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**		**(For National Authority Use only)**
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BIRT 1696 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 29 JUL 2003	**Number:** U03-1502	**Study period (dates):** 05 MAY - 23 JUL 2002		

Title of study:	Safety, pharmacokinetics and pharmacodynamics of single rising oral doses of BIRT 1696 BS as a solution (10, 100, 400, 1000, 2000, 3000 mg) in 15 ml PEG 400 to healthy human subjects. A three part study: part 1 placebo-controlled, randomised, dose escalating double blinded within each dose level; part 2 open label grapefruit juice effect in 100 mg dose level group; part 3 open label food effect in 400 mg dose level group.
Investigator:	[redacted]
Study center:	Human Pharmacology Centre Boehringer Ingelheim Pharma KG, D-88397 Biberach an der Riss Phone: [redacted] Facsimile: [redacted]
Publication (reference):	
Clinical phase:	I
Objectives:	1. To assess safety, pharmacokinetics, and pharmacodynamics of BIRT 1696 BS in rising single doses. 2. To assess safety, pharmacokinetics, and pharmacodynamics of single dose of 100 mg BIRT 1696 BS after grapefruit juice. 3. To asses safety and pharmacokinetics of single dose of 400 mg BIRT 1696 BS after a 67 g fat and high caloric breakfast.
Methodology:	1. Single rising dose, randomised, placebo controlled, blinded at each dose level 2. Grapefruit juice effect: single dose, open label, intra-individual and group comparison 3. Food effect: single dose, open label, intra-individual and group comparison
No. of subjects:	
planned:	entered: in total 48 male or female subjects, 8 at each of the 6 dose levels.
actual:	enrolled: 70 Active treatment: entered: 33 (planned: 34; 6 per dose group except 1000 mg group where only 5 were entered) treated: 32 (planned 34; 6 per dose group except 1000 mg group where only 4 were treated) Placebo: 12 entered and treated as planned (= 2 per dose group)
Diagnosis and main criteria for inclusion:	healthy, 18 to 60 year old male or female (post menopausal or surgically sterile) volunteers
Test product:	BIRT 1696 BS in 15 ml PEG 400

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dose:	1. 10, 100, 400, 1000, 2000, 3000 mg (dose escalation) 2. 100 mg (grapefruit effect) 3. 400 mg (food effect)
mode of admin.:	per os
batch no.:	BIRT 1696 BS: 2167-2172
Duration of treatment:	Single oral administration. In food and grapefruit effect groups subjects received second single dose, each separated by 5 to 6 weeks.
Reference therapy:	PEG 400
dose:	15 ml
mode of admin.:	per os
batch no.:	2178
Criteria for evaluation:	
Efficacy:	Efficacy: assessment of receptor occupancy as measured by inhibition of competitive R3.1 Fab binding, inhibition of IL-2 production in response to super-antigen challenge *ex vivo.* Pharmacokinetics: single dose plasma concentration-time profiles of BIRT 1696 BS, 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, assessment of grapefruit juice and food effects on PK.
Safety:	Safety: adverse events, vital signs, laboratory values, electrocardiogram, physical examination, tolerability
Statistical methods:	Descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy results:

Efficacy:

Treatment with BIRT 1696 BS at doses of 100 mg and above resulted in substantial receptor occupancy as measured by inhibition of R3.1 Fab binding to lymphocytes (> 75 % inhibition) 2 hours after dosing in most subjects. Beyond 2 hours extent and duration of the inhibition depended on the dose administered. In the highest dose groups (2000 and 3000mg) some effect was still present 48 hours after dosing. There was a strong correlation between receptor occupancy and plasma levels. An E_{max} model was adequate in describing the concentration-effect relationship with an EC_{50} of 1.11 ng/mL and an E_{max} of 81.1%. An EC_{90} of 10 ng/mL can be estimated from the model for RO. There were no apparent differences between those early and later data points obtained following drug administration. Consistent with previous ex vivo testing of untreated volunteers, the levels of IL-2 and the sensitivity to LFA-1 inhibitors was variable. Even with this anticipated spread in sensitivity, an apparent trend in IL-2 inhibition, consistent with the increase in plasma levels of BIRT 1696 BS at higher doses, was discernible. Clear IL-2 inhibition, ranging from a mean of 35% - 65%, was observed in doses from 400 mg to 3000 mg in the first 4 hours post treatment. BIRT 1696 BS inhibited ex vivo SEB-induced IL-2 production with an EC50 of 47.5 ng/mL and an Emax of 66.2%. No apparent difference between those early and later data points were observed. An EC90 was estimated to be 427 ng/mL from the SEB-induced IL-2 model.

Pharmacokinetics:
Mean t_{max} values under fasting conditions ranged from approximately 0.5 to 3 hours and tended to increase slightly with dose. Both C_{max} and AUC_{0-tz} increased supra-proportionately to dose up to the 1000 mg dose group. Doses above 1000 mg exhibited a gradual decrease in systemic exposure.
BIRT 1696 BS exhibited high inter-subject variability (CV for AUC_{0-tz} higher than 60%). Mean elimination $t_{1/2}$ obtainable at higher doses ranged approximately from 5 to 7 hours. Grapefruit juice co-administration at 100 mg dose resulted in a slight increase in C_{max} of 22% and a 29% increase in $AUC_{0-\infty}$. A high fat meal caused a moderate increase in C_{max} of 35% and a 34% increase in $AUC_{0-\infty}$ at 400 mg dose. Urinary excretion of unchanged drug accounted for less than 1% of dose.

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Safety results:	BIRT 1696 BS at single doses of 10 mg to 3000 mg reconstituted in PEG 400 was generally satisfactorily to well tolerated and did not increase the overall frequency of AEs (compared with placebo). Cardiac (orthostatic reaction, sinus tachycardia, and sinus bradycardia) and gastrointestinal AEs (diarrhea, flatulence, loose stools, nausea, vomiting) were observed in actively treated subjects only. A relationship with BIRT 1696 BS appears unlikely, as these AEs were not reproduced with repeated BIRT 1696 BS administration. There was no evidence of an impact of BIRT 1696 BS on any lab parameter and there was no evidence of QT prolongation or any other ECG change due to BIRT 1696 BS treatment in the current study. At the doses administered in the study BIRT 1696 BS appears to be safe.
Conclusions:	A strong relationship between systemic exposure and receptor occupancy was found. Systemic exposure of BIRT 1696 BS was supra proportional to dose up to 1000 mg single dose. Doses above 1000 mg showed a trend of absorption limited phenomenon in drug exposure. Both grapefruit juice and food caused a moderate increase in systemic exposure at the doses studied. BIRT 1696 BS exhibited high PK inter-subject variability. Elimination $t_{1/2}$ was relatively short. The safety profile in this study was found to be acceptable and does not limit the use of BIRT 1696 BS in further clinical trials.