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***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: BIIL 284 BS				
Name of active ingredient: BIIL 284 BS		**Page:**	**Number:**	
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Report date: 18 September 2001	**Number:**	**Study period (years):** MAY-JUL 2000		

Title of study:	The effects of multiple doses of BIIL 284 BS on the pharmacokinetics of a single dose of theophylline in healthy male volunteers (A randomized, double-blind, placebo-controlled, two-period, two-way crossover study).	
Investigator:	[redacted]	
Study centre:	[redacted] The Netherlands	
Publication (reference):	Not applicable	
Clinical phase:	I	
Objectives:	To evaluate the effect of multiple doses of BIIL 284 BS on the pharmacokinetics of a single dose of theophylline.	
Methodology:	A randomized, double-blind, placebo-controlled, two-period, two-way crossover study. Volunteers were treated for 9 days with either BIIL 284 BS, or matching placebo. On the seventh day of dosing with BIIL 284 BS or placebo volunteers received a single dose of theophylline.	
No. of subjects entered:	16	
total:	16	
each treatment:	16	
Diagnosis and main criteria for inclusion:	Healthy Male Volunteers	
Test product:	BIIL 284 BS	Theophylline tablets 125 mg
Dose:	150 mg (2x75 mg WIF tablet)	125 mg (Teva Pharma/Pharmachemie BV)
Mode of admin.:	Oral	oral
Batch no.:	B990105 (75 mg WIF tablet)	99B17UA
Duration of treatment:	BIIL 284 BS - 9 days, once daily treatment Theophylline – a single dose on day 7 of the BIIL 284 BS treatment period	

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Reference therapy:	Placebo – 9 days, once daily treatment. A single theophylline dose was administered on day 7 of the placebo treatment period.
Dose:	-
Mode of admin.:	Oral
Batch no.:	B990206
Criteria for evaluation:	
Pharmacokinetics:	Pharmacokinetic parameters for theophylline ($AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, MRT_{tot}, CL_{tot}/F, V_z/F) and BIIL 315 ZW (AUC_{ss}, $C_{max,ss}$, t_{max}, $t_{½}$, MRT_{tot}, CL_{tot}/F, V_z/F) were analyzed.
Safety:	Elicited and volunteered adverse events, pulse rate, blood pressure, ECG routine Blood, urine chemistry and physical examination.
Statistical methods:	Ratios of $AUC_{0-\infty}$ and C_{max} for theophylline with and without BIIL 284 BS were tested for equivalence using two one-sided tests methodology. Statistical model used was an ANOVA on log transformed parameters. Criteria for no interaction was that 90% Cis on ratios of AUC are contained in the range 80-125% and of C_{max} in the range 70-143%. Point estimates and CIs for $AUC_{0-\infty}$ and C_{max} are provided. Descriptive statistics for all other endpoints.

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SUMMARY – CONCLUSIONS:

Safety results:
Based on the observations made in the present study, BIIL 284 BS was shown to be safe and well tolerated in healthy male volunteers following a single oral theophylline dose of 125 mg on day seven of the 9-day once daily dosing phase with 150 mg BIIL 284 BS or placebo. The most frequent adverse events were somnolence (BIIL 284 BS: 2 volunteers; placebo: 5 volunteers) and headache (BIIL 284 BS: 2 volunteers; placebo: 2 volunteers). The safety parameters blood pressure, pulse rate, ECG-recordings and the standard laboratory tests did not reveal any obvious clinically significant drug-related changes. The results of the present study do not raise objections to further clinical studies in volunteers or patients.

Other results:
The primary pharmacokinetic parameters of theophylline, C_{max} and $AUC_{0-\infty}$, were very similar when theophylline was administered with placebo or BIIL 284 BS pre-treatment (gMean values of 2.70 and 2.79 µg/mL, respectively for C_{max} and 28.3 and 29.8 µg*hr/mL, respectively for $AUC_{0-\infty}$). The confidence interval (two-sided 90% C.I.) of C_{max} ratios of theophylline was estimated to range from 96% to 111% with a mean ratio of 104%. The confidence interval (two-sided 90% C.I.) of $AUC_{0-\infty}$ ratios of theophylline was estimated to range from 101% to 109% with a mean ratio of 105%.

All secondary pharmacokinetic parameters of theophylline T_{max}, $t_{1/2}$, MRT_{tot}, CL_{tot}/F and V_z/F were also similar when theophylline was administered with placebo or BIIL 284 BS pre-treatment. The range for observed theophylline t_{max} values after placebo pre-treatment was slightly broader than after BIIL 284 BS pre-treatment with 0.5-4.0 hr and 0.5-2.0 hr, respectively.

The pharmacokinetic parameters derived for BIIL 315 ZW showed considerable interindividual variability with a 59.4 gCV% for $C_{max,ss}$ and 67.3 gCV% for AUC_{ss}. These variabilities are similar to those observed in a previous multiple dose study of BIIL 284 BS. Maximum concentrations (C_{max}) of BIIL 315 ZW were achieved between 2.0 and 4.0 hours (t_{max}) after dosing of the parent drug. For BIIL 315 ZW the gMean of $C_{max,ss}$ was 30.4 ng/mL, while the gMean AUC_{ss} was 177 ng*hr/mL. These results indicate that co-administration of a single dose of theophylline had no relevant impact on steady state plasma levels of BIIL 315 ZW when compared to previous multiple dose study results for BIIL 315 ZW.

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SUMMARY – CONCLUSIONS:

Conclusions:
BIIL 284 BS was safe and well tolerated in healthy male volunteers following a single oral theophylline dose of 125 mg on day seven of the 9-day once daily dosing phase with 150 mg BIIL 284 BS or placebo.

Based on the observations made in the present study it is concluded that a 9-day treatment of BIIL 284 BS (once daily 150 mg as 2x75 mg WIF tablet formulation) had no effect on the pharmacokinetics of theophylline when administered as a concomitant single oral dose of 125 mg on day seven of the treatment phase; the 90% confidence intervals for the ratio of $AUC_{0-\infty}$ and C_{max} of theophylline were well within the acceptance region of 80-125% and 70%-143%, respectively.

It can be assumed that BIIL 284 BS treatment in further clinical trials will have no effects on pharmacokinetics and safety of theophylline when administered concomitantly.