Clinical Study Synopsis for Public Disclosure

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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.

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-004718-15	
Name of active ingredient: BI 34021 FU2		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 APR 2009	**Trial No. / U No.:** 1258.1/U09-1321-01	**Dates of trial:** 28 MAR 2008 - 23 JUN 2008	**Date of revision :** Not applicable

Title of trial:	Safety, tolerability and pharmacokinetics of BI 34021 FU2 oral drinking solution in healthy male volunteers (dose range: 5 - 500 mg). A double-blind (within dose groups), randomised, placebo-controlled within dose groups, single-rising dose study, including re-dosing at 50 mg and 150 mg (food effect) and at 100 mg (two 50 mg tablets)
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim/Rhein, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	Evaluation of safety, tolerability and pharmacokinetics of single rising doses of BI 34021 FU2 in healthy male volunteers, comparison of the drinking solution (100 mg) with the tablet formulation (two 50 mg tablets), and assessment of a possible food effect (dose levels 50 mg, 150 mg) on the bioavailability of BI 34021 FU2.
Methodology:	Randomised, double-blind, placebo-controlled (within dose groups), single-rising-dose, single-centre study
No. of subjects:	
planned:	entered: 64
actual:	enrolled: 66 entered: 63 BI 34021 FU2 drinking solution: entered: 48, treated: 48, analysed (for primary endpoint): 48 BI 34021 FU2 tablets: entered: 6, treated: 6, analysed (for primary endpoint): 6 Placebo: entered: 15, treated: 15, analysed (for primary endpoint): 15

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Diagnosis and main criteria for inclusion:	The main inclusion criteria were: healthy male volunteers, age ≥21 and ≤50 years, and a body mass index (BMI) range of ≥18.5 and ≤29.9 kg/m^2.
Test product 1:	BI 34021 FU2 powder in the bottle (PiB) for application as drinking solution
dose:	5 mg, 20 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, 500 mg of BI 34021 FU2
mode of admin.:	Oral
batch no.:	B071004040 (oral stock solution 40 mg BI 34021 FU2)
	B071004333 (oral stock solution 400 mg BI 34021 FU2)
Test product 2:	BI 34021 FU2 tablets (50 mg)
dose:	100 mg (single dose of 2 tablets of BI 34021 FU2)
mode of admin.:	Oral
batch no.:	B081000420
Reference therapy:	Placebo solution matching BI 34021 FU2 PiB
	Placebo tablets matching 50 mg BI 34021 FU2 tablets
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B071004017 (oral stock solution 40 mg Placebo matching BI 34021 FU2 PiB)
	B071004018 (oral stock solution 400 mg Placebo matching BI 34021 FU2 PiB)
	B071004200 (Placebo matching BI 34021 FU2 tablets)
Duration of treatment:	For each treatment, a single dose was administered. For dose groups 50 mg, 100 mg, and 150 mg, a second dose was administered at least 13 days after the first dose.

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Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic parameters of BI 34021 FU2, BI 44422 ZW and BI 55022 BS: C_{max}, t_{max}, AUC_{0-2h}, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, $MRT_{p.o.}$, CL/F, V_z/F, AUC_{0-tz}, AUC_{0-2h}, Ae_{t1-t2}, fe_{t1-t2}, CLR_{t1-t2}
Safety:	Physical examination, vital signs (blood pressure [BP], pulse rate [PR], respiratory rate [RR], oral body temperature), 12-lead ECG, laboratory tests, adverse events, and tolerability
Statistical methods:	Descriptive statistics for safety and PK endpoints were calculated. Dose proportionality (linearity) of BI 34021 FU2, BI 44422 ZW, and BI 55022 BS was explored using a regression model. A 95% confidence interval for the slope was computed. An analysis of variance (ANOVA) on the logarithmic scale was used to analyse the relative bioavailability (fasted vs. fed, tablet vs. drinking solution).
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	Overall, 66 subjects were enrolled and 64 subjects were randomised into the study. In the treated set were the 63 subjects entered and receiving at least 1 dose of trial medication. For the analysis of dose proportionality, 48 subjects receiving active treatment were included. The 63 male subjects entered into this study were Caucasian (100%), with a mean age of 34.2 years, and a mean BMI of 25.15 kg/m^2. There were no relevant differences between treatment groups in demographic data and baseline characteristics, and there were no subjects with relevant medical history. In healthy male Caucasian subjects, BI 34021 BS, administered as BI 34021 FU2, was rapidly absorbed and metabolised to BI 44422 ZW and BI 55022 BS. All 3 substances reached maximum concentrations within at mean 1 h after administration of BI 34021 FU2. Based on the graphical presentations, the increase in BI 34021 BS C_{max} and $AUC_{0-\infty}$, with increasing doses, was over-proportional at doses of 100 mg and 150 mg and seemed to be proportional at doses ≤100 mg and ≥150 mg. The terminal half-lives of both BI 34021 BS and BI 44422 ZW were short, being 2 to 2.6 h at dosages higher than 150 mg. At doses below 150 mg, $t_{1/2}$ was slightly shorter. Based on the point estimators and 95% CIs, an over-proportional

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increase in exposure over the entire dose range was found for all 3 analytes (except BI 34021 BS, C_{max}). The fraction of BI 34021 BS metabolised to BI 44422 ZW and BI 55022 BS was constant over the entire dose range investigated (100 to 500 mg BI 34021 BS), as exposure to both descendants increased linearly with the one of BI 34021 BS.

For BI 34021 BS, after administration of 100 mg BI 34021 FU2 PiB and tablets, intra-individual parameters of median [h] and range [%] were for t_{max} 0.359 hours and 0.233-0.500% for the PiB, 0.759 hours and 0.500-0.767% for the tablet formulation. The values for AUC_{0-tz} and C_{max} are displayed in the table below.

100 mg BI 34021 BS	BI 34021 BS 100 mg PiB		BI 34021 BS 100 mg (2 tablets of 50 mg)	
	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-tz} [nmol·h/L]	5.92	54.1	5.52	57.5
C_{max} [nmol/L]	9.01	50.5	6.44	21.0

The tablet and the PiB, reconstituted as oral drinking solution, showed similar overall bioavailability expressed as AUC_{0-tz} (93.2% for the tablet compared to the solution). However, peak exposure (C_{max}) was reduced with the tablet to 71.48%, and t_{max} was prolonged by 24 minutes compared to the PiB.

When BI 34021 FU2was given with food (test), a marked reduction in C_{max} was observed for all 3 analytes in comparison to the fasted condition (reference). After administration of 50 mg BI 34021 BS, t_{max} was prolonged, if the analytes were measurable. However, for dose group 150 mg BI 34021 BS, t_{max} was shortened under fed conditions, but showed a much higher variability, as did C_{max}. The adjusted gMean ratio of C_{max} (test/reference) was 33.3% at dose level 50 mg and 10.0% at dose level 150 mg for BI 34021 BS, 12.1% at dose level 50 mg and 12.4% at dose level 150 mg for BI 44422 ZW, and 4.3% at dose level 50 mg and 13.2% at dose level 150 mg for BI 55022 BS. At dose group 150 mg, the adjusted gMean ratio of $AUC_{0-\infty}$ (test/reference) was 35.3% for BI 34021 BS, 26.8% for BI 44422 ZW, and 20.4% for BI 55022 BS.

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Safety results:

In the single-rising dose part of the study, 63 subjects were treated in the fasted state in 8 sequential dose groups (5 mg, 20 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, and 500 mg). In each group, 6 subjects received active treatment and 2 subjects received placebo (dose group 20 mg: 1 subject received placebo). Subjects of dose groups 50 mg and 150 mg underwent a second treatment period at least 13 days after the first treatment period, receiving a second dose of study medication as oral drinking solution after the ingestion of a high-fat, high-calorie breakfast. Subjects in dose group 100 mg underwent a second treatment period receiving a second dose of study medication in the tablet formulation (two 50 mg tablets) in the fasted state.

In the course of the study, 12 subjects (19.0%) out of 63 subjects experienced at least 1 AE. During treatment period 1, 7 subjects out of 63 subjects reported 7 AEs and during treatment period 2, 5 subjects out of 24 subjects reported a total of 5 AEs. At screening 1 subject reported an AE. No subject reported any AE during washout and in the post-treatment period. The reported AEs by preferred term were headache (3 subjects, 4.8%), fatigue (2 subjects, 3.2%), pharyngolaryngeal pain (1 subject, 1.6%), diarrhoea (1 subject, 1.6%), nausea (1 subject, 1.6%), sinusitis (1 subject, 1.6%), frequent bowel movements (1 subject, 1.6%), conjunctivitis (1 subject, 1.6%), and cough (1 subject, 1.6%). AEs of moderate intensity were reported by 6 subjects, 5 subjects reported AEs of mild intensity, and 1 subject reported 2 severe AEs. The subject with the 2 severe AEs experienced headache in both treatment periods. There was no dose pattern, no food effect, or formulation effect for AEs by preferred term or intensity.

In this trial 5 subjects reported AEs that were considered to be drug-related (500 mg PIB: 2 subjects, 150 mg PiB fed: 2 subjects, placebo tablet: 1 subject). The 5 subjects with drug-related AEs reported headache (2), fatigue (2) and nausea (1). All subjects with drug-related AEs recovered without additional therapy. There was no dose pattern, no food effect, or formulation effect for AEs by drug relatedness. All subjects completed the trial as planned.

In the course of this trial, no death, no SAE, and no other significant AE were reported. None of the subjects discontinued the trial prematurely.

The laboratory evaluation revealed no clinically relevant increases from baseline. For some parameters of haematology and clinical chemistry, transitions

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	relative to the reference range from baseline to the end of the study were observed in few subjects in individual treatment groups. Overall, no clinically relevant changes in laboratory values monitored for safety were observed. No relevant differences in PR or BP were seen between subjects treated with placebo and subjects treated with different doses of BI 34021 FU2. There was no evidence of a clinically relevant effect of BI 34021 FU2 on ECG parameters; in particular, there was no indication of a prolongation of the QT-interval. There was no association identified between the dose of study medication, or the formulation, and prolongations or changes from baseline in QTcB or QTcF. There were some subjects with prolongations in QTcB or QTcF or changes in QTcB or QTcF from baseline. There were some subjects with notable findings regarding the heart rate. However, none of the ECG findings was considered to be clinically relevant. The overall tolerability was assessed as 'good' for all treated subjects. No dose effect of BI 34021 FU2, no formulation effect, and no food effect with regard to safety criteria was detected in this trial.
Conclusions:	In healthy male Caucasian subjects, BI 34021 BS (administered as BI 34021 FU2) was rapidly absorbed and metabolised to BI 44422 ZW and BI 55022 BS. No dose effect, no formulation effect, and no food effect of BI 34021 BS were found with regard to safety in this trial. A slightly over-proportional increase in exposure over the entire dose range was observed for all 3 analytes. For the tablet formulation compared with the PiB, a similar bioavailability, but a reduced maximum plasma concentration and a prolonged time to maximum plasma concentration were found. Food markedly reduced the bioavailability of BI 34021 BS, BI 44422 ZW, and BI 55022 BS, both with respect to peak and overall exposure. BI 34021 FU2 was shown to be safe and well tolerated by all subjects at all doses administered in this study. No relevant safety issues were identified.