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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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 Study Report**		
Name of finished product:		**SUPPLEMENTARY SHEET**		
Name of active ingredient: BI 201335 NA		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 22 August 2007	**Number:** U07-1819-02	**Study period (dates):** 14 SEP 06 - 09 DEC 06		**Date of revision:** 28 May 2008

Title of study:	Safety, tolerance, and pharmacokinetics of single oral doses of 4 mg, 16 mg, 48 mg, 120 mg, 240 mg, 480 mg, 800 mg, and 1200 mg BI 201335 NA (PEG 400/TRIS/meglumine/water solution) in healthy male subjects, in a randomised single blind, placebo controlled rising dose study, followed with an open-label intra-subject two-stage crossover pilot bioavailability comparison of 480 mg BI 201335 NA in a PEG 400/TRIS/meglumine/water solution co-administered with food
Investigator:	[redacted]
Study centre:	[redacted] [redacted] D-[redacted]
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	The objective of this study was to investigate the safety, tolerability, and pharmacokinetics of BI 201335 NA following administration of single rising doses from 4 mg to 1200 mg. In addition, the food effect on the bioavailability of BI 201335 NA (480 mg) was investigated.
Methodology:	Randomised, single-blind, placebo-controlled, within dose groups, single rising dose, single centre. The food effect was investigated at a dose of 480 mg (placebo-controlled, randomised, cross-over comparison without and with a high fat breakfast)
No. of subjects:	
planned:	Entered (total): 74 (single rising dose and food effect part)
actual:	Enrolled: 74 Entered (total): 74 (single rising dose and food effect part) Part 1- single rising dose: BI 201335 NA: Entered: 48 treated: 48 analysed (for primary endpoint): 48 Placebo: Entered: 16 treated: 16 analysed (for primary endpoint): 16 Part 2 - bioavailability/food effect: BI 201335 NA: Entered: 8 treated: 8 analysed (for primary endpoint): 8 Placebo: Entered: 2 treated: 2 analysed (for primary endpoint): 2

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥ 18 and ≤ 50 years, BMI range: ≥ 18.5 and ≤ 29.9 kg/m^2
Test product:	BI 201335 NA in a mixture of 30 mL of PEG 400, 4 mL TRIS/water (1:9 w/v), and 4 mL meglumine/water (1:9 w/v)
doses:	4 mg, 16 mg, 48 mg, 120 mg, 240 mg, 480 mg, 800 mg, and 1200 mg
mode of admin.:	Single rising dose part: Oral (p.o.) taken fasted with 240 mL water Food effect part: p.o. taken fasted or after a high fat breakfast
batch nos.:	PD-2763, PD-2764, PD-2765, PD-2766, PD-2767, PD-2768, PD-2769, PD-2770
Duration of treatment:	Single dose
Reference therapy:	Placebo: mixture of 30 mL of PEG 400, 4 mL TRIS/water (1:9 w/v), 4 mL meglumine/water (1:9 w/v)
dose:	-
mode of admin.:	Single rising dose part: p.o. taken fasted with 240mL water Food effect part: p.o. taken fasted or after a high fat breakfast
batch nos.:	PD-2771, PD-2772, PD-2773
Criteria for evaluation:	
Efficacy:	PK: plasma concentration time profiles of BI 201335; PK parameters C_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, t_{max}, $t_{1/2}$, CL/F, MRT_{po}, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$, λ_Z
Safety:	Physical examination, vital signs (BP, PR), ECG, laboratory tests, adverse events, and tolerability
Statistical methods:	Descriptive statistics for safety and PK endpoints were calculated. Dose proportionality of BI 201335NA was explored using a regression model. A 95% confidence interval for the slope was computed. The statistical model for the determination of food effect was ANOVA with term "subject" and "treatment".

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SUMMARY – CONCLUSIONS:

Pharmacokinetic results: PK of BI 201335 NA after single oral administration showed some unique characteristics. The drug was very slowly absorbed, especially at the initial low doses with a t_{max} of more than 10 h. Mean t_{max}, CL/F, and $t_{1/2}$ of BI 201335 NA were dose dependent. Both, $AUC_{0-\infty}$ and C_{max} increased more than proportionately with dose. PK of BI 201335 NA exhibited moderately high inter-subject variability; the coefficient of variation (CV) values for $AUC_{0-\infty}$ were mostly in the range of 50 to 60% for higher dose groups, but tended to be lower at about 30% for most of the lower dose groups. Urinary excretion of BI 201335 NA was less than 0.1% of the administered dose and was therefore negligible. There was only a very slight food effect when BI 201335 NA was co-administered with a high fat breakfast. The administration with food led to a slightly higher C_{max} (relative bioavailability = 108.89% with 90% CI 82.31 - 144.06%). For $AUC_{0-\infty}$, the relative bioavailability for administration with food was 113.56% with 90% CI 92.70 - 139.12%. The median time to maximal observed plasma level t_{max}, was 6 h under fasted conditions and 4 h under fed conditions; the non-parametric 90% CI for the difference fed-fasted was -5.00 to -0.017 h.

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Safety results:	BI 201335 NA administered as oral solution was generally well tolerated. All subjects who experienced an AE recovered without sequelae. No serious AEs occurred during the study. In the single rising dose part of the study, the administration of ascending single doses led to a higher incidence of AEs including hyperbilirubinaemia, particularly in the 1200 mg group. In both parts of the trial, the most frequently observed AEs were gastrointestinal disorders, particularly loose stools or diarrhoea, nausea, retching and vomiting. A total of 17 subjects had nervous system disorders, which were by preferred term headache and dizziness. Marked hyperbilirubinaemia (>3.0 mg/dL) reported as an AE was observed in 7 subjects (2 subjects in the 480 mg group and 5 subjects in the 1200 mg group) and therefore constituted the second frequent AE in this study. The observed hyperbilirubinaemia was caused by an elevation of unconjugated bilirubin and is not considered a toxicity. Pre-clinical and in-vitro studies showed that BI 201335 NA inhibits UGT in concentrations greater than 200 ng/mL [U04-3332]. This threshold level will be exceeded in the blood of humans treated with 240 mg or more. For a number of drugs, such as irinotecan, indinavir or atazanvir, unconjugated hyperbilirubinaemia is known to be caused by a polymorphism in the UGT1A1 causing reduced enzyme activity, that is typical for the benign unconjugated hyperbilirubinaemia in Gilbert's Syndrome [P04-02605, R07-2450, R07-2453]. Genotyping in the 7 subjects with an elevation of indirect bilirubin of >3.0 mg/dL showed a polymorphism in the UGT1A1 gene in 6 of these subjects. Thus, the findings in these subjects confirmed the results from pre-clinical and in-vitro studies. One of the 7 subjects developed mild transient jaundice of skin and sclera. No genotyping was performed in the remaining subjects with no or lower bilirubin elevation, probably leading to under-estimation of the real allele frequency. This close correlation together with the in-vitro inhibition of UGT1A1 by BI 201335 NA is strongly suggestive of a causal relationship between the UGT1A1 polymorphisms and the benign unconjugated hyperbilirubinaemia under high doses of BI 201335 NA. When comparing pre-dose and post-dose laboratory values an increase from normal to elevated levels of total bilirubin was observed in a dose dependent manner in 2 subjects in the 120 mg group, 3 subjects in the 240 mg group, 4 subjects in the 480 mg group, all 6 subjects of the 800 mg group, all 6 subjects of the 1200 mg group and all 8 subjects of the 480 mg food effect part. Three subjects on placebo were also affected. The measurement of the direct bilirubin fractions using the standard Diazo method uncovered mild elevations of direct bilirubin in 14 subjects, that correlated with the total bilirubin.

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	The calculation of indirect bilirubin revealed, that hyperbilirubinaemia in all subjects was due to elevations of unconjugated bilirubin, while the mild elevations of direct bilirubin in some subjects were due to the well known methodical overestimation of conjungated bilirubin by the Diazo reaction [R07-2472, R07-2636]. Anaemia or concomitant increases of one of the hepatic enzymes (AST, ALT, AP or GGT) were not observed, except in 1 subject who had slightly elevated ALT and LDH values. Thus, haemolysis or liver toxicity as reason for the unconjugated hyperbilirubinaemia was excluded. In both parts of the trial, AEs with a potential causal relationship to the treatment were observed in a total of 24 out of 56 (42.9%) of the subjects treated with BI 201335 NA. Drug-related AEs which occurred in at least 3 subjects overall were diarrhoea (15 subjects), nausea (7 subjects), retching (4 subjects), vomiting (3 subjects), hyperbilirubinaemia (7 subjects), and dizziness (4 subjects). Apart from increased bilirubin, the overall laboratory evaluation revealed no evidence of a major impact of BI 201335 NA on any other lab parameters and no clinically significant deviations from normal occurred. No clinically relevant changes in ECG data, which included the analysis of QTcF-and QTcB-intervals, or vital signs were observed, neither in the single-rising dose part nor in the bioavailability/food effect part of the study. Furthermore, physical examinations revealed no changes in physical status. No relevant differences with regard to safety were noted when administering BI 201335 NA in the fasted or fed state.
Overall Conclusions:	BI 201335 NA after single oral administration was very slowly absorbed. Mean t_{max}, CL/F, $t_{1/2}$ of BI 201335 NA were dose dependent. Both $AUC_{0-\infty}$ and C_{max} increased more than proportionately with dose. The PK of BI 201335 NA exhibited moderately high inter-subject variability; the CV values for $AUC_{0-\infty}$ were mostly in the range of 50 to 60% for higher dose groups, but tended to be lower at about 30% for most of the lower dose groups. Urinary excretion of BI 201335 NA was negligible. Only a very small effect of food on the PK parameters of BI 201335 NA was observed. BI 201335 NA was safe and well tolerated at the doses administered. The tolerability was good at doses up to 240 mg. At doses higher than 240 mg a lower tolerability and an increased incidence of AEs including gastrointestinal symptoms and predominantly unconjugated hyperbilirubinaemia was observed.