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:				
Name of active ingredient: BILN 2061 ZW		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 22 February 2002	**Number:** 605.1	**Study period (years):** 6-9/2001		

Title of study:	Safety, Tolerance, and Pharmacokinetics of Single Oral Doses of 5 mg, 20 mg, 60 mg, 100 mg, 200 mg, 400 mg, 600 mg, 800 mg, 1000 mg, 1200 mg, 1500 mg, 2000 mg and 2400 mg BILN 2061 ZW (PEG 400:ethanol solution) in Healthy Male Subjects, Combined With Preliminary Evaluation of Food effect of the Dose of 200 mg (Two-Stage Trial Design With Randomised Double Blind Placebo Controlled Rising Dose Part and Subsequent Open Intraindividual Comparison Part).
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre Boehringer Ingelheim Pharma KG, D-88397 Biberach/Riss Clinical Research
Publication (reference):	N/A
Clinical phase:	I
Objectives:	To assess the safety, tolerance and pharmacokinetics of 5 mg to 2400 mg BILN 2061 ZW 1. In rising single doses 2. With and without a 64 g fat breakfast at one selected dose (200 mg chosen)
Methodology:	1. Single rising dose, randomised, placebo controlled, blinded at each dose level 2. Food effect: single dose, randomised, intra-individual comparison
No. of subjects entered:	
total:	103 (planned 104)
each treatment:	6 on active drug, 2 on placebo per dose level (only 1 placebo on 60 mg level). Food effect arm: 8 on active drug, previously treated.
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 50 years
Test product:	BILN 2061 ZW in 12 ml of a polyethylene glycol 400 (PEG 400) – ethanol 80%-20% mixture.
dose:	5 mg, 20 mg, 60 mg, 100 mg, 200 mg, 400 mg, 600 mg, 800 mg, 1000mg, 1200 mg, 1500 mg, 2000 mg and 2400 mg (10ml)
mode of admin.:	p.o.
batch no.:	powder: PD-2070 to PD-2082; solvent: PEG 400, PD-2067; ethanol: 100788;
Duration of treatment:	single dose

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BILN 2061 ZW		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 22 February 2002	**Number:** 605.1	**Study period (years):** 6-9/2001		

Reference therapy:	Placebo: PEG 400-Ethanol 80%-20% mixture (12 ml)
dose:	0 mg, 10 ml
mode of admin.:	p.o.
batch no.:	PEG 400, PD-2067; ethanol: 100788;
Criteria for evaluation:	
Efficacy/	no efficacy endpoints;
Pharmacokinetics:	plasma concentration-time profiles of BILN 2061 ZW, pharmacokinetic parameters (C_{max}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, CL/F, MRT, V_z/F)
Safety:	Adverse events; tolerability; vital signs; ECG; physical examination; routine laboratory values.
Statistical methods:	Descriptive statistics

SUMMARY - CONCLUSIONS:

Efficacy results
Pharmacokinetics::

The time course of BILN 2061 ZW exhibited an initial rise, followed by a biphasic decline in plasma concentrations. C_{max} occurred mostly within 2 to 4 hours after administration, although much longer t_{max} values were observed in a few subjects at doses ≥ 800 mg. Both C_{max} and $AUC_{0-\infty}$ appeared to be dose-proportional up to the 1,200 mg dose group. Mean elimination half-life was around 4 hours and was independent of dose. Inter-individual variability was high, with a number of subjects displaying higher than usual peaks, higher overall plasma concentrations and $AUC_{0-\infty}$ values. In the higher dose groups, some subjects displayed C_{max} values which were secondary peaks at 12 hours or longer following drug administration. The coefficient of variation varied between 30 and 200% based on the $AUC_{0-\infty}$ values. A high fat breakfast caused a significant decrease in mean C_{max} (39%) and a smaller decrease (9%) in mean $AUC_{0-\infty}$ after a 200 mg dose.

Safety results:

An oral single dose of 2000 mg is considered as the highest well tolerated dose in healthy subjects. BILN 2061 ZW as single doses in 10 ml PEG 400:ethanol was well tolerated up to 2000 mg. Single dose tolerance of BILN 2061 ZW in 10 ml PEG 400:ethanol is limited by intestinal adverse events. There was no influence on liver enzymes

Conclusions:

Absorption was adequate and dose-proportional up to 1200 mg. There was little effect on the amount absorbed by food intake. A dose range of single oral doses of up to 1200 mg with or without food is optimal based on pharmacokinetic data. Based on tolerability the lack of relevant adverse events allows single oral doses of up to 2000 mg. This Phase I study 605.1 by Boehringer Ingelheim supports the further development of BILN 2061 ZW in a PEG 400:ethanol solution for treatment with patients suffering from hepatitis C.