Boehringer Ingelheim

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 Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-000844-85	
Name of active ingredient: BI 135585 XX		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 26 NOV 2013	**Trial No. / U No.:** 1283.34 / U13-2645-01	**Dates of trial:** 02 AUG 2012 – 05 SEP 2012	**Date of revision:** Not applicable

Title of trial:	Pharmacokinetics and pharmacodynamics of BI 135585 XX administered as oral dose in healthy male volunteers (open-label, single-dose trial)
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data from this trial have not been published
Clinical phase:	I
Objectives:	To investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of 200 mg BI 135585 XX following single dose administration. Additional objectives were: 1) to explore the PK/PD relationship between plasma and tissue BI 135585 concentration and 11β-HSD1 inhibition, 2) to assess the safety and tolerability of the treatment, 3) to evaluate the potential influence of 2 different sample workup methods on the PK/PD results in adipose tissue, 4) to analyse potential target desensitisation, and 5) to support optimal modelling from single dose to multiple rising dose using similarly acting compounds.
Methodology:	Open-label, single dose, one treatment
No. of subjects:	
planned:	entered: 9
actual:	entered: 9 treated: 9 analysed (for primary endpoint): 9
Main criteria for inclusion:	Healthy male volunteers, age 18 to 55 years (inclusive), overweight or obese, body mass index (BMI) ≥28 kg/m^2
Test product:	BI 135585 XX as immediate release tablet
dose:	200 mg (1 tablet)
mode of admin.:	Oral administration with 240 mL water after an overnight fast of at least 10 h
batch no.:	B111000515
Reference product:	Not applicable

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Duration of treatment:	Single dose
Criteria for evaluation:	
Pharmacokinetics:	Primary PK endpoints: C_{max}, AUC_{0-tz}, Secondary PK endpoint: $AUC_{0-\infty,}$ Further PK endpoints: t_{max}, $t_{1/2}$, MRT_{oral}, CL/F, V_z/F Concentration of BI 135585 in adipose tissue following two different methods of sample workup
Pharmcodynamics:	Further endpoint: 11β-HSD1 activity in adipose tissue (*ex vivo*) including post-dose/pre-dose ratio as indicator for 11β-HSD1 inhibition using two different methods of sample workup (methods A and B)
Safety:	Further endpoints: Adverse events (AEs), clinical laboratory tests, vital signs (blood pressure [BP], pulse rate [PR]), 12-lead ECG, and physical examination
Statistical methods:	Descriptive statistics for PK, PD and safety parameters were calculated. 11β-HSD1 activity in adipose tissue (*ex vivo*) including post-dose/pre-dose ratio was compared for the two different methods of sample workup (B vs. A).
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	A total of 9 subjects were entered and treated with one single dose of 200 mg BI 135585 XX. All subjects completed the trial according to the CTP. All subjects were white men with a mean (SD) age of 39.3 (± 8.3) years. No relevant concomitant medical conditions and concomitant therapies were reported.

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Clinical pharmacology results (continued):

Pharmacokinetic results

Following a single oral dose of 200 mg BI 135585 XX, the absorption from the gut appeared to be relatively quick (t_{max} ~2 - 4 h). Regarding its distribution and elimination, BI 135585 exhibited a low apparent clearance (CL/F range, 2.17 - 4.82 L/h), a moderate apparent volume of distribution (V_z/F range, 80.9 - 182 L) and a relatively long apparent terminal half-life ($t_{1/2}$ range, 20.7 - 39.9 h). Based on the geometric coefficient of variation (gCV) for the plasma exposure parameters (C_{max} and $AUC_{0-\infty}$), the inter-subject variability was moderate for BI 135585 (18% and 26%, respectively).

Pharmacodynamic results

The sample preparation process used for method A led to much lower BI 135585 concentrations (-49% to -44%) measured in adipose tissue at 10 h and 24 h post dosing compared to method B. These data suggest that the use of method A can lead to an underestimation of the actual concentrations of BI 135585 in adipose tissue specimens. Overall, BI 135585 adipose tissue concentrations were relatively low compared to plasma (gMean, 7 - 8% for method A and 13 - 16% for method B).

In contrast to BI 135585 concentrations measured in adipose tissue, 11β-HSD1 activity does not appear to be affected by the sample preparation process since the inhibition effect was comparable between method A and method B for both assessments at 10 h and 24 h post dosing (gMean, 94.1% for method A vs. 95.2% for method B and 88.1% for method A vs. 88.9% for method B, respectively). Therefore, the difference in BI 135585 concentrations observed between the two methods did not apparently translate into an effect on the inhibition of 11β-HSD1.

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Safety results:	In total 3 out of the 9 subjects reported at least 1 AE after administration of a single dose of 200 mg BI 135585 XX. AEs reported for 1 subject each were mild dizziness, moderate headache and mild diarrhoea. Of these, the investigator considered mild dizziness and mild diarrhoea as drug-related. All subjects recovered from their AEs by the end of the trial. No deaths, no AEs leading to discontinuation, and no SAEs occurred during the trial. There were no notable findings with respect to clinical laboratory evaluations, vital signs, and ECG recordings. After administration of a single dose of 200 mg BI 135585 XX, hormones of the HPA-axis (mean cortisol, ACTH, DHEAs, androstenedione and total testosterone) slightly increased at time point 24:00 h compared with baseline. SHBG basically remained unchanged. Hormones of the thyroid gland slightly increased at 24:00 h for free T3 and T4 and remained unchanged for TSH.
Conclusions:	BI 135585 was absorbed relatively quickly (t_{max} ~ 2 - 4 h), and exhibited a low apparent clearance (CL/F range, 2.17 - 4.82 L/h), a moderate apparent volume of distribution (Vz/F range, 80.9 - 182 L), a relatively long apparent terminal half-life ($t_{1/2}$ range, 20.7 - 39.9 h), and a moderate plasma exposure inter-subject variability based on C_{max} and $AUC_{0-\infty}$ (18% and 26%, respectively) after oral administration of a single dose of 200 mg BI 135585 XX. The sample preparation process used for method A and method B does not appear to affect the inhibition of 11β-HSD1 activity in adipose tissue generated by BI 135585. However, the difference in BI 135585 concentrations measured in adipose tissue between the two preparation processes suggest that method A can lead to an underestimation of the actual concentration of BI 135585 in adipose tissue specimens. Therefore, method B appears to be preferable to determine BI 135585 concentrations in adipose tissue biopsies. Overall, BI 135585 adipose tissue concentrations were relatively low compared to plasma. Based on the safety and tolerability assessments in this trial, the oral administration of 200 mg BI 135585 XX was well tolerated by healthy male subjects.