Clinical Study Synopsis for Public Disclosure

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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:**	
Ref. to Documentation:	**Volume:**	**Page:** xxx **to** xxxx		**Addendum No.:**
Report date: 22 June 2001	**Number:** U01-3411	**Study period (years):** 19 April 2000 to 14 July 2000		

Title of study:	The Effect of Multiple Doses of BIIL 284 BS on the Pharmacokinetics of a Single Dose of Prednisone in Healthy Male Subjects (A randomized, double-blind, placebo-controlled, two period, two-way cross-over study)	
Investigator:	[redacted]	
Study center(s):	[redacted]	
Publication (reference):	N/A	
Clinical phase:	I	
Objectives:	To evaluate the effect of multiple doses of BIIL 284 BS on the pharmacokinetics of a single dose of prednisone.	
Methodology:	A randomized, double-blind, placebo-controlled, two period, two-way cross-over study. Subjects were treated for 9 days with either BIIL 284 BS or matching placebo. On the seventh day of dosing with BIIL 284 BS subjects received a single dose of prednisone. Blood samples were obtained beginning on Day 7 at the following timepoints: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post-dose. Plasma levels of prednisolone (prednisone metabolite) and BIIL 315 ZW (BIIL 284 BS metabolite) were determined.	
No. of subjects entered:	20	
total:	20	
each treatment:	20	
Diagnosis and main criteria for inclusion:	Healthy male volunteers, aged 21 to 50 years.	
Test product:	BIIL 284 BS	Prednisone
dose:	150 mg	20 mg
mode of admin.:	Oral	Oral
batch no.:	PD-1982	
Duration of treatment:	9 days	1 dose, each period
Reference therapy:	Placebo	
dose:	N/A	
mode of admin.:	Oral	
batch no.:	PD-1983	

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Name of active ingredient: BIIL 284 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** xxx to xxxx		**Addendum No.:**
Report date: 22 June 2001	**Number:** U01-3411	**Study period (years):** 19 April 2000 to 14 July 2000		

Criteria for evaluation:	
Efficacy:	N/A
Safety:	Elicited and volunteered adverse events, pulse rate, blood pressure, ECG, routine blood chemistry, hematology, urinalysis and physical examinations. T cell proliferation assay, IL-2 and IFNγ levels determined from peripheral blood.
PK	Pharmacokinetic parameters for prednisone ($AUC_{0-\infty}$, 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.
Statistical methods:	Ratios of $AUC_{0-\infty}$ and C_{max} of prednisolone with and without BIIL 284 BS were tested for equivalence using two one-sided tests methodology. The statistical model used was an ANOVA on log transformed parameters. Criteria for no interaction was that 90% CIs on ratios of AUC were 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} were provided. Descriptive statistics for all other endpoints.
SUMMARY - CONCLUSIONS:	
Efficacy results:	N/A
Pharmacokinetic results:	Pharmacokinetics: The two-sided 90% confidence intervals for the ratio of prednisolone C_{max}^{pone} and $AUC_{0-\infty}^{pone}$ (ratio of parameter with BIIL 284 BS pre-treatment to that with placebo) were 97.7% - 119.5% and 95.6% - 113.6%, respectively, both of which fall within the acceptance ranges of 70% - 143% for C_{max}^{pone} and 80% - 125% for $AUC_{0-\infty}^{pone}$. The mean plasma prednisolone concentration-time profiles after treatment with BIIL 284 BS and prednisone and placebo and prednisone were practically superimposable indicating that pre-treatment with BIIL 284 BS does not alter the pharmacokinetic characteristics of prednisone.

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Pharmacokinetic results:	All individual C_{max}^{pone} and $AUC_{0-\infty}^{pone}$ subject ratios (ratio of parameter with BIIL 284 BS pre-treatment to that with placebo) were within the range of 68% and 170% with gmean % ratios of 108% and 104% for C_{max}^{pone} and $AUC_{0-\infty}^{pone}$, respectively. Intersubject variability in both parameters for both treatment groups was low (below 40%). Median t_{max}^{pone} was 1.5 hours and mean half-life of 3 hours following either treatment. All other secondary parameters of prednisolone were comparable. Plasma concentrations and pharmacokinetic parameters of BIIL 315 ZW displayed high interindividual variability. BIIL 315 ZW $C_{max,\,ss}^{BIIL}$ ranged from 2.27 to 68.5 ng/mL and the area under the curve over the dosing interval (AUC_{ss}^{BIIL}) also displayed a large range of 17.1 to 451 ng·hr/mL. The median t_{max}^{BIIL} was 2.0 hours.
Safety results:	Nine-day treatment with BIIL 284 BS and two doses (20 mg) of prednisone was well tolerated and no deaths or serious adverse events were reported. The most common complaint in this study was headache reported by two volunteers in the BIIL 284 BS period and three in the placebo period. The most prominent change was the observation of a decrease in hemoglobin and hematocrit in some volunteers in both arms of the study regardless of the order of treatment. In some volunteers this decrease can be considered clinically meaningful but fully reversible. It is not apparent whether this change in hematology is related to active principle (BIIL 315 ZW) or is due to frequent venipunctures. With the exception of the hematology changes noted above, we failed to find any effect of treatment on any other blood chemistry or urinalysis measurements. There were no immunomodulatory changes as assessed by T-cell proliferation or levels of IFNγ or IL-2.
Conclusions:	It is concluded that a 7-day treatment of BIIL 284 (once daily 150 mg as 2x75 mg WIF tablet formulation for a total of 9 days) had no effect on the pharmacokinetics of prednisone when administered as a concomitant single oral dose of 20 mg on day 7 of the treatment phase. The 90% confidence intervals for the ratio of $AUC_{0-\infty}$ and C_{max} of prednisolone 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 prednisone when administered concomitantly.