Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
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Report date: 19 AUG 2005	**Number:** U05-2074	**Study period (dates):** 08 Mar - 08 Jun 2004		

Title of study:	Safety, pharmacokinetics, and pharmacodynamics of single rising oral doses of BIRT 2584 XX (5, 30, 100, 200, 350, 500, and 700 mg) as a solution in PEG 400 administered to healthy male volunteers. Placebo controlled and blinded at each dose level.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre Biberach
Publication (reference):	N.A.
Clinical phase:	I
Objectives:	To assess safety, tolerability, pharmacokinetics, and pharmacodynamics of BIRT 2584 XX in single rising oral doses of 5 mg to 700 mg in a polyethylene glycol 400 (PEG 400) solution in healthy subjects
Methodology:	Single rising dose, randomised, placebo controlled, blinded at each dose level
No. of subjects:	
planned:	entered: 56 (42 active, 14 placebo)
actual:	enrolled: 80 Active treatment entered: 41 treated: 41 analysed (for primary endpoint): 41 Placebo treatment: entered: 14 treated: 14 analysed (for primary endpoint): 14
Diagnosis and main criteria for inclusion:	Healthy, 18 to 50 year old male volunteers
Test product:	BIRT 2484 XX as a solution in 10 mL PEG 400
dose:	5, 30, 100, 200, 350, 500, and 700 mg
mode of admin.:	Per os
batch no.:	PD-2435 (5 mg), PD-2436 (30 mg), PD-2437 (100 mg), PD-2438 (200 mg), PD 2439 (350 mg), PD-2440 (500 mg), PD-2441 (700 mg)
Duration of treatment:	Single Dose
Reference therapy:	Vehicle (PEG 400) 10 mL alone
dose:	N.A.
mode of admin.:	Per os

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batch no.:	PD-2435, PD 2436, PD 2437, PD 2438, PD 2439, PD 2440, PD 2441, PD-2442
Criteria for evaluation:	
Efficacy:	Pharmacodynamics: assessment of receptor occupancy (RO) as measured by inhibition of competitive R3.1 antibody fragment (Fab) binding, inhibition of interleukin-2 (IL-2) production in response to super-antigen challenge *ex vivo,* white blood cell (WBC) counts. Pharmacokinetics: single dose plasma concentration-time profiles of BIRT 2584 XX, pharmacokinetic parameters (including C_{max}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, CL/F, V_z/F, MRT), urinary excretion of parent drug, assessment of relationship between plasma concentrations and pharmacodynamic endpoints:
Safety:	Adverse events, vital signs, laboratory values, electrocardiogram, physical examination, tolerability
Statistical methods:	Descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy results:

Receptor occupancy was assessed in whole blood in a flow cytometry-based assay. Binding of an anti-lymphocyte function associated antigen-1 (LFA-1) Fab R3.1, competititve with drug binding, was compared by ratio to a non-competitive control Fab (TS 2/4). At time points less than 24 hours after dosing, it appears there is a direct relationship between BIRT 2584 XX plasma concentration and BIRT 2584 XX receptor occupancy. However, it appears at later time points, receptor occupancy is greater than and lasts longer than can be accounted for by a simple direct Emax model.

A significant metabolite of BIRT 2584 in plasma has been identified. Prolonged receptor occupancy may be due to the presence of this metabolite, designated as BI 610100 (section 11.5.3).

Inhibition of IL-2 production in response to *ex vivo* superantigen challenge was measured. Whole blood samples were stimulated with staphylococcal enterotoxin B (SEB) and the IL-2 levels were determined by enzyme-linked immunosorbent assay (ELISA). No clear trend between dose level or exposure and inhibition was evident.

Additional exploratory counts of WBC populations suggested a transient increase in leucocytes, including a dose dependent increase in lymphocytes.

Pharmacokinetic analysis indicated that BIRT 2584 exhibits near dose-linear pharmacokinetics within a dose-range of 5 – 700 mg. The terminal half life was consistently 9-11 hours. Exploratory data with a validated but non-GLP assay from the 500 and 700 mg dose groups shows that the metabolite BI 610100 is formed slowly and has a long half life of 80-90 h. C_{max} values for BI 610100 are less than one-tenth the corresponding C_{max} values for the parent BIRT 2584 and, $AUC_{0-\infty}$ values for the metabolite were 60-65% of the corresponding values for BIRT 2584.

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Safety results:	BIRT 2584 XX at single doses of 5 mg to 700 mg, reconstituted in PEG 400 was generally well or satisfactorily tolerated. The overall rate of AEs was highest in the 500mg and 700 mg active treatment group. Diarrhea was reported only in these groups (2 reports each). A relationship between study treatment and diarrhea appears to be likely, there is however no evidence for a relationship with any other AE. A dose dependent increase in WBC counts (mainly driven by lymphocytes and neutrophils) was observed. Also, there appears to be a relationship between BIRT 2584 plasma concentrations and lymphocyte and leukocyte cell counts. This finding is considered to be the result of the inhibition of marginalization and transmigration of neutrophils and lymphocytes in the bloodstream and therefore related to the desired mechanism of action of BIRT 2584 XX and it is not considered a safety issue. There is no evidence of an impact of BIRT 2584 XX on any other lab parameter as well as there is no evidence for ECG changes due to BIRT 2584 XX treatment. At the doses administered in the study BIRT 2584 XX appears to be safe.
Conclusions:	Systemic exposure of BIRT 2584 XX was near dose proportional up to 700 mg single dose. A strong relationship between systemic exposure and receptor occupancy was found for the first 12 hours after dosing. The elimination $t_{1/2}$ was moderate. A major metabolite with a long $t_{1/2}$ and potential receptor binding activity was identified. Above 100 mg, BIRT 2584 XX showed a dose dependent temporary increase on circulating lymphocytes and neutrophils. The safety profile in this study was found to be acceptable and does not limit the use of BIRT 2584 XX in further clinical trials.