. BIRT 2584 XX was safe and well tolerated at a daily dose of 500 mg and with concomitant administration of the CYP3A4 probe substrate midazolam.