Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-018856-28	
Name of active ingredient: BI 135585 XX		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 MAY 2011	**Trial No. / U No.:** 1283.1 / U11-1683-01	**Dates of trial:** 14 JUN 2010 – 16 SEP 2010	**Date of revision:** Not applicable

Title of trial:	A randomised, double-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of 10 mg to 1200 mg of BI 135585 XX administered as a solution to healthy male volunteers (trial part 1), followed by an open, randomised, single-dose, intra-individual bioavailability comparison of 200 mg BI 135585 XX as tablet and as solution (trial part 2)
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Biberach, Germany
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	The objectives were to investigate the safety, tolerability, pharmacokinetics (including dose proportionality), and pharmacodynamics of BI 135585 XX, as well as the relative bioavailability of 2 different immediate release tablet formulations versus the solution.
Methodology:	Single rising dose (SRD) part (= trial part 1): randomised, double-blind and placebo-controlled within dose groups Relative bioavailability (BA) part (= trial part 2): randomised, open-label, single-dose, 3-way crossover design
No. of subjects:	
planned:	total entered: 84 SRD part: 72 (6 on active drug, 2 on placebo at each of 9 planned dose levels) BA part: 12 (all on active drug)
actual:	total entered: 60 SRD part: 48 (6 on active drug, 2 on placebo at each of the investigated 6 dose levels) Placebo: treated: 12 analysed (for primary endpoints): 12 BI 135585 XX: treated: 36 analysed (for primary endpoints): 36 BA part : 12 treated: 12 analysed (for primary endpoints): 12

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥18 and ≤45 years, body mass index (BMI): ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 135585 XX as powder in the bottle (PIB) and as 2 different immediate release tablets with wet-milled or jet-milled active pharmaceutical ingredient (API)
dose:	SRD part[1]: 10 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg BA part[2]: 50 mg [1]Dose levels 600 mg, 900 mg, and 1200 mg were prespecified by the clinical trial protocol but were not investigated. [2]Dose administered in BA part was 50 mg BI 135585 XX instead of 200 mg as planned in the clinical trial protocol.
mode of admin.:	Oral
batch no.:	BI 135585 XX PIB: LG01540 (11.87 mg), LG01541 (29.69 mg), LG01542 (59.37 mg), LG01543 (118.7 mg), LG01544 (237.5 mg), LG01545 (479.9 mg) BI 135585 XX 50 mg tablet, wet-milled API: B101002055 BI 135585 XX 50 mg tablet, jet-milled API: B101002409
Reference therapy:	Placebo (in the SRD part)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	Propylene glycol (PG): LG01549, polyethylene glycol 400 (PEG 400): LG01548
Duration of treatment:	SRD part: administration of 1 single dose; BA part: administration of 3 single doses separated by 2 washout periods of at least 7 days. In both trial parts, each drug administration was followed by pharmacokinetic blood sampling for 72 h.
Criteria for evaluation:	
Clinical pharmacology:	Pharmacokinetic endpoints: $AUC_{0-\infty}$, AUC_{0-tz}, C_{max}, t_{max}, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, MRT_{oral}, CL/F, V_z/F (both trial parts); Ae_{t1-t2}, fe $_{t1-t2}$, $CL_{R,t1-t2}$ (SRD part only) Pharmacodynamic endpoints: Based on the amounts excreted in urine of urinary free cortisol (UFF), urinary free cortisone (UFE), 5α-tetrahydrocortisol (5α-THF), 5β-tetrahydrocortisol (5β-THF), and tetrahydrocortisone (THE), the following endpoints were

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	calculated: (5α-THF + 5β-THF)/THE ratio as an indicator of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibition, UFF/UFE ratio as an indicator of 11β-HSD2 inhibition, and total urinary corticosteroids (5α-THF + 5β-THF + THE + UFF + UFE) as an indicator of activation of the HPA axis.
Safety:	Physical examination, vital signs (blood pressure, pulse rate, respiratory rate), 12-lead electrocardiogram (ECG), cardiopulmonary monitoring, clinical laboratory parameters (including hormones of the hypothalamus-pituitary-adrenal [HPA] axis and thyroid gland), adverse events (AE), tolerability assessment
Statistical methods:	Descriptive statistics for safety, pharmacokinetic, and pharmacodynamic endpoints were calculated. In the SRD part, dose proportionality was explored using a log-transformed power model. A 2-sided 95% confidence interval (CI) for the slope was computed. In addition, an exploratory inferential analysis of pharmacodynamic parameters was performed. In the BA part, the relative bioavailability of the tablets in comparison to the PIB solution was investigated based on the pharmacokinetic parameters $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max}. Point estimates (geometric means [gMean]) of the intrasubject ratios and their 2-sided 90% CIs were calculated. An analysis of variance (ANOVA) model on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment' was used.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	All 60 entered subjects were healthy white men. The subjects' mean age was 32.7 years, ranging from 18 to 45 years, and the mean BMI was 24.79 kg/m^2, ranging from 19.4 to 29.2 kg/m^2. The dose groups were comparable with respect to demographic characteristics. All subjects completed the trial according to protocol. The planned dose groups 600, 900, and 1200 mg were not entered in the study based on preliminary exposure data obtained from dose levels 10 to 200 mg. *Pharmacokinetic results (SRD part)* Following single rising doses of 10 to 400 mg BI 135585 XX, gMean maximum plasma concentration (C_{max}) values ranged from 38.4 nmol/L (at 10 mg) to 17400 nmol/L (at 400 mg) and gMean area under the plasma concentration-time curve over the time interval from 0 to infinity ($AUC_{0-\infty}$) values ranged from

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Clinical pharmacology results (cont.):

3480 nmol·h/L (at 10 mg) to 180000 nmol·h/L (at 400 mg). The interindividual variability for C_{max} and $AUC_{0-\infty}$ was low to moderate with geometric coefficient of variation (gCV) values ranging from 15.3 to 30.0% for C_{max} and from 13.8 to 40.3% for $AUC_{0-\infty}$. The median time to reach plasma peak concentrations (t_{max}), the gMean apparent terminal half-life ($t_{1/2}$), and the gMean apparent volume of distribution (V_z/F) decreased with increasing dose. Values of gMean apparent oral clearance (CL/F) showed a dose-independent pattern. The gMean fraction of BI 135585 XX excreted in the urine over 72 h (fe_{0-72}) increased dose-dependently from 7.77% (at 10 mg) to 18.3% (at 400 mg).

A summary of key pharmacokinetic parameters of BI 135585 XX by dose group in subjects receiving active treatment is provided in the following table.

BI 135585 XX dose	10 mg N=6 gMean	25 mg N=6 gMean	50 mg N=6 gMean	100 mg N=6 gMean	200 mg N=6 gMean	400 mg N=6 gMean
$AUC_{0-\infty}$ [nmol·h/L]	3480	8660	15700	39900	66600	180000
AUC_{0-tz} [nmol·h/L]	1710	6260	13800	37700	64700	177000
C_{max} [nmol/L]	38.4	169	716	2490	5720	17400
t_{max}[1] [h]	7.50	2.75	1.25	0.792	0.509	0.50
$t_{1/2}$ [h]	69.6	37.4	25.6	17.3	15.0	12.7
V_z/F [L]	628	338	255	136	141	88.5
CL/F [mL/min]	104	105	115	90.8	109	80.3
fe_{0-72} [%]	7.77	12.9	13.8	12.4	15.8	18.3

[1] Median is given.

Over the entire dose range tested, an approximately proportional increase in gMean $AUC_{0-\infty}$ was observed, while gMean C_{max} and AUC_{0-tz} increased supra-proportionally with increasing dose. The point estimates of the slope parameter β were 1.0544 (95% CI 0.9827, 1.1260), 1.2326 (95% CI 1.1692, 1.2960), and 1.6729 (95% CI 1.6016, 1.7441) for $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max}, respectively. In the dose range 100 to 400 mg, $AUC_{0-\infty}$ and AUC_{0-tz} increased dose-proportionally, while C_{max} increased supra-proportionally with increasing dose.

Pharmacodynamic results (SRD part)

Compared to baseline values, the placebo-corrected (5α-THF + 5β-THF)/THE ratio, an indicator of 11β-HSD1 inhibition, decreased by 66.1 to 77.4% following single doses of 10 to 400 mg BI 135585 XX. The placebo-corrected

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Clinical pharmacology results (cont.):

UFF/UFE ratio, an indicator of 11β-HSD2 inhibition, decreased by 11.6 to 54.0%, and placebo-corrected total urinary corticosteroids, an indicator of activation of the HPA axis, increased by 52.1 to 73.6% compared to baseline values. These results suggest a significant inhibitory effect of BI 135585 XX on 11β-HSD1 activity even at the lowest dose of 10 mg accompanied by a compensatory activation of the HPA axis. The measured decrease in UFF/UFE ratio is considered to be a result of 11β-HSD1 inhibition, since an inhibition of 11β-HSD2 activity would have resulted in an increased UFF/UFE ratio.

The placebo-corrected percentage changes from baseline in daily urinary metabolite ratios and total urinary corticosteroids are given in the table below.

BI 135585 XX dose	10 mg (N=6)	25 mg (N=6)	50 mg (N=6)	100 mg (N=6)	200 mg (N=6)	400 mg (N=6)
(5α-THF + 5β-THF)/ THE ratio[1] [%]	-66.1	-72.5	-74.9	-79.1	-76.8	-77.4
UFF/UFE ratio[1] [%]	-11.6	-13.6	-25.0	-28.5	-48.0	-54.0
Total urinary corticosteroids[1] [%]	52.1	82.3	86.7	93.0	96.0	73.6

[1]Data are adjusted gMean placebo-corrected percentage changes from baseline.

Relative bioavailability of 2 tablet formulations vs. PIB solution (BA part)

The relative bioavailability in terms of $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} was 109.4%, 112.5%, and 135.1%, respectively, when wet-milled tablets were compared with the PIB solution, and it was 125.1%, 125.8%, and 165.0%, respectively, when jet-milled tablets were compared with the PIB solution (see table below).

Parameter (N=12)	Comparison	Adjusted gMean ratio [%]	Two-sided 90% confidence interval	
			Lower limit [%]	Upper limit [%]
$AUC_{0-\infty}$	Wet-milled tablet vs. PIB	109.4	102.1	117.2
	Jet-milled tablet vs. PIB	125.1	116.7	134.0
AUC_{0-tz}	Wet-milled tablet vs. PIB	112.5	105.1	120.3
	Jet-milled tablet vs. PIB	125.8	117.6	134.6
C_{max}	Wet-milled tablet vs. PIB	135.1	121.3	150.5
	Jet-milled tablet vs. PIB	165.0	148.2	183.9

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Safety results:

Of the 48 subjects entered in the SRD part, 12 subjects received placebo and, per each dose level, 6 subjects received a single dose of BI 135585 XX. The 12 subjects entered in the BA part received 3 single doses of 50 mg BI 135585 XX as PIB solution, wet-milled tablet, and jet-milled tablet. No deaths, other SAEs, or other significant AEs were reported in this study.

In the entire SRD part, a total of 16 subjects (33.3%) reported at least 1 AE. Six subjects (12.5%) reported AEs during the screening period. In the treatment period, AEs were reported for 4 subjects (33.3%) receiving placebo and for 9 subjects (25.0%) on active treatment (1 subject each in the 10, 25, and 200 mg dose groups, 2 subjects each in the 50, 100, and 400 mg dose groups). The incidence of possibly drug-related AEs was comparable for subjects receiving placebo (1 of 12 subjects, 8.3%) and subjects on active treatment (3 of 36 subjects, 8.3%). In subjects receiving active drug, diarrhoea (1 subject in 50 mg group), nausea (1 subject in 100 mg group), and headache (1 subject in 400 mg group) were assessed as possibly drug-related by the investigator.

In the entire BA part, a total of 5 subjects (41.7%) reported at least 1 AE. One subject (8.3%) reported an AE during screening. Four subjects (33.3%) reported AEs in the treatment period with the PIB solution and 1 subject (8.3%) each in the treatment periods with the wet-milled and jet-milled tablets. For 1 subject who reported headache and diarrhoea in the treatment period with the PIB solution and for 1 subject who reported headache in 2 of the treatment periods (PIB solution, wet-milled tablet), the AEs were assessed as possibly drug-related.

In both trial parts, the most frequently reported AE on treatment was headache. Headache was reported by 2 subjects (16.7%) receiving placebo and by 3 subjects (8.3%) on active treatment in the SRD part, as well as by 3 subjects (25.0%) in the BA part. All AEs were of mild or moderate intensity except for 1 severe AE (syncope) in the screening period. All AEs resolved completely.

There were no clinically relevant findings with respect to vital signs including respiratory rate, ECG, and standard safety laboratory parameters. In all dose groups of the SRD part, cortisol levels slightly decreased directly after drug administration, while an increase in adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulphate (DHEA-s), and androstenedione, mainly within the reference ranges, was observed 24 h post dose.

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Safety results (cont.): The investigator assessed the tolerability of the treatments as 'good' for all subjects with 2 exceptions: for 1 subject in the SRD part (100 mg group) and 1 subject in the BA part (PIB solution), tolerability was assessed as 'satisfactory'.

Conclusions: BI 135585 XX was well tolerated across all doses studied (10 to 400 mg) when administered as a single oral dose to healthy male subjects. There were no notable differences between the dose groups with respect to safety and tolerability.

In the dose range investigated, an approximately proportional increase in gMean $AUC_{0-\infty}$ of BI 135585 XX was observed (from 3480 nmol·h/L at 10 mg to 180000 nmol·h/L at 400 mg), while gMean C_{max} increased supra-proportionally with increasing dose (from 38.4 nmol/L at 10 mg to 17400 nmol/L at 400 mg). The median time to reach plasma peak concentrations decreased dose-dependently from 7.50 h to 0.50 h. Pharmacodynamic results suggest a significant inhibitory effect of BI 135585 XX on 11β-HSD1 activity even at the lowest dose of 10 mg.

When 2 tablet formulations of BI 135585 XX were compared with the powder for oral solution at a dose of 50 mg, the relative bioavailability based on $AUC_{0-\infty}$ was approximately 109% for wet-milled tablets and approximately 125% for jet-milled tablets.