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
Name of finished product: Not applicable		**EudraCT No.:** 2009-009923-12	
Name of active ingredient: BI 207127		**Page:** **1 of 6**	**Synopsis No.:**
Module:		**Volume:**	
Report date: 04 AUG 2010	**Trial No. / U No.:** 1241.9 / U10-1109-01	**Dates of trial:** 26 MAY 2009 – 17 SEP 2009	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of BI 207127 trial formulation II prototypes versus BI 207127 trial formulation I administered orally as tablet in single doses of 800 mg to healthy volunteers, and evaluation of the effect of food on the bioavailability of a selected prototype (an open-label, two-stage, within parts randomised six-way and two-way crossover phase I study)
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of 5 new 400 mg tablet formulations (trial formulation II prototypes) of BI 207127 compared to the current 200 mg BI 207127 tablet formulation (trial formulation I) in healthy male volunteers with the aim to identify the best formulation for further drug development (formulation finding part / trial part 1) and to investigate the effect of food on the relative bioavailability of the most promising one of these trial formulation II prototypes (food-effect part / trial part 2).
Methodology:	Two stage, open-label, single-dose, within the formulation finding and food-effect arms randomised six-way and two-way crossover design

No. of subjects:

planned:

entered total:	42
entered trial part 1:	24 (formulation finding part)
entered trial part 2:	18 (food effect part)

actual:

	Formulation finding part	*Food effect part*
entered:	24	18
treated:	24	18
analysed (for primary and secondary endpoints):	24	18

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥18 and ≤50 years, BMI ≥18.5 and ≤ 29.9 kg/m^2
Test product 1:	BI 207127 NA tablets, 400 mg (trial formulation II [TF-II] prototype)
dose:	800 mg of BI 207127, single dose
mode of admin.:	Formulation finding part: oral administration with 240 mL water directly after a standard continental breakfast (treatment B) Food effect part: oral administration with 240 mL water directly after an overnight fast (treatment G) and after a FDA standard high-fat and high calorie meal (treatment H)
batch no.:	B083001293
Test product 2:	BI 207127 NA tablets, delayed release (DR), 400 mg (TF-II prototype)
dose:	800 mg of BI 207127, single dose
mode of admin.:	Formulation finding part: oral administration with 240 mL water directly after a standard continental breakfast (treatment C)
batch no.:	B083001288
Test product 3:	BI 207127 NA tablets, extended release (ER), 400 mg (10% HPMC) (TF-II prototype)
dose:	800 mg of BI 207127, single dose
mode of admin.:	Formulation finding part: oral administration with 240 mL water directly after a standard continental breakfast (treatment D)
batch no.:	B093000306

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Test product 4:	BI 207127 NA tablets, extended release, 400 mg (15% PEO) (TF-II prototype)
dose:	800 mg of BI 207127, single dose
mode of admin.:	Formulation finding part: oral administration with 240 mL water directly after a standard continental breakfast (treatment E)
batch no.:	B093000308
Test product 5:	BI 207127 NA tablets, extended release, 400 mg (20% HPMC) (TF-II prototype)
dose:	800 mg of BI 207127, single dose
mode of admin.:	Formulation finding part: oral administration with 240 mL water directly after a standard continental breakfast (treatment F)
batch no.:	B093000307
Reference therapy:	BI 207127 NA tablets, 200 mg (trial formulation I [TF-I])
dose:	800 mg of BI 207127, single dose
mode of admin.:	Formulation finding part: oral administration with 240 mL water directly after a standard continental breakfast (treatment A)
batch no.:	B083001248
Duration of treatment:	Single-dose during each treatment period with pharmacokinetic (PK) blood sampling for 48 hours followed by a wash-out period of 7 days after drug administration

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Criteria for evaluation:

Efficacy / clinical pharmacology:

Pharmacokinetic parameters for BI 207127 and its metabolite CD 6168:

Primary endpoints: $AUC_{0-\infty}$ and C_{max} (BI 207127 only)

Secondary endpoints: AUC_{0-tz}, AUC_{0-12}, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, C_{max}/C_{12}, $RC_{max,Met}$, $RAUC_{0-\infty,Met}$, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$ (food-effect part only), $AUC_{0-\infty}$ and C_{max} (CD 6168 only), plasma protein binding (BI 207127 / treatment H only)

Safety:

The safety evaluation was based on physical examinations, vital signs (blood pressure, pulse rate), 12-lead electrocardiograms (ECGs), laboratory tests (haematology, clinical chemistry, and urinalysis), the analysis of adverse events (AEs) and assessment of tolerability by the investigator.

Statistical methods:

Point estimators (geometric means [gMean]) of the median intra-subject ratios of $AUC_{0-\infty}$ and C_{max} and their 2-sided 90% CIs were calculated.

The statistical model used was an analysis of variance (ANOVA) model on log-transformed parameters including effects for 'sequence groups', 'subjects within sequence groups', 'periods', and 'treatments'. CIs were based on the residual error from ANOVA.

Descriptive statistics for all other parameters were calculated.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

In trial part 1, 23/24 subjects and in trial part 2 all 18 subjects completed the trial as planned. The data from all 42 subjects were analysed for the primary endpoints of the trial. Some data were excluded for single subjects for single treatment periods.

The relative bioavailabilities of the tested formulations were 90.9% for immediate release (IR-B), 60.3% for delayed release (DR-C) and only few %, but not precisely reportable, for extended release with 15% PEO polymer (ER-15PEO-E), extended release with 10% HMPC polymer (ER-10HPMC-D), and

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extended release with 20% HPMC polymer (ER-20HPMC-F).

The only formulation that showed comparable plasma concentration profiles and similar inter-subject variability to TF-I-ref-A (reference) was the immediate release formulation IR-B. It therefore was selected as the new trial formulation II (TF-II).

The IR-B tablet (TF-II) as the selected new trial formulation was tested in the food-effect part. The food-effect part of the trial showed that administration of the selected IR-B formulation under fed conditions increased bioavailability significantly (2.7 fold in average) compared to the fasted state. There was no significant plasma exposure difference between the high-fat and the uncontrolled breakfast. Therefore, to achieve ideal plasma exposure of BI 207127 in humans, administration with food is recommended.

Analyte: BI 207127

Parameter	TF-II-fed (test)		TF-II-fasted (reference)		Ratio fed: fasted [%]	90% CI		Intra-individual gCV [%]
	N	gMean	N	gMean		lower lim. [%]	upper lim. [%]	
$AUC_{0-\infty}$ [ng·h/mL]	18	17900	18	6600	270	234	314	25.7
C_{max} [ng/mL]	18	3330	18	1330	250	216	289	25.3

The plasma concentration-time profile of CD 6168 was proportional to BI 207127. The highest plasma concentration of CD 6168 was also observed after administration of IR-B.

Safety results:

No SAEs and no AEs leading to discontinuation occurred during the trial. 17/24 subjects (71%) entered into Part 1 and 12/18 subjects (67%) entered into Part 2 experienced a total of 77 and 36 AEs, respectively. The majority of AEs were of mild or moderate intensity. Only 1 AE was rated as severe: headache starting during wash-out in Part 1 of the trial.

Overall, BI 207127 treatment was mainly associated with gastrointestinal

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	disturbances such as diarrhoea, nausea, and abdominal pain as had been expected from previous clinical trials. The most common drug-related AEs during both parts of this study were diarrhoea, followed by fatigue and headache. The incidence of diarrhoea was highest after treatment with TF-II-fast in part 2 of the trial. For all other AEs reported, no remarkable difference in incidence or kind of AE could be observed for any of the treatments administered. Global tolerability was rated as good for all subjects and treatments except for three single cases of satisfactory rating. There were no notable findings with respect to the clinical laboratory evaluation, vital signs, and ECG recordings.
Conclusions:	The tablet formulation IR-B showed the desired pharmacokinetic properties and was hence selected for further Phase II studies. Plasma exposure of BI 207127 was relevantly increased after intake of food. Thus, it is strongly recommended to administrate BI 207127 after food intake. The different BI 207127 formulations were safe and well tolerated at a single dose of 800 mg with no remarkable differences between the treatments concerning the pattern of AEs. There was a tendency of a higher number of subjects affected by gastrointestinal AEs and higher number of gastrointestinal AEs following administration of BI 207127 under fasted conditions. No treatment related effects could be detected concerning vital signs, ECGs, and clinical laboratory parameters examined.