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.

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
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Name of active ingredient: BI 201335 NA		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 Aug 2009	**Trial No. / U No.:** 1220.6 / U09-3498-02	**Date of trial:** 18 MAY 2007 – 18 FEB 2008	**Date of revision:** 08 July 2013

Title of trial:	Safety, tolerability and pharmacokinetics of multiple rising oral doses of 20 mg, 48 mg, 120 mg, and 240 mg once a day of BI 201335 NA (oral solution) in healthy male subjects, in a randomized double blind, placebo controlled study
Principal Investigator:	[redacted]
Trial site:	[redacted] Canada. [redacted]
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The main objective was to investigate the safety, tolerability and the pharmacokinetics (PK) of BI 201335 NA in healthy male subjects without Gilbert's syndrome or polymorphism (GS) following oral administration of a single dose (Day 1) and repeated doses (Days 4-24) of 20 mg, 48 mg, 120 mg, and 240 mg. Additionally, the safety, tolerability, and the PK of the highest tolerated dose of BI 201335 NA (determined during the multiple-rising-dose phase) were assessed in healthy male subjects with GS over a 28-day continuous drug administration period.

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Methodology:

This was a randomized, double-blind, and placebo-controlled (within dose groups) trial with multiple-rising doses that was conducted at 1 study center. The study consisted of two phases: the first in which a single-dose and multiple-rising doses of BI 201335 NA were administered to subjects without GS and a second phase in which the highest tolerated dose, determined from the first phase of the study, was administered to subjects with GS. The study population consisted of healthy male subjects with and without UGT1A1 polymorphisms predisposing to GS. Those subjects without GS received a single dose of drug or placebo on Day 1 to determine the 72-hour single-dose pharmacokinetic (PK) parameters of BI 201335 NA. These subjects then initiated a 21-day multiple-rising-dose segment of the trial on Day 4. These subjects without GS were admitted to and maintained in the clinic on Days 1 to 14 and Days 24 to 26 of the trial. Subjects had daily ambulatory visits to the clinic for all other study days. Subjects with GS received the highest tolerated dose of BI 201335 NA (selected from the multiple-rising-dose segment of the trial using the 4 dose levels); no placebo group was used for these subjects. These subjects were admitted to and maintained in the clinic on Days 1 to 14 and Days 28 to 30 of the trial. Subjects had daily ambulatory visits to the clinic for all other study days.

Four sequential groups of 8 subjects each without GS participated in the single-dose, multiple-rising-dose phase of the trial. Within each of these 4 dose groups, 6 subjects were to receive the active drug, and 2 were to receive placebo. One dose level was tested within each of these 4 groups (20 mg, 48 mg, 120 mg, and 240 mg). The different dose groups were investigated consecutively in ascending order of daily doses, with at least 7 days between successive groups. The remaining group of 9 subjects (group 5) consisted of subjects with GS. At the end of the multiple-rising-dose phase of the trial, these subjects with GS were treated (open-label) for 28 days with the highest tolerated dose of BI 201335 NA; no placebo group was used for these subjects.

A BI medical safety assessment group, including the investigator, reviewed safety on an ongoing basis. This group was mandated to make the decision if progress to the next dose level could occur based on safety data and clinical laboratory test results of the previous dose group in this study. Data was collected via remote data capture (RDC) to facilitate the timely availability of safety data to the safety assessment group.

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No. of subjects:	
planned:	entered: 41
actual:	enrolled: 39
	Treatment 20 mg: entered: 6 treated: 6 analysed: 6
	Treatment 48 mg: entered: 6 treated: 6 analysed: 6
	Treatment 120 mg: entered: 6 treated: 6 analysed: 6
	Treatment 240 mg: entered: 5 treated: 5 analysed: 5
	Treatment 240 mg Gilbert's subjects: entered: 9 treated: 9 analysed: 9
	Placebo: entered: 7 treated: 7 analysed: 7
Diagnosis and main criteria for inclusion:	Healthy male subjects, age ≥18 to ≤55 years, BMI range: ≥18.5 to ≤30 kg/m^2
Test product:	BI 201335 NA oral solution.
dose:	20 mg, 48 mg, 120 mg, and 240 mg QD
mode of admin.:	Oral
batch no.:	BI 201335 NA Powder for the following Oral Solutions: 315.2 mg, B063000677; 754.4 mg: B063000678; 1888 mg: B063000679; 3780 mg: B063000680
	Solvent for BI 201335 NA: B063000676

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Reference therapy:	Placebo oral solution
dose:	Number of units of placebo corresponded to the units of the respective dose level for that cohort.
mode of admin.:	Oral
batch no.:	B063000676
Duration of treatment:	22 days (Day 1 and Days 4-24) for each dose group in the multiple-rising-dose phase of the trial (subjects without GS). 28 days for the group with GS.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Efficacy was not evaluated in this study The following PK parameters were determined (where feasible) : • After the first dose: C_{max}, t_{max}, $AUC_{\tau,1}$, $AUC_{0-\infty}$, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, λ_z. • After the last dose: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{\tau,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss,}$ $\lambda_{z,ss,}$.
Safety:	Findings from physical examinations; vital signs (blood pressure [BP], pulse rate [PR]); 12-lead electrocardiograms (ECGs); clinical laboratory tests; assessment of adverse events (AEs); and tolerability, as assessed by the investigator.
Statistical methods:	Dose proportionality of BI 201335 NA was explored using a power model that quantified the functional relationship between dose and the PK endpoints, $C_{max,}$ $C_{max,ss}$ and $AUC_{0-\infty}$, $AUC_{\tau,ss}$. A regression model of log-transformed data with a two sided 95% confidence interval for the slope was computed. The assumption of a linear relationship between the log-transformed PK endpoint and the log-transformed dose was evaluated including dose range limitations. The attainment of steady state was investigated. In addition, descriptive statistics were used to summarize PK parameters. For safety, tabulations of frequencies/proportions were used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics were used to analyze continuous (quantitative) data.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Pharmacokinetic results: First dose and steady state key mean parameters are summarized in the table below. AUC and C_{max} increased supra proportionately with dose after a single dose and at steady-state. t_{max}, $t_{1/2}$ tend to be longer at lower dose, whereas CL/F and V_z/F tend to decrease with increasing dose. Steady-state was achieved 6-7 days after initiation of multiple dosing, and accumulation ratio for AUC and C_{max} is approximately 2 to 3, respectively. PK parameters between non-Gilbert's and Gilbert's subjects (GS) appear to be similar after first dose, and appear to be slightly lower at steady state.

Single dose

Dose (mg)	$AUC_{0-\infty}$ [ng*h/mL]	$AUC_{\tau,1}$ [ng*h/mL]	C_{max} [ng/mL]	t_{max} [h]	$t_{1/2}$ [h]	CL/F [mL/min]
20 (N=6)	1,290	446	24.7	8.67	35.8	279
48 (N=6)	5,010	2,220	165	4.34	28.9	178
120 (N=6)	13,700	7,350	518	2.67	23.3	152
240 (N=5)	27,500	18,800	1,850	4.01	17.5	150
240 (GS, N=9)	--	19,400	2,130	3.89	--	--

Steady State

Dose (mg)	$AUC_{\tau,ss}$ [ng·h/mL]	$C_{max,ss}$ [ng/mL]	$t_{max,ss}$ [h]	$C_{min,ss}$ [ng/mL]	$t_{1/2,ss}$ [h]	$CL/F_{,ss}$ [mL/min]
20 (N=3)	1,750	99.3	5.33	52.5	30.9	188
48 (N=5)	5,600	400	3.80	147	30.1	161
120 (N=6)	17,000	1,700	2.17	314	24.9	130
240 (N=5)	53,800	5,680	2.20	765	22.3	84.3
240 (GS, N=8)	48,300	5,290	2.00	767	18.4	105

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Safety results:

No serious AEs or deaths occurred during this trial. Of 39 subjects participating in the study, 28 (71.8%) experienced AEs. The majority of these subjects (21/39, 53.8%) experienced AEs of mild intensity. Only17.9% of subjects experienced AEs of moderate intensity. The most frequently reported AE of moderate intensity was headache. A total of 6 subjects (15.4%) had AEs deemed drug-related by the investigator. These were ocular icterus in 5 subjects (12.8%) four of which were subjects with GS, jaundice in 1 subject (2.6%), and increased hepatic enzyme in 1 subject (2.6%).

No clinically relevant changes in ECG parameters were observed. Particularly, there was no indication of an increase of the QT/QTc interval after multiple dosing of BI 201335 in all dose groups tested.

There were no DAIDS Grade 4 laboratory abnormalities observed during this trial. DAIDS Grade 3 laboratory abnormalities were reported for amylase (1 subject in the Placebo group), total cholesterol (1 subject in the Placebo group), lipase (1 subject in the Placebo group) and total bilirubin (2 subjects in the 240 non-GS group and 5 subjects in the 240 mg GS group). With the exception of 2 subjects (both in the 240 mg GS group), total bilirubin values for the last value on treatment were within the normal range. Nine subjects with ALT values within normal range at baseline had increases in ALT values on treatment. Three of these subjects in the placebo group; 1 in the 48 mg non-GS group; 1 in the 120 mg non-GS group; and 4 in the 240 mg GS group. These elevated values were transient, and almost all returned to within the normal range by Day 20, and all had values that were within the normal range as the last value on treatment.

Conclusions:

Over all, BI 201335 NA was safe and well tolerated at all the doses administered. Independent from dose, individual subjects experienced reversible asymptomatic ALT elevations. At higher doses an increased incidence of headache, gastrointestinal symptoms and unconjugated hyperbilirubinemia was observed. Individual healthy volunteers with Gilbert's syndrome experienced scleral icterus at the dose of 240 mg. Drug exposure of BI 201335 increased supra proportionately with dose after a single dose and after the last dose at steady-state. Peak time and half-life tend to be longer at lower dose, whereas oral clearance and apparent volume of distribution tend to decrease with dose. Steady-state was achieved 6-7 days after initiation of multiple dosing.