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:				
Name of active ingredient: BILB 1941 ZW		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 23 Dec 2005	**Number:** U05-2666	**Study period (dates):** 08 Jan – 29 Sept 04		

Title of study:	Safety, Tolerance, and Pharmacokinetics of Single Oral Doses of 5 mg, 20 mg, 60 mg, 120 mg, 200 mg, 300 mg, 600 mg, 1000 mg, 1500 mg, 2000 mg, 2400 mg, and 3000 mg BILB 1941 ZW (PEG 400/TRIS solution) in Healthy Male Subjects, in a Randomised Double Blind, Placebo Controlled Rising Dose Study, Followed With an Open-label Intra-subject Three-Way Crossover Bioavailability Comparison of 600 mg BILB 1941 ZW in a PEG 400/TRIS solution and 600 mg BILB 1941 ZW tablet and 600 mg BILB 1941 ZW tablet administered with Food.
Investigator:	[redacted]
Study center:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Research, D-88397 Biberach/Riss
Publication (reference):	N.A.
Clinical phase:	I
Objectives:	To assess the safety, tolerability and pharmacokinetics. Planned: 1. In rising single doses 5 mg to 3000 mg, administered 5 to 300 mg BILB 1941 ZW 2. Planned: three-way crossover bioavailability comparison of 600 mg BILB 1941 ZW as a liquid formulation with 600 mg BILB 1941 ZW as a tablet fasted and with 600 mg of BILB 1941 ZW as a tablet given with food. Actual: two-way crossover with 60 mg oral solution (fasted and after breakfast) performed.
Methodology:	1. Single rising dose, randomised, placebo controlled, blinded at each dose level 2. Bioavailability comparison: single doses, randomised, crossover, open-label.
No. of subjects:	
planned:	To be entered: 98 Single rising dose part: 6 on active drug, 2 on placebo per dose level (N=88) Bioavailability arm: planned 10 on active drug,
actual:	enrolled: 93 Single rising dose part: entered: 48, treated: 47 analysed: 47: Bioavailability arm: entered: 8, treated: 8, analysed: 8
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 50 years
Test product:	BILB 1941 ZW in 20 to 30mL of a polyethylene glycol 400 (61% PEG 400)/5% TRIS/34% water mixture.
dose:	administered: 5, 20, 60, 120, 300; 200 mg; planned: 5 mg, 20 mg, 60 mg, 120 mg, 300 mg, 600 mg, 1000 mg, 1500 mg, 2000 mg, 2400 mg, and 3000 mg (20 to 30mL)

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mode of admin.:	p.o.
batch no.:	BILB 1941 ZW: PD-2369, PD-2370, PD-2371, PD-2372, PD-2373, PD-2375; PD-2410; TRIS: PD 2378, PD 2454; PEG 400: PD-2379,
Duration of treatment:	Single administration; Bioavailability arm: 60 mg two times single administration
Reference therapy:	Single Rising Dose part: Placebo: 61% PEG 400/5% TRIS / 34% Water, 0 mg, 20 to 30 mL Bioavailability arm: 60 mg fasted;
dose:	Single Dose Arm: - Bioavailability arm: 60 mg fasted
mode of admin.:	p.o.
batch no.:	TRIS (PD-2378), PEG 400 (PD - 2454),
Criteria for evaluation:	
Efficacy:	C_{max}, $AUC_{0-\infty}$, $AUC_{0-tz,,}$ λ_z ,t_{max}, $t_{1/2}$, CL/F, MRT, V_z/F, Ae_{0-48}, $fe_{0-48,,}$ $CL_{R,\ 0-48}$
Safety:	Adverse events; tolerability; vital signs; 12-lead ECG; physical examination; routine laboratory values.
Statistical methods:	Descriptive statistics
SUMMARY – CONCLUSIONS:	
Efficacy results:	Based on AUC and C_{max} values, it can be concluded that BILB 1941 ZW exhibits near doselinear pharmacokinetics within a dose-range of 5 – 300 mg. The mean terminal half lives were 2-3 hours. There was negligible excretion of BILB 1941 ZW in urine. The subjects who were administered BILB 1941 ZW with meal had a Tmax about 1 hour longer and C_{max} 40% lower than those of the fasted subjects while AUC was not reduced. This suggests that the absorption rate of BILB 1941 ZW was slower when administered with a high fat meal.
Safety results:	The increase in liver enzyme levels was unexpected from the preclinical findings. One single dose on the lower end of the dose range (300 mg) was already sufficient to cause an increase in liver enzyme levels in all actively treated subjects whereas the preceding 120 mg dose group did not show any change of liver enzymes as did all the other preceding dose levels. Four out of the six subjects on active drug showed an increase of ALT/AST, all six of the GLDH. However all enzyme elevations were minimal. In subjects who experienced elevation in ALT or AST, the maximum changes observed were less than 1.5x the upper limits of normal. Two hundred mg led to a minimal increase suggesting a dose - dependence. The observed changes are most likely contributed to the liver. There were no other AEs of clinical relevance.

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Conclusions:	Based on AUC and C_{max} values, it can be concluded that BILB 1941 ZW exhibits near doselinear pharmacokinetics within a dose-range of 5 – 300 mg. There was negligible excretion of BILB 1941 ZW in urine. Ingestion of a high fat meal slows absorption and reduces C_{max} but not AUC. BILB 1941 ZW was well tolerated. However 300 mg caused already an increase in liver enzymes in all subjects in at least one parameter. Two-hundred (200) mg lead to a minimal change of liver enzyme levels suggesting a dose dependent effect. However all enzyme elevations were minimal. In subjects who experienced elevation in ALT or AST, the maximum changes observed were less than 1.5x the upper limits of normal.