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: 17 July 2007	**Number:** U07-1697	**Study period (dates):** 16 AUG 06 – 14 NOV 06		

Title of study:	A study to evaluate the effect of a single oral dose and multiple oral doses of 500 mg of BIRT 2584 XX tablets on the pharmacokinetic parameters of amitriptyline and nortriptyline in healthy male and female subjects
Investigator:	[redacted]
Study centre:	[redacted] Germany
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objective:	The objective of the study was to demonstrate that there is no clinically relevant interaction between amitriptyline (or its metabolite nortriptyline) and BIRT 2584 XX (or its metabolite BI 610100) when BIRT 2584 XX is administered as a tablet formulation to near steady state in an estimated high therapeutic dose. Pharmacokinetics (PK) of amitriptyline and nortriptyline were measured before dosing of BIRT 2584 XX, after the first dose of BIRT 2584 XX, and after repeated doses of BIRT 2584 XX near steady state
Methodology:	Multiple-dose, one-sequence, open-label study
No. of subjects:	
planned:	entered: 24
actual:	enrolled: 41 entered: 24 treated: 24 analysed (for primary endpoint): 24
Diagnosis and main criteria for inclusion:	24 healthy subjects, female or male, age ≥ 18 and ≤ 55 years, BMI ≥ 18.5 and ≤ 29.9 kg/m^2, written informed consent given
Test product:	BIRT 2584 XX
dose:	Days 1 and 2: 500 mg twice daily (bid) Days 3 to 21: 500 mg once daily (qd)
mode of admin.:	Oral (p.o.)
batch no.:	PD-2792
Duration of treatment:	21 days
Reference therapy:	Amitriptyline (Saroten® Tabs 50 mg)
dose:	Single dose of 50 mg on day -8, day 1, and day 15

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Name of active ingredient: BIRT 2584 XX		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
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mode of admin.:	Oral (p.o.)
batch no.:	261905
Criteria for evaluation:	
Efficacy:	Pharmacokinetics: Primary endpoints: $AUC_{0-\infty}$ of amitriptyline and $AUC_{0-\infty}$ ratio of amitriptyline/nortriptyline on day 15 Secondary endpoints: $AUC_{0-\infty}$ of amitriptyline and $AUC_{0-\infty,}$ ratio of amitriptyline/nortriptyline on day 1, C_{max} of amitriptyline on days 1 and 15, $AUC_{0-\infty}$ and C_{max} of nortriptyline on days 1 and 15, t_{max}, λ_Z, $t_{1/2}$, MRT_{po}, CL/F, Vz/F of amitriptyline and nortriptyline, pre-dose levels of BIRT 2584 XX and BI 610100 on days 1 and 2, and 13 to 15
Safety:	Adverse events, vital signs, ECG, physician's global tolerability assessment, laboratory parameters, and general physical examination
Statistical methods:	Point estimators (geometric means) of the median intra-subject ratios of PK endpoints and their two-sided 90% confidence intervals (CIs) were calculated. The statistical model was ANOVA 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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Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
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SUMMARY – CONCLUSIONS:

Efficacy results:

Amitriptyline is metabolised to some degree by CYP2C9 but also to a significant extent by several other CYPs. BIRT 2584 XX and/or its metabolite BI 610100 have been identified as important inhibitors of CYP2C9. Data on day 1 are consistent with a lack of inhibition of the metabolism of amitriptyline. After administration of a single dose of BIRT 2584 XX, the mean plasma $AUC_{0-\infty}$ of amitriptyline and the amitriptyline/nortriptyline $AUC_{0-\infty}$ ratio did not change significantly from baseline. BIRT 2584 XX and/or BI 610100 are important inducers of CYP3A4. Data on day 15 are all consistent with a substantial induction of amitriptyline and nortriptyline metabolism after multiple dosing. The mean amitriptyline $AUC_{0-\infty}$ decreased to 39% of the baseline value and the amitriptyline/nortriptyline $AUC_{0-\infty}$ ratio decreased to 49% of the baseline value. A similar induction of amitriptyline and nortriptyline metabolism was seen with St. John's Wort, a known CYP3A4 inducer. The potency of BIRT 2584 XX or its metabolite BI 610100 to induce amitriptyline metabolism was slightly greater than published for St. John's Wort, which was reported to reduce the AUC of amitriptyline by 22% from baseline value. The potency of induction of nortriptyline metabolism was lower than published (reduction of AUC by 41% from baseline value). Concentrations measured for BIRT 2584 XX and BI 610100 in this study were similar to what was observed for 500 mg qd dosing in the multiple rising dose study [U06-1061]. Therefore, exposure to BIRT 2584 XX and BI 610100 was reasonable for assessing the drug-drug interaction with amitriptyline and nortriptyline.

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Safety results:

BIRT 2584 XX administered as tablet formulation was generally well tolerated at the dose administered (500 mg bid/qd). No deaths and no serious adverse events (SAE) occurred in this study. All AEs observed were of mild or moderate intensity. Loose or watery stools and skin disorders were the most frequently observed drug-related AEs. Loose or watery stools occurred in 5 subjects. In all cases, these stool abnormalities were mild in intensity and had a short duration. The frequency and intensity of loose stools appeared to be comparable to that observed in other studies conducted with BIRT 2584 XX [U06-1059, U06-1061 and U06-1729]. Localised skin events (erythema, and rash) occurred in 8 subjects on treatment with BIRT 2584 XX alone or in combination with amitriptyline, and were all considered drug related; these AEs were mild or moderate in intensity and resolved without specific treatment. Increases in WBC counts and absolute lymphocyte counts were observed. These changes were similar in degree and frequency to those observed in previous studies with BIRT 2584 XX [U06-1059, U06-1061 and U06-1729] and are assumed to be a mechanism-related effect caused by a decrease of margination and transmigration of lymphocytes from the blood stream; increases in WBC counts and absolute lymphocyte counts are therefore not regarded as a safety concern. Apart from the increases in WBC and lymphocyte counts, there were no relevant changes in haematology or coagulation parameters. The observed liver function test (LFT) abnormalities on treatment with BIRT 2584 XX (elevation of ALT (max.: 2-3-fold the ULN) in 5 subjects and elevation of AST (max.: 2-3-fold the ULN) in 3 subjects were similar to those observed in previous studies [U05-2074 and U06-1729]. All LFT abnormalities returned to normal or decreased after drug discontinuation. Uric acid level tend to fall in 21 out of 24 subjects. Other serum parameters did not change. No relevant cardiovascular abnormalities were reported throughout the study and at the additional follow-up visits which were scheduled due to unusual cardiac findings (hydropic degeneration of cardiomyocytes) in a preliminary toxicology study in mice [U07-3018]. No clinically relevant effects of BIRT 2584 XX on vital signs or electrocardiograms (ECGs) were observed. The physical examination did not reveal any abnormalities. The global tolerability was judged as good for 13 subjects and as satisfactory for 8 subjects. Associated with their AEs, the tolerability was judged as not satisfactory for 3 subjects.

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Conclusions:	Exposure to BIRT 2584 XX 500 mg bid/qd was reasonable to assess the drug-drug interaction with amitriptyline and nortriptyline. The data are consistent with a lack of inhibition of the metabolism of amitriptyline after a single dose of BIRT 2584 XX and with a substantial induction of amitriptyline and nortriptyline metabolism after multiple dosing. BIRT 2584 XX was safe at a dose of 500 mg bid/qd and was well tolerated by the majority of the subjects.