Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**		Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2006-004404-38		
Name of active ingredient: BI 207127 NA		**Page:**	**Number:**	**Synopsis No.:**
Ref. to Documentation:	**Module:**	**Volume:**		
Report date: 17 December 2007	**Trial No. / U No.:** 1241.1 / U07-2391	**Date of trial:** 23 JAN 2007– 31 MAY 2007		**Date of revision** (if applicable)**:** Not applicable

Title of trial:	Safety, tolerability, and pharmacokinetics of single rising oral doses (5 mg to 3000 mg) of BI 207127 NA as powder in the bottle reconstituted with PEG 400/Tris/SDS in healthy male subjects. A randomised, placebo-controlled and within dose groups double-blinded trial. Followed by an intra-individual, partially randomised, open comparison of powder in the bottle and tablet without and with food
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre Biberach, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	The objective of this trial was to investigate the safety, tolerability, pharmacokinetics, and relative bioavailability of BI 207127 NA as powder in the bottle (PIB) and solid oral dosage form (tablets) without and with food.
Methodology:	Part 1 – Single rising dose (SRD) part: Randomised, double-blind (within dose groups), placebo controlled. Part 2 – Bioavailability/food effect part: Partly randomised, open, intra-individual comparison.
No. of subjects:	
planned:	entered: 92
actual:	enrolled: 110
	BI 207127 NA (PIB) entered: 65 (part 1: 54; part 2: 11) treated: 64 (part 1: 54; part 2: 10) analysed (for primary endpoint): 64 (part 1: 54; part 2: 10)

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	BI 207127 NA (tablets) entered: 11 (part 2) treated: 11 (part 2) analysed (for primary endpoint): 11 (part 2) Placebo entered: 17 (part 1) treated: 17 (part 1) analysed (for primary endpoint): 17 (part 1)	
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 207127 NA	
dose:	Part 1:	5 mg, 25 mg, 80 mg, 200 mg, 400 mg, 800 mg, 1400 mg, 2000 mg, and 2500 mg as PIB
	Part 2:	800 mg as 4 tablets of 200 mg each
mode of admin.:	Part 1:	p.o., taken fasted with 240 mL of water
	Part 2:	p.o., taken fasted with 240 mL of water for evaluation of bioequivalence; p.o., taken after high-fat breakfast with 240 mL of water for investigation of food effect
batch no.:	Part 1:	LG01484 to LG01492 (BI 207127 NA powder); LG01494 (TRIS); LG01493 (PEG); LG01495 (SDS)
	Part 2:	B063000668 (BI 207127 NA tablets)
Reference therapy:	Part 1:	Placebo solution
	Part 2:	PIB solution for evaluation of bioequivalence; tablets for investigation of food effect
dose:	Part 1:	Not applicable
	Part 2:	800 mg as PIB for evaluation of bioequivalence; 800 mg as 4 tablets of 200 mg each for evaluation of food effect
mode of admin.:	Part 1:	p.o., taken fasted with 240 mL of water
	Part 2:	p.o., PIB taken fasted with 240 mL of water for evaluation of bioequivalence; p.o., tablets taken fasted with 240 mL of water for investigation of food effect

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batch no.:	Part 1: Part 2:	LG01494 (TRIS); LG01493 (PEG); LG01495 (SDS) PIB solution: LG01488; Tablets: B063000668
Duration of treatment:	Part 1: Part 2:	Single dose 3 times a single dose
Criteria for evaluation:		
Efficacy / clinical pharmacology:	Pharmacokinetic parameters:	C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{oral}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Safety:	Physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, laboratory tests, adverse events (AEs), and overall tolerability	
Statistical methods:	Descriptive statistics for safety and pharmacokinetic endpoints were calculated. Dose proportionality was explored using a regression model; a 95% confidence interval for the slope was computed. ANOVA was applied for determination of the relative bioavailability of the tablet and of the food effect.	

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Of the 71 subjects participating in the SRD part, 54 subjects were treated with single rising oral doses of BI 207127 NA as PIB at nine dose levels between 5 mg and 2500 mg, and 17 subjects received placebo. A total of 11 subjects participated in the bioavailability and food effect part. Ten of these subjects received three single doses (800 mg each) of BI 207127 NA as PIB in the fasted state, as tablet in the fasted state, and as tablet in the fed state. One subject received only the tablets in fasted and fed condition.

Pharmacokinetics:

Part 1 – SRD part: BI 201727 NA administered as PIB formulation was absorbed and eliminated rapidly. The mean terminal half-life was 2.0 – 3.4 hours with no correlation with the dose amount administered. In many subjects who had received BI 2017127 NA (PIB) at a dose level of 800 mg or above, the plasma concentration-time profile exhibited a secondary or shoulder peak about 5 hours after drug administration. Because the subjects were provided with lunch about 4 hours after drug administration, it was assumed that the absorption of BI 207127 NA was increased by food consumption. Pharmacokinetic parameters were not assessed for the dose level 2500 mg, because four of the six subjects in this dose group experienced emesis shortly after drug administration. In the analysed dose range of 5 mg to 2000 mg, both C_{max} and $AUC_{0-\infty}$ were close to

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	dose proportional. However, the highest values for C_{max} (3001 ng/mL) and $AUC_{0-\infty}$ (19107 h·ng/mL) were reached with the 1400 mg dose, which might be explained by the small sample size and the high inter-subject variability. The geometric means of the apparent clearance were in the range of 73 to 147 L/h, and the mean apparent volume of distribution ranged from 277 to 618 L, indicating poor absolute bioavailability of BI 207127 NA when administered as PIB formulation. The amount of unchanged drug in the urine was low; renal excretion was negligible. Part 2 – Bioavailability/food effect part: The terminal half-life of BI 207127 NA administered as tablet in the fasted state or after a high-fat breakfast was 2.8 h or 3.1 h, respectively. Eight hours after drug administration, the plasma concentration was 282 ng/mL for the PIB (fasted), 239 ng/mL for the tablet fasted, and 592 ng/mL for the tablet fed. The values of apparent volume of distribution and apparent clearance had the order of tablet-fast > PIB-fast > tablet-fed. The relative bioavailability of the tablet (fasted) compared with the PIB was 68.6% and 66.2% in terms of $AUC_{0-\infty}$ and C_{max}, respectively, with comparable inter-subject variability. Compared with the tablet administered in the fasted state, the relative bioavailability of the tablet administered after a high-fat breakfast was 220.4% and 227.5% in terms of $AUC_{0-\infty}$ and C_{max}, respectively. The inter-subject variability in the fed state was considerably lower than in the fasted state.
Safety results:	A total of 28 subjects in this study experienced adverse events that were possibly related to treatment with BI 207127 NA; two subjects had adverse events that were considered related to treatment with placebo. Most of the AEs were considered to be of mild intensity. In the SRD part, the highest incidence of AEs was seen in the dose groups 1400 mg, 2000 mg, and 2500 mg; each subject in these dose groups experienced at least one AE. Most of the AEs were gastrointestinal disorders. The most common AE was diarrhoea, which was reported for 17 subjects receiving BI 207127 NA and one subject receiving placebo. Flatulence occurred only in the dose groups 1400 mg and above; it was reported for a total of eight subjects. Four subjects who received the 2500 mg dose experienced vomiting. In the bioavailability/food effect part, diarrhoea and nausea were the most frequently reported AEs. Diarrhoea occurred in four and five subjects after the intake of the PIB (fasted) and the tablet (fasted), while nausea was reported in two and six subjects after administration of the PIB (fasted) and the tablet (fasted). No AEs were reported for the tablet administered fed. BI 207127 NA administered as PIB formulation was well tolerated up to the

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	2000 mg dose level. The tolerability of the 2500 mg dose level was assessed as not satisfactory in four of six subjects. The 3000 mg dose level was therefore not administered. Overall tolerability of BI 207127 NA administered as tablet in the fasted state was assessed as good in five of 11 subjects, whereas tolerability was assessed as satisfactory, not satisfactory, and bad for two subjects each. In contrast, the tablet administered fed was well tolerated by all subjects. There were no deaths, no serious adverse events, and no other significant adverse events in this study. None of the subjects discontinued the trial prematurely. There was no evidence of a clinically relevant effect of BI 207127 NA on the ECG, in particular there was no indication of a prolongation of the QT-interval. The laboratory evaluation revealed no clinically relevant deviations from normal in any of the parameters assessed. Slight increases from baseline in total and direct bilirubin values were monitored for two and three subjects, respectively, whereas no transitions in AST and ALT values were observed in any of the subjects. There was no relevant elevation of serum creatinine during the study.
Conclusions:	BI 207127 NA was absorbed and eliminated rapidly. In the dose range from 5 mg to 2000 mg, BI 207127 NA pharmacokinetics were close to dose proportional, although the highest exposure was reached with the 1400 mg dose. Bioavailability of BI 207127 NA administered as PIB or tablet in the fasted state was poor, but was considerably increased by administration of the tablet after a high-fat breakfast. Single doses BI 207127 NA administered as PIB were well tolerated up to 2000 mg, whereas the tolerability of 2500 mg was unsatisfactory. A higher frequency of AEs was observed in the dose groups 1400 mg, 2000 mg, and 2500 mg. Compared with the administration in the fasted state, the tolerability of single doses of 800 mg BI 207127 NA given as tablets was considerably improved by the administration after a high-fat breakfast. The results of this trial suggest that BI 207127 NA should be administered in the fed state for pharmacokinetic as well as tolerability purposes.