Clinical Study Synopsis for Public Disclosure

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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: 25 JAN 06	**Number:** U06-1061	**Study period (dates):** 20 JAN 05 - 5 JUL 05		

Title of study:	Safety, pharmacokinetics, and pharmacodynamics of BIRT 2584 XX administered as multiple doses of 100 mg to 750 mg qd for 14 or 28 days (randomised, double-blind placebo controlled design), and safety and pharmacokinetics of 500 mg of BIRT 2584 XX administered with and without food as single dose (open, intra-individual comparison) to healthy male volunteers
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Biberach
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	The study comprised two parts. The objective of the first study period was to assess the safety and pharmacokinetics of 500 mg of BIRT 2584 XX tablets administered with and without food in male healthy volunteers and to determine the relative bioavailability of the BIRT 2584 XX tablet formulation compared by historical comparison to BIRT 2584 XX powder in PEG 400 (U05-2074) (part 1). The second and major phase of the trial was aimed at evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of BIRT 2584 XX (100 mg, 250 mg, and 500 mg bid on the first 2 days and qd on the following 12 days, or 750 mg qd for 28 days) in healthy male subjects (part 2).
Methodology:	Part 1 - bioavailability/food effect: intra-individual comparison Part 2 – multiple rising doses: randomised, double-blind, placebo controlled
No. of subjects:	
planned:	entered: 74 (part 1: 10 BIRT 2584 XX; part 2: 48 BIRT 2584 XX, 16 placebo)
actual:	enrolled: 74 (part 1: 10 BIRT 2584 XX; part 2: 48 BIRT 2584 XX, 16 placebo) BIRT 2584 XX: entered: 58 (part 1: 10, part 2: 48) treated: 58 (part 1: 10, part 2: 48) analysed (for primary endpoint): 58 (part 1: 10, part 2: 48) Placebo: entered: 16 treated: 16 analysed (for primary endpoint): 16

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Name of active ingredient: BIRT 2584 XX		**Page:**	**Number:**	
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Diagnosis and main criteria for inclusion:	Healthy, male, ≥ 18 and ≤ 63 years old, BMI ≥ 18.5 and ≤ 29.9 kg/m^2
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:	Part 1 - bioavailability/food effect: two single doses of 500 mg Part 2 – multiple rising doses: 100 mg, 250 mg, and 500 mg bid on the first 2 days and qd on the following 12 days 750 mg qd for 28 days
mode of admin.:	Per os
batch no.:	PD-2520 (BIRT 2584 XX 50 mg), PD-2522 (BIRT 2584 XX 100 mg)
Duration of treatment:	Part 1 – bioavailability/food effect: two single doses Part 2 – multiple rising doses: 14 days (100 mg, 250 mg, and 500 mg qd with a bid regimen on the first 2 days), 28 days (750 mg qd)
Reference therapy:	Placebo with the excipients lactose, povidone K30, avicel PH 102, sodium starch glycolate, and magnesium stearate
dose:	N. A.
mode of admin.:	Per os
batch no.:	PD-2521 (placebo 50 mg), PD-2523 (placebo 100 mg)
Criteria for evaluation:	
Efficacy:	Pharmacodynamics of BIRT 2584 XX: assessment of receptor occupancy as determined by a competitive binding assay using anti-LFA-1 antibody fragment as competitor, *ex vivo* suppression of superantigen (SEB)-induced IL-2 production, total number of white blood cells and leukocyte differential cell count including relative percent of T- and B- cells Pharmacokinetics of BIRT 2584 XX and its metabolite BI 610100: Part 1 - bioavailability/food effect: $AUC_{0\text{-}inf}$, C_{max}, t_{max} Part 2 – multiple rising doses: $C_{max,1}$, $t_{max,1}$, $AUC_{0\text{-}12}$, $AUC_{tau,1}$, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $Vz/F_{,ss}$, $Ae_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss}$, and the accumulation ratios $R_{A,Cmax}$ and $R_{A,AUC}$
Safety:	Adverse events, vital signs (pulse rate, systolic and diastolic blood pressure), laboratory values, 12-lead electrocardiograms, physical examination, and tolerability

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Statistical methods: Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics: Analysis of the pharmacokinetic parameters showed that BIRT 2584 XX and/or its metabolite BI 610100 induced the metabolism of BIRT 2584 XX after multiple dosing. The mean half-life of BIRT 2584 XX was 6-7 hours. Although BI 610100 accumulated 3-4 fold on multiple dosing, it appeared its disposition was also induced to some extent. The mean BI 610100 half-life was 38-68 hours. The increase in BI 610100 and decrease in BIRT 2584 XX concentrations meant that BI 610100 is the predominant compound after multiple dosing. BIRT 2584 XX and BI 610100 pharmacokinetics appeared to be dose proportional at doses of 250 mg qd and above. Steady state was not reached for BIRT 2584 XX or BI 610100 by day 14 at the 100 mg or 250 mg qd doses. Steady state was reached by day 13 for the 500 mg qd dose (earlier for BIRT 2584 XX) , and most likely by day 24 for both compounds at the 750 mg qd dose, although the differences between C_{pre} values between some of the days after day 24 and the value for day 28 were small but statistically significant.

Pharmacodynamics: Receptor occupancy was assessed in whole white blood in a flow cytometry-based assay. Binding of an anti-LFA-1 Fab R3.1, competititve with drug binding, was compared by ratio to a non-competitive control Fab (TS2/4). Multiple dosing of BIRT 2584 XX with the top two doses of 500 mg and 750 mg qd was sufficient to achieve saturation of the receptor (~ 95% inhibition) through 14 days and 28 days, respectively. Prolonged receptor occupancy may be partially attributed to the presence of metabolite BI 610100. However, receptor occupancy declined at a slower rate than either the BIRT 2584 XX plasma concentration or the BI 610100 plasma concentration and was still above placebo response when parent and metabolite could no longer be measured. Inhibition of IL-2 production in response to *ex vivo* superantigen (SEB) challenge was measured. Whole blood samples were stimulated with SEB and the IL-2 levels were determined by FACS analysis. Clear inhibition of IL-2 was measured in all doses following adjustment for an increase in lymphocytes and normal diurnal fluctuation of IL-2 levels. IL-2 inhibition appeared to be related to BIRT 2584 XX concentrations after a single dose, but appeared to be more closely related to BI 610100 concentrations on multiple dosing, as indicated by responses and BI 610100 concentrations after BIRT 2584 XX could no longer be measured. Exploratory counts of WBC populations indicated an increase in leukocytes, driven primarily by lymphocytes and consistent across doses starting at 100 mg qd. No other cell type showed a consistent dose-related increase. The lymphocyte cell count increase appeared to be related to BIRT 2584 XX concentrations after a single dose, but appeared to

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Name of active ingredient: BIRT 2584 XX		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
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	be more closely related to BI 610100 concentrations on multiple dosing. An increase in both T- and B-cells was observed as measured by ratio. The ratio did not change with dose. Based on the data, it appears that both BIRT 2584 XX and BI 610100 were responsible for the effect observed on the biomarkers. When trough data on day 8 and 14 were compared, all biomarkers (receptor occupancy, IL-2 production, and peripheral lymphocyte counts) consistently showed stable effects over time and a dose-dependent increase up to including the 500 mg qd dose, whereas the 750 mg qd dose was not different from the 500 mg qd dose.
Safety results:	BIRT 2584 XX administered as tablet formulation was generally well tolerated in the dose groups 100 mg, 250 mg, and 500 mg qd over a treatment duration of 14 days (bid regimen on the first two days) and in the dose group 750 mg qd over a treatment period of 28 days. No deaths occurred in this study. In the multiple rising dose part of the trial (part 2), 3 subjects discontinued the trial prematurely due to AEs (tonsillitis, varicella infection, severe gastroenteritis). Since the subject with gastroenteritis had to be hospitalized for 24 hrs, the case was reported as a serious adverse event (SAE). The adverse events (AEs) with the highest incidences occurred in the three following system organ classes: gastrointestinal disorders (14 subjects on BIRT 2584 XX), skin and subcutaneous tissue disorders (9 subjects on BIRT 2584 XX) and infections and infestations (7 subjects on BIRT 2584 XX). The overall rate of AEs was highest in the 750 mg qd dose group. This became already apparent within the first 14 days of treatment. Soft, loose, or watery stools and skin and subcutaneous tissue disorders (exanthema, eczema, and rash) were the most frequently reported AEs. A relationship between BIRT 2584 XX and these AEs was considered likely. Soft, loose, or watery stools usually occurred about 1 to 5 hrs after drug intake. Exanthema, eczema, and rash were most frequently seen in the 750 mg qd dose group after a treatment period of more than 14 days. The exanthema were heterogeneous, mild, and localised, rapidly resolved, and could be successfully treated with topical corticosteroids. Most adverse events were of mild intensity. A total of 7 subjects (6 subjects on BIRT 2584 XX vs. 1 subject on placebo) experienced AEs of moderate intensity. In part 1, no relevant differences regarding AEs were seen when administering BIRT 2584 XX in the fasted or in the fed state. The overall laboratory evaluation revealed no clinically relevant abnormalities. An increase of WBCs mainly attributable to rising lymphocyte and neutrophil counts was noted in the majority of subjects. The higher WBC counts on treatment are considered a mechanism-related effect due to a decrease of margination and transmigration of lymphocytes from the blood stream. In

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Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
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	several subjects, elevated ALT levels were seen with the highest incidence in the placebo group. Re-analysis showed that level of impurities in the placebo tablets were substantially lower than allowed and that no interchange with active tablets had occurred. No clinically relevant effects of BIRT 2584 XX on any cardiologic parameter were observed. Analysis of QTcF- and QTcB-intervals indicated that BIRT 2584 XX does not prolong the QT-interval.
Conclusions:	BIRT 2584 XX and/or BI 610100 induced the metabolism of BIRT 2584 XX and possibly also induced the disposition of BI 610100. After a single dose, BIRT 2584 XX plasma levels greatly exceeded those of the metabolite BI 610100, but BI 610100 was the predominant compound after multiple dosing. BIRT 2584 XX and BI 610100 pharmacokinetics appeared to be dose proportional at doses of 250 mg qd and above. Steady state was not reached for BIRT 2584 XX by day 14 at the 100 mg qd or 250 mg qd doses. Steady state was reached by day 13 for the 500 mg qd dose, and most likely by day 24 for the 750 mg qd dose. At trough, all biomarkers consistently showed stable effects over time and a dose-dependent increase including the 500 mg qd dose, whereas the 750 mg qd dose was not different from the 500 mg qd dose. Over the whole time of the study, dose-related responses were observed in general for receptor occupancy, IL-2 inhibition up to the 750 mg qd dose level, and mechanism-based increase in peripheral lymphocytes up to the 500 mg qd dose. The biomarker responses appeared to be related to both BIRT 2584 XX and BI 610100 plasma concentrations. BIRT 2584 XX was safe and well tolerated at the doses administered. A higher incidence of AEs was observed in the 750 mg qd dose group.