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: N/A		**EudraCT No.:**	
Name of active ingredient: BI 201335 NA		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 24 December 2008	**Trial No. / U No.:** 1220.10 / U08-3427-01	**Date of trial:** 14 January 2008 to 25 February 2008	**Date of revision** (if applicable)**:**

Title of trial:	An open-label, randomized, crossover relative bioavailability study of a new soft gelatin capsule formulation of BI 201335 NA compared to the current solution formulation (powder in bottle (PIB)), after single dose oral administration in healthy volunteers
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted]
Publication (reference):	Data from this study has not been published
Clinical phase:	I
Objectives:	The objective of this study was to establish the relative bioavailability of a new soft gelatin capsule (SGC) formulation of BI 201335 NA compared to the current solution formulation (powder in bottle, PIB) for two doses (40 mg, 240 mg) in a parallel, two-way cross-over study design.
Methodology:	Open-label, randomised, two-way crossover design

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No. of subjects:	
planned:	entered: 34
actual:	enrolled: 66 Treatment 40 mg (milligram): 7 subjects received single dose 40mg solution formulation followed by single dose 40mg soft gelatin capsule, and 7 subjects received single dose 40 mg soft gelatin capsule, followed by single dose 40 mg solution. entered: 14 treated: 14 analyzed (for primary endpoint) Treatment 240 mg: 10 subjects received single dose 240 mg solution formulation followed by two 120mg soft gelatin capsules, and 10 subjects received two 120 mg soft gelatin capsules, followed by single dose 240 mg solution. entered: 20 treated: 20 analyzed (for primary endpoint)
Diagnosis and main criteria for inclusion:	Healthy male/female volunteers, age ≥18 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 201335 NA
dose:	40 mg and 240 mg
mode of admin.:	Oral
batch no.:	B073001180 (40 mg SGC); B073001181 (120 mg SGC); B073001177 (40 mg/dose solution); B073001178 (240 mg/dose solution); B073001179 (solvent for BI201335 NA)
Reference therapy:	N/A
dose:	
mode of admin.:	
batch no.:	
Duration of treatment:	Single dose, followed by second single dose after 14 days

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Criteria for evaluation:

Efficacy / clinical pharmacology:

Pharmacokinetic parameters:
Primary endpoints: Comparison of plasma $AUC_{0-\infty}$ and C_{max} between the same dose and two different drug formulations to determine relative bioavailability of BI201335 NA soft gelatin capsule formulation compared to the solution formulation.

Key secondary endpoint included comparisons of t_{max}, AUC_{0-tz}, $t_{1/2}$ and CL/F between same dose and the two different drug formulations.

Other secondary pharmacokinetic parameters, λ_z, MRT_{po}, V_z/F, and C_{24} were included as needed in comparisons between same dose and two different drug formulations of BI 201335 NA.

Safety: Vital signs (blood pressure, pulse rate), laboratory tests, adverse events

Statistical methods:

Geometric mean ratios and corresponding 90% confidence intervals were calculated for all pharmacokinetic parameters, and pairwise comparisons were made between groups receiving solution formulation versus soft gelatin capsule formulation of BI201335.

Descriptive statistics for all other parameters were calculated.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Relative bioavailability (gMean) of BI 201335 NA SGC when compared to the PIB formulation for the 40 mg dose was: AUC0-∞ 92.2% (CI: 81.7%-104.1%), Cmax 87.2% (CI: 78.7%-96.6%), and for the 240 mg dose was: AUC0-∞ 70.5% (CI: 58.1-85.4%), Cmax 59.5% (CI: 44.2%-80.1%). The key secondary endpoint time to Cmax (tmax) was increased at the 240 mg dose level for the SGC formulation (gMean / gCV[%]) to 5.56 hours/28.2%, when compared to tmax of 3.6 hours/28.8% for the PIB formulation. Consistent with previous observation, systemic drug exposure increased supra-proportionately with dose. Each dose group included equal (1:1) male and female subjects, and PK parameters of BI 201335 NA were similar between genders. Inter-subject variability was higher with the 240 mg dose compared with the 40 mg dose, regardless of oral formulation.

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Safety results:	No serious adverse events were observed. Consistent with previous observations, most frequent adverse events (AEs) associated with BI201335 NA included gastrointestinal (nausea, diarrhea) and CNS (headache) organ system. All AEs were of mild to moderate intensity, regardless of oral formulation and were resolved by end of the study. Frequency of AEs was higher in the 240 mg dose group when compared to 40 mg dose group. Mild, asymptomatic and reversible indirect hyperbilirubinemia was observed in eight (40%) subjects in the 240 mg dose group, all of whom had non wild-type UGT1A1 genotypes and consistent with reduced enzyme activity.
Conclusions:	Taken together, the relative bioavailability (BA) of BI201335 NA SGC formulation was dependent on dose. Relative BA of a single 40 mg dose SGC formulation was similar to that of a single 40 mg dose PIB formulation, and reduced by approximately 30-40% for a single 240 mg dose SGC formulation when compared to a single 240 mg dose PIB formulation. Time to C_{max} (t_{max}) was increased in the median by 2 hours following a single 240 mg dose with the SGC formulation when compared to the PIB formulation.