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 Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable			
Name of active ingredient: BI 201335 NA		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2009	**Trial No. / U No.:** 1220.13/ U09-3242-01	**Date of trial:** 24 APR 2008 – 3 DEC 2008	**Date of revision** (if applicable)**:** Not applicable

Title of trial:	Safety, tolerability, and pharmacokinetics of single rising oral doses (40 mg to 480 mg) of BI 201335 NA as capsule(s) administered to healthy male subjects – a randomised, placebo-controlled (within dose groups) and double-blind trial
Principal Investigator:	[redacted]
Trial sites:	[redacted] Japan
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	To investigate safety, tolerability, and pharmacokinetics of BI 201335 ZW after administration of single rising doses from 40 mg to 480 mg of BI 201335 NA in healthy Japanese male volunteers
Methodology:	Single-centre, randomised, double-blind, placebo-controlled within dose groups, open about dose level, and single rising dose
No. of subjects	
planned:	to be entered: 50 subjects
actual:	enrolled: 105 subjects, entered: 50 subjects Treatment with BI 201335 NA 40 mg: entered: 8, treated: 8, analysed (for primary endpoint): 8 Treatment with BI 201335 NA 80 mg: entered: 8, treated: 8, analysed (for primary endpoint): 8 Treatment with BI 201335 NA 120 mg: entered: 8, treated: 8, analysed (for primary endpoint): 8 Treatment with BI 201335 NA 240 mg: entered: 8, treated: 8, analysed (for primary endpoint): 8 Treatment with BI 201335 NA 480 mg: entered: 8, treated: 8, analysed (for primary endpoint): 8 Treatment with placebo: entered: 10, treated: 10, analysed (for primary endpoint): 10

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥20 and ≤35 years, body mass index range: ≥18.5 and <25.0 kg/m^2
Test product:	BI 201335 NA soft gel capsules: 40 mg and 120 mg
dose:	40 mg, 80 mg, 120 mg, 240 mg, and 480 mg
mode of admin.:	Oral administration fasted with 150 mL of water
batch no.:	BI 201335 NA 40 mg capsules: PR08/30005
	BI 201335 NA 120 mg capsules given to the 120 mg and the 240 mg dose groups: PR08/30005
	BI 201335 NA 120 mg capsules given to the 480 mg dose group: PR08/30075
Reference therapy:	Placebo
dose:	Matching placebos for individual doses of 40 mg, 80 mg, 120 mg, 240 mg, and 480 mg of BI 201335 NA
mode of admin.:	Oral administration fasted with 150 mL of water
batch no.:	Matching placebo to BI 201335 NA 40 mg capsules: PR08/30005
	Matching placebo to BI 201335 NA 120 mg capsules given to the 120 mg and the 240 mg dose groups: PR08/30005
	Matching placebo to BI 201335 NA 120 mg capsules given to the 480 mg dose group: PR08/30075
Duration of treatment:	One day
Criteria for efficacy:	Pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, and $CL_{R,t1-t2}$
Criteria for safety:	Physical examination, vital signs (blood pressure and pulse rate), 12-lead electrocardiography, clinical laboratory tests, adverse events, and tolerability
Statistical methods:	Descriptive statistics for safety and pharmacokinetic endpoints were calculated.
	Dose proportionality of BI 201335 ZW was explored by using a regression model. A 95% confidence interval for the slope was computed.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

C_{max} of BI 201335 ZW was reached at 10.0 hours and 6.00 hours (as median of t_{max}) in the 40 mg treatment group and 80 mg treatment group, respectively, and at 4.00 hours (as median of t_{max}) in the higher treatment groups (120, 240, and 480 mg) after single oral administration.
C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ increased more than proportionately with dose.
The geometric mean (gMean) terminal half-life of BI 201335 ZW decreased with increasing dose from 38.7 hours in the 40 mg treatment group to 16.4 hours in the 480 mg treatment group. CL/F decreased with increasing dose from 126 mL/min in the 40 mg treatment group to 32.2 mL/min in the 480 mg treatment group. The gMean V_z/F also decreased with increasing dose from 423 L in the 40 mg treatment group to 45.8 L in the 480 mg treatment group. MRT_{po} also decreased with increasing dose from 55.5 hours in the 40 mg treatment group to 22.7 hours in the 240 mg treatment group and 22.9 hours in the 480 mg treatment group.
Urinary excretion of BI 201335 ZW was negligible (fe_{0-96}: <0.08%).
The inter-individual variability of pharmacokinetic parameters of BI 201335 ZW in plasma (geometric coefficient of variation %) was low to moderate (4.73% to 52.0%).

Safety results:

No serious adverse event or other significant adverse event was reported. No subjects prematurely discontinued the trial because of an adverse event.
In total, 15 drug-related adverse events of mild to moderate intensities, mostly gastrointestinal adverse events at the highest dose, were reported by 11 (27.5%) of the 40 subjects treated with BI 201335 NA.
The treatment with BI 201335 NA was associated with an increase of indirect bilirubin in a dose-dependent manner. No jaundice was noted. Other liver function test values remained normal.
Clinically relevant changes from the baseline values were not noted in 12-lead electrocardiograms or vital signs.
Global tolerability was satisfactory to good.

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Conclusions:

After single oral administration, BI 201335 ZW showed dose-dependent pharmacokinetic profile. The absorption was faster in the higher treatment groups (≥120 mg), and the exposure showed more than proportional increase while the values of $t_{1/2}$, CL/F, V_z/F, and MRT_{po} decreased with increasing dose. Urinary excretion of BI 201335 ZW was negligible.

The most frequent adverse event was gastrointestinal disorders of mild to moderate intensities. Furthermore, a mild, transient, dose-dependent increase of indirect bilirubin was noted at the two highest doses (240 and 480 mg). In summary, BI 201335 NA up to 480 mg given as a single dose was safe and tolerated in the healthy Japanese male subjects.