Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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Name of active ingredient: BI 201335 NA		**Page:** 1 of 7	**Synopsis No.:**
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Report date: 23 SEP 2009	**Trial No. / U No.:** 1220.16 / U09-1853-01	**Date of trial:** 18 JUN 2008 – 07 OCT 2008	**Date of revision** (if applicable)**:** Not applicable

Title of trial:	Assessment of the effect of 480 mg and 1200 mg of BI 201335 as single dose on the QT interval in healthy female and male subjects; a randomised, placebo-controlled, double-blind, four-way crossover Phase I study with moxifloxacin as positive control
Principal Investigator:	[redacted]
Trial sites:	[redacted] Germany
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	*Primary objective:* To demonstrate that BI 201335 does not prolong the QT interval more than placebo. *Secondary objective:* To assess the tolerability of 1200 mg of BI 201335 as single dose in female subjects (double-blind, randomised, placebo-controlled) before inclusion of female subjects in the crossover part of the trial.
Methodology:	Double-blind (moxifloxacin: open), randomised, placebo-controlled, crossover of 4 treatments: 480 mg BI 201335, 1200 mg BI 201335, placebo (negative control), and 400 mg moxifloxacin (positive control) in male subjects and female subjects; assessment of tolerability of 1200 mg of BI 201335 as single dose in female subjects (double-blind, randomised, placebo-controlled) before inclusion of female subjects in the crossover part of the trial
No. of subjects:	
planned:	entered: 56 subjects
actual:	Treatments 480 mg BI 201335, 1200 mg BI 201335, placebo, and 400 mg moxifloxacin (*four-way crossover part*): entered: n=48 treated and analysed (for primary endpoint): placebo n=45, 480 mg BI 201335 n=48, 1200 mg BI 201335 n=46, moxifloxacin n=46 Treatments 1200 mg BI 201335 and placebo (*tolerability part*): entered: n=8 treated: n=8 analysed (for secondary endpoints only): n=8

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Diagnosis and main criteria for inclusion:	Healthy Caucasian female and male subjects were included in this clinical trial provided they were between 18 years and 50 years of age, had a body mass index (BMI) of 18.5 kg/m^2 to 29.9 kg/m^2, and were characterised by genotyping as a homozygote or heterozygote wild type UGT1A1 ("non-Gilbert").
Test product:	BI 201335 soft gel capsules 120 mg
dose:	480 mg, 1200 mg
mode of admin.:	Oral administration with 240 mL water
batch no.:	B073001114
Reference therapy:	BI 201335 placebo soft gel capsules as negative control Moxifloxacin (Avalox®) tablets as active control
dose:	BI 201335 placebo: not applicable Moxifloxacin (Avalox®): 400 mg
mode of admin.:	Oral administration with 240 mL water
batch no.:	Moxifloxacin: B071000389 placebo: B073001112
Duration of treatment:	One day, single dose for each treatment
Criteria for evaluation:	
Clinical pharmacology:	*Primary endpoint:* • QTcI interval (QT interval individually corrected for heart rate based on a parabolic model) derived as the mean of the ECG measurements taken between 3 h and 8 h after dosing minus the mean of the baseline ECGs obtained pre-dose separately for each treatment period. Each QT interval was derived as the mean value of 3 ECG measurements with 4 wave forms each. The 5-hour time window 3 to 8 h post-dose was chosen to assure relevant exposure to both BI 201335 and moxifloxacin. *Secondary endpoints:* • The mean value of QTcI changes from baseline between 2 h and 24 h after dosing • The change from mean baseline of the QTcI at any point in time between 2 h and 24 h after dosing • The time-matched changes versus placebo (i.e., the differences between measurements taken after dosing of BI 201335 or moxifloxacin and measurements taken after dosing of placebo) in QTcI at any point in time between 2 h and 24 h after dosing

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Clinical pharmacology (cont.):	*Other parameters of interest:* • Other QT correction modes (QTcN, QTcF, and QTcB) and uncorrected QT • Notable changes in QT intervals (new onset of prolongations >450 ms, >480 ms, and >500 ms; changes from baseline >30 ms and >60 ms) • Assay sensitivity as expressed by QT prolongation seen for moxifloxacin • Pharmacokinetics (PK) of BI 201335 (if applicable): C_{max} , t_{max}, AUC_{t1-t2}, AUC_{0-tz}, $AUC_{0-\infty}$, $t_{1/2}$, CL/F, V_z/F, MRT_{po}
Safety:	Safety measures included medical examination, blood pressure (BP), pulse rate (PR), laboratory parameters, adverse events (AEs), cardiologic assessment, and global tolerability.
Statistical methods:	The mean QTcI change from baseline from 3 h to 8 h was assessed applying an ANCOVA model with the factors 'sequence', 'subjects nested within sequence', 'treatment', 'period', and 'baseline' as a covariate. The subsequent pairwise comparisons of treatments were based on the computation of two-sided 90% CIs for the mean differences and corresponding point estimators adjusted for baseline. A repeated measurements model was used to analyse the QTcI changes from mean baseline at each time point including the above stated factors and the additional factors 'time', 'time-by-treatment', and 'time-by-period interactions'. Descriptive statistics were calculated for the PK parameters of BI 201335.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Tolerability part:
Adequate safety and tolerability of 1200 mg BI 201335 were confirmed in the 6 female subjects which received active treatment.

PD (effects on the QTc interval) data were not evaluated in these subjects.

Median t_{max} occurred 7.13 h after dosing, with a gmean C_{max} of 17400 ng/mL and a gmean AUC_{0-24} of 222000 ng·hr/mL. Geometric mean $t_{1/2}$ was 13.9 h with a CL/F of 54.8 ml/min and Vz/F of 65.7 L. Post-dose vomiting decreased BI 201335 exposure.

Crossover part:
The crossover part included 28 male subjects and 20 female subjects with a mean (SD) age of 39.4 (8.8) years.

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Clinical pharmacology results (cont.):

Crossover part (cont.)

Pharmacodynamics:

Primary endpoint:

Mean QTcI over 3 h to 8 h after dosing of placebo and after dosing of BI 201335 decreased as compared to baseline. The difference between BI 201335 and placebo was about -1.1 ms with the 480 mg dose and about -2.9 ms with the 1200 mg dose; the upper limits of the two-sided 90% CIs remained below 1 ms for both doses. Thus, the hypothesis of a significant QTcI prolongation (with an upper limit of the two-sided 90% CI exceeding 10 ms) was clearly rejected.

Moreover, for both dose groups the upper limits of the two-sided 90% CIs remained clearly below 10 ms also in the subgroup of non-vomiters (n=21 subjects) showing a higher BI 201335 exposure compared to vomiters.

Secondary endpoints and other parameters of interest:

QTcI: The placebo-corrected mean QTcI changes from baseline over the time interval 2 h to 24 h after dosing of BI 201335 480 mg and 1200 mg were very small and did not exceed ±1 ms. The adjusted mean differences of QTcI between BI 201335 and placebo for all single time points of 2 h to 24 h after dosing ranged from −3.1 ms to 2.5 ms for the 480 mg dose and from −4.0 ms to 2.4 ms for the 1200 mg dose. The maximum upper limits of the two-sided 90% CIs were 4.8 ms at 10 h after dosing of 480 mg BI 201335 and 5.0 ms at 2 h after dosing of 1200 mg BI 201335. Thus, also all upper confidence limits for the single time points from 2 h to 24 h did not exceed the pre-defined non-inferiority margin of 10 ms.

HR effects: In general, HR increased following treatment with placebo and with BI 201335. The largest placebo-corrected increases from baseline were observed at 4 h after dosing reaching 3.1 bpm for 480 mg BI 201335 and 5.8 bpm for 1200 mg BI 201335. As a consequence of these HR increases the uncorrected QT interval shortened; the placebo-corrected adjusted mean decreases in uncorrected QT from baseline between 3 h and 8 h after dosing reached -3.7 ms with 480 mg BI 201335 and -8.6 ms with 1200 mg BI 201335.

QTcN, QTcF, QTcB: The mean changes from baseline over 3 h to 8 h after dosing in QTcN were -3.0 ms for 480 mg BI 201335 and -3.8 ms for 1200 mg BI 201335. The QTcN analyses were in good agreement with those for QTcI. QTcF and QTcB overestimated the correction of QT values for HR and thus these data do not add additional information.

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Clinical pharmacology results (cont.):

Crossover part (cont.):

Pharmacodynamics (cont.):

Secondary endpoints and other parameters of interest (cont.):

Notable QTc findings: There were no notable findings (for definition see 'criteria for evaluation') in QTcI, QTcN, and QTcF for either placebo or BI 201335.

Gender effects: For both genders, the absence of a clinically relevant increase in QTcI following dosing of 480 mg and 1200 mg BI 201335 was confirmed.

Pharmacokinetic-pharmacodynamic relationship: Evaluations of the exposure-response relationship did not indicate any relationship between exposure to BI 201335 and prolongation of QTcI.

Assay sensitivity: The analysis of the difference in QTcI between placebo and moxifloxacin yielded a mean QTcI prolongation of 15.1 ms (90% CI: 13.07, 17.16). Thus, an appropriate assay sensitivity was confirmed.

Pharmacokinetics:

The gmean AUC_{0-24} for 480 mg and 1200 mg BI 201335 was 68000 ng·hr/mL and 142000 ng·hr/mL, respectively. Median t_{max} was 6 h in both dose groups. After dosing of 480 mg, gmean C_{max} and AUC_{0-24} were quite comparable in female subjects (C_{max}: 6360 ng/mL, AUC_{0-24} 73900 ng·hr/mL) and in male subjects (C_{max}: 5900 ng/mL, AUC_{0-24} 65300 ng·hr/mL). In contrast, after dosing of 1200 mg, AUC_{0-24} and C_{max} were approximately 1.9-fold higher in male subjects (AUC_{0-24}: 186000 ng·hr/mL; C_{max}: 14700 ng/mL) than in female subjects (AUC_{0-24}: 97600 ng·hr/mL, C_{max}: 7660 ng/mL, males). Post-dose vomiting, more prevalent in females, decreased BI 201335 exposure.

Safety results:

Tolerability part:

Five female subjects (83.3%) exposed to 1200 mg BI 201335 experienced 18 AEs as compared to no subject on placebo. All but 2 AEs were judged by the investigator as treatment-related. All AEs were mild or moderate in intensity and had resolved at the end of the observation period. Post-dose vomiting occurred in 66.7% of subjects on active treatment. Deaths or other SAEs were not observed. None of the subjects developed 'other significant AE' (definitions as of the ICH E3 Guideline), no subject discontinued the trial medication due to an AE.

The AE profile as well as laboratory observations, vital signs, and ECG data did not indicate any clinically relevant safety findings precluding the participation of female subjects in the crossover part of the trial.

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Safety results (cont.):

Crossover part:

Adverse events: Overall, 66.7% of subjects exposed to 480 mg BI 201335 experienced 76 AEs and 87.0% of subjects exposed to 1200 mg BI 201335 experienced 115 AEs. In comparison, 22.2% of subjects exposed to placebo developed 17 AEs and 8.7% of subjects exposed to moxifloxacin developed 8 AEs. Nearly all events were judged by the investigator as drug-related.
All AEs were mild or moderate in intensity and resolved at the end of the trial. Deaths or other SAEs were not observed. Two subjects developed 'other significant AEs' leading to dose reduction (1 event allocated to placebo) or trial drug discontinuation (1 event allocated to post-treatment of 480 mg BI 201335).
The most frequent AEs following all treatments were gastrointestinal (GIT) disorders, mainly nausea, vomiting, and diarrhoea. GIT AEs occurred in 66.7% of subjects on 480 mg BI 201335 and in 87% of subjects on 1200 mg BI 201335 compared with 22.2% of subjects on placebo and 6.5% of subjects on moxifloxacin. In general, female subjects were more prone to experience AEs than male subjects, irrespective of the treatment administered.
A considerably higher percentage of female subjects (84.2%) than male subjects (37.0%) experienced post-dose vomiting with the 1200 mg dose. This translated into an on average lower BI 201335 exposure in female subjects than in male subjects for this dose level

Safety laboratory: Hyperbilirubinaemia (increases above upper normal limit) occurred in 58.3% of subjects exposed to the 480 mg dose and in 69.8% of subjects exposed to the 1200 mg dose in the crossover part. In some subjects it was accompanied by urinary excretion of urobilinogen. Increases of more than 3 times upper normal limit occurred in male subjects only. No additional, systematic treatment-related changes in safety laboratory data were observed.

Vital signs: Systolic and diastolic BP did not reveal any clinically relevant, consistent treatment-induced changes. The slight increase in heart rate is probably secondary to the GIT AE profile of BI 201335.

ECG: A few abnormal ECG findings not present at baseline occurred with all treatments. They concerned mainly rhythm (11.1% of subjects on placebo, 12.5% of subjects on 480 mg BI 201335, 13% of subjects on 1200 mg BI 201335, and 6.5% of subjects on moxifloxacin) or conduction (1 subject repeatedly developed 1st degree AV block throughout the course of the trial) and were not considered clinically relevant. PR and QRS intervals were not relevantly changed following dosing of BI 201335 compared with placebo.

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Safety results (cont.):	*Crossover part (cont.):* *Global tolerability:* The overall tolerability was rated by the investigator as good in more than 90% of subjects exposed to placebo and moxifloxacin but in only 66.7% of subjects exposed to 480 mg BI 201335 and 34.8% of subjects exposed to 1200 mg BI 201335. These ratings reflected the gastrointestinal AE profile.
Conclusions:	Single oral doses of 480 mg and 1200 mg BI 201335 did not prolong the QTc interval compared to placebo in healthy male and female subjects. In line with the pharmacodynamic effects of BI 201335 (inhibition of UGT1A1) and with results of previous clinical trials with this compound, transient hyperbilirubinaemia occurred in 58.3% of subjects exposed to the 480 mg dose and in 69.8% of subjects exposed to the 1200 mg dose. The overall tolerability of BI 201335 was compromised by a high frequency of gastrointestinal events, especially with the 1200 mg dose. The incidence of vomiting increased dose-dependently. Neither the transient hyperbilirubinaemia nor the moderate gastrointestinal tolerability observed in healthy male and female subjects are considered a safety risk for the administration of BI 201335 to patients in the target population.