# Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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***.

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| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:**<br>Not applicable | | **EudraCT No.:**<br>2009-010881-49 | |
| **Name of active ingredient:**<br>BI 207127 NA<br>BI 201335 NA | | **Page:**<br>1 of 8 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
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| **Title of trial:** | An open-label, fixed sequence Phase I study in healthy male volunteers to assess sequentially the effects of multiple doses of BI 207127 NA, BI 201335 NA followed by the combination of BI 207127 NA and BI 201335 NA, on the single dose pharmacokinetics of midazolam and tolbutamide and on the systemic exposure of BI 207127 NA and BI 201335 NA |
| **Principal Investigator:** | [redacted] |
| **Trial sites:** | [redacted]<br>Germany |
| **Publication (reference):** | None as of the date of this clinical trial report |
| **Clinical phase:** | I |
| **Objectives:** | The primary objectives of this clinical trial were to:<br>• Determine the pharmacokinetic drug-drug interaction potential of BI 207127 NA and BI 201335 NA on each other at steady-state;<br>• Quantify the effect of BI 207127 NA, and BI 207127 NA combined with BI 201335 NA, on the activity of CYP2C9 and CYP3A4 using the probe substrates tolbutamide (CYP2C9) and midazolam (CYP3A4).<br>A secondary objective of this clinical trial was to:<br>• Compare the plasma exposure of BI 207127 NA and CD 6168 at the first-dose and at steady-state in healthy subjects. |
| **Methodology:** | Open-label, fixed sequence trial in healthy male volunteers |

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| **No. of subjects:** | |
| **planned:** | entered: 36 subjects |
| **actual:** | enrolled: 37 subjects<br>Treatment: 5 mg midazolam / 500 mg tolbutamide (Day 1);<br>entered: 37 treated: 37 analysed (for the primary objective): 34<br><br>Treatment: 800 mg BI 207127 NA t.i.d. (Days 3 to 8) + 5 mg midazolam / 500 mg tolbutamide (Day 7);<br>entered: 36 treated: 21 analysed (for the primary objective): 21 |
| **Diagnosis and main criteria for inclusion:** | Healthy male volunteers, aged ≥21 and ≤50 years, BMI range: ≥19 and ≤29.9 kg/m$^2$ |
| **Test product:** | BI 207127 NA and tolbutamide plus midazolam |
| **dose:** | Multiple dose of 800 mg of BI 207127 NA t.i.d. on Day 3 to Day 8<br>Single dose of 500 mg tolbutamide on Day 7<br>Single dose of 5 mg midazolam on Day 7 |
| **mode of admin.:** | Oral administration with 240 mL of water |
| **batch nos.:** | BI 207127 NA: B091000623<br>Tolbutamide: PR08/10517<br>Midazolam: F030611 |
| **Test product:** | BI 201335 NA and tolbutamide plus midazolam |
| **dose:** | Loading dose of 480 mg and 240 mg BI 201335 NA on Day 15, followed by 240 mg BI 201335 NA b.i.d. on Day 16 to Day 24<br>Single dose of 500 mg tolbutamide on Day 23<br>Single dose of 5 mg midazolam on Day 23 |
| **mode of admin.:** | Oral administration with 240 mL of water |
| **batch nos.:** | BI 201335: B091000622<br>Tolbutamide: PR08/10517<br>Midazolam: F030611 |

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| **Test product:** | BI 207127 NA plus BI 201335 NA and tolbutamide plus midazolam |
| **dose:** | Multiple dose of 800 mg of BI 207127 NA t.i.d. on Day 25 to Day 30<br>Single dose of 500 mg tolbutamide on Day 29<br>Single dose of 5 mg midazolam on Day 29 |
| **mode of admin.:** | Oral administration with 240 mL of water |
| **batch nos.:** | BI 201335: B091000622<br>Tolbutamide: PR08/10517<br>Midazolam: F030611 |
| **Reference therapy:** | Tolbutamide: 500 mg |
| **dose:** | Single dose of 500 mg tolbutamide on Day 1 |
| **mode of admin.:** | Oral administration with 240 mL of water |
| **batch no.:** | PR08/10517 |
| **Reference therapy:** | Midazolam: 1 mg/mL |
| **dose:** | Single dose of 5 mg midazolam on Day 1 |
| **mode of admin.:** | Oral administration with 240 mL of water |
| **batch no.:** | F030611 |
| **Duration of treatment:** | Thirty days including all planned treatments.<br>The trial was performed as planned until Day 10, when it was prematurely stopped for increased liver enzymes: ALT, AST and GLDH) following 5 or 6 days of treatment with BI 207127 NA and co-administration of midazolam/tolbutamide on Day 7. |

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**Criteria for evaluation:**

**Pharmacokinetics:**

Primary endpoints:

- Co-primary endpoints were the steady-state plasma $C_{max}$ and AUC for BI 207127 NA alone (Day 7).
- Co-primary endpoints for each probe drug (midazolam, 1-OH-midazolam, tolbutamide, 4-OH-tolbutamide, carboxytolbutamide) were $C_{max}$ and AUC at baseline (Day 1) compared to $C_{max}$ and AUC with steady-state BI 207127 alone (Day 7). In addition, $C_{24}$ of tolbutamide as evaluated on Day 2 and Day 7.

Secondary endpoints:

- Pharmacokinetic parameters for BI 207127 NA, CD6168, midazolam, 1-OH-midazolam, tolbutamide, 4-OH-tolbutamide and carboxytolbutamide:

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| BI 207127 NA (Day 3): | $C_{max,N}$, $t_{max,N}$, $C_{pre,N.}$ $AUC_{0-6,N,}$ $AUC_{0-12,N}$ $AUC_{0-24,N,}$ $Cavg_{0-24,N}$. |
| CD6168 (Day 3): | $C_{max,N}$, $t_{max,N}$, $C_{pre,N.}$ $AUC_{0-6,N,}$ $AUC_{0-12,N}$ $AUC_{0-24,N,}$ $Cavg_{0-24}$, $RC_{max,\ Met,\ N}$, $RAUC_{0-24,Met}$. |
| BI 207127 NA (Day 7): | $C_{max,ss,N}$, $t_{max,}$, $C_{pre,N.}$ $AUC_{0-6,ss,N,}$ $AUC_{0-12,ss,N}$ $AUC_{0-24,ss,N,}$ $CL/F_{,N}$, $V/F_{0-24,ss}$,$Cavg_{0-24,ss}$. |
| CD6168 (Day 7): | $C_{max,ss,N}$, $t_{max,N}$, $C_{pre,N.}$ $AUC_{0-6,ss,N,}$ $AUC_{0-12,ss,N}$ $AUC_{0-24,ss,N,}$ $CL/F_{,N}$, $V/F_{0-24,ss}$,$Cavg_{0-24,ss}$, $RC_{max,\ Met,ss,N}$, $RAUC_{0-24,Met,ss}$. |
| midazolam (Days 1 + 7): | $C_{max,N}$, $t_{max,N}$, $C_{last,N}$, $AUC_{0-48,N}$,$AUC_{0-\infty,N}$, $CL/F_{,N}$, $Vz/F_{,N}$, $T_{1/2,N}$, $T_{last,N}$. |
| 1-OH-midazolam (Days 1 + 7): | $C_{max,N}$, $t_{max,N}$, $C_{last,N}$, $AUC_{0-48,N}$,$AUC_{0-\infty,N}$, $t_{1/2,N}$, $T_{last,N}$, $RAUC_{0-48,Met,N}$. |

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| **Pharmacokinetics (cont.):** | tolbutamide (Days 1 + 7): | $C_{max,N}$, $t_{max,N}$, $C_{last,N}$, $AUC_{0-48,N}$,$AUC_{0-\infty,N}$, $CL/F_{,N}$, $Vz/F_{,N}$, $T_{1/2,N}$, $T_{last,N}$. |
| | 4-OH-tolbutamide (Days 1 + 7): | $C_{max,N}$, $t_{max,N}$, $C_{last,N}$, $AUC_{0-48,N}$,$AUC_{0-\infty,N}$, $t_{1/2,N}$, $T_{last,N}$, $RAUC_{0-48,Met,N}$. |
| | carboxytolbutamide (Days 1 + 7): | $C_{max,N}$, $t_{max,N}$, $C_{last,N}$, $AUC_{0-48,N}$,$AUC_{0-\infty,N}$, $t_{1/2,N}$, $T_{last,N}$. |
| **Safety:** | Medical examination, pulse rate, blood pressure, 12-lead ECG, laboratory parameters, adverse events and global assessment of tolerability. | |
| **Statistical methods:** | Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-\infty}$, $C_{max}$ and $C_{24}$ of tolbutamide and of $AUC_{0-\infty}$ and $C_{max}$ of 4'-OH-tolbutamide, carboxytolbutamide, midazolam and 1-OH-midazolam and their two-sided 90% CIs (Confidence intervals) were calculated.<br><br>The statistical model was an ANOVA on log-transformed parameters including effects for "subject" and "treatment". Confidence intervals were to be based on the residual error from the investigated treatment comparison.<br><br>Point estimators (median) of the intra-subject differences of $t_{max}$ of tolbutamide, 4-OH-tolbutamide, midazolam and 1-OH-midazolam were calculated.<br><br>Descriptive statistics for all other parameters were calculated. | |

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**SUMMARY – CONCLUSIONS:**

**Pharmacokinetics:**

The geometric mean test/reference ratios (GMR) of $AUC_{0-\infty}$ and $C_{max}$ of midazolam indicated that the exposure after co-administration of 5 mg midazolam/500 mg tolbutamide with steady-state of BI 207127 NA increased compared with combined administration of 5 mg midazolam/500 mg tolbutamide alone and reached 135.7% for $AUC_{0-\infty}$ and 139.7% for $C_{max}$ for midazolam and 172.5% for $AUC_{0-\infty}$ and 133.3% for $C_{max}$. Regarding the data, a higher level of variability seemed to be associated with these values.

The geometric mean test/reference ratios (GMR) of $AUC_{0-\infty}$, $C_{max}$ and $C_{24}$ of tolbutamide, indicated, that the exposure after administration of 5 mg midazolam/500 mg tolbutamide with steady-state of BI 207127 NA remained unaffected, while geometric mean $C_{max}$ was marginally reduced with 93.2% and geometric mean $C_{24}$ was slightly elevated with 118.7% if compared with combined administration of 5 mg midazolam and 500 mg tolbutamide alone. Regarding the data, a higher level of variability seemed to be associated with these values. The 90% CI showed no changes for tolbutamide and 4-OH-tolbutamide for $AUC_{0-\infty}$ and $C_{max}$.

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**Safety results:**

Overall, AEs were reported by 5 (13.5%) subjects after single combined treatment with 5 mg midazolam/500 mg tolbutamide, by 17 (47.2%) subjects for the time period of dosing of BI 207127 NA 800 mg t.i.d including the combined treatment with 5 mg midazolam/500 mg tolbutamide at steady-state of BI 207127 NA 800 mg t.i.d. on Day 7, and by 7 (18.9%) subjects during the post-treatment phase. All AEs were of mild to moderate intensity and the majority of AEs was considered to be related to treatment. There was one SAE (calculus ureteric; renal disorder) not considered to be related to treatment which occurred during the post-treatment phase. One subject was discontinued due to AEs (increased ALT on treatment and directly thereafter increased AST and GLDH at post-treatment.

The co-administration of 5 mg midazolam and 500 mg tolbutamide with BI 207127 NA at steady-state was not well tolerated by healthy subjects. Liver enzymes (AST, ALT, GLDH), for whom an increase within the normal ranges were already seen on Day 8 (5 days of dosing of BI 207127 NA), increased clearly and consistently above the upper limit of normal in a total of 22 subjects, starting predominantly on Day 10, 3 days after combined co-administration of midazolam/ and tolbutamide on Day 7 at steady-state of BI 207127 NA. Based on the absence of associated signs of liver failure and the lack of similar findings in HCV patients, these mild to moderate, asymptomatic and reversible ALT elevations are considered as benign ALT elevations, similar to what is observed with therapeutic doses of acetaminophen or heparins in healthy volunteers.

For none of these subjects, a relevant increase of bilirubin or INR above normal could be observed on Day1, 10 and 13. All values above normal were followed up until they were again within the normal ranges.

The most frequently observed AEs considered to be related to treatment with trial medication were of gastrointestinal nature; among those were diarrhoea, nausea, discoloured faeces and abdominal pain. All of these AEs, most often of mild intensity, started during treatment with 800 mg BI 207127 NA t.i.d. but were resolved before co-administration of midazolam/tolbutamide.

The evaluation of vital signs did not reveal any relevant changes potentially related to treatment with the trial medication. None of the findings in ECG and physical examination evaluations were classified as AE.

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**Conclusions:**

- 800 mg BI 207127 NA t.i.d. exerted at steady-state a weak inhibitory effect on CYP 3A4.
- No relevant effect of 800 mg BI 207127 NA t.i.d. on CYP 2C9 activity was observed.
- Co-administration of 5 mg midazolam and 500 mg tolbutamide to BI 207127 NA 800 mg t.i.d. at steady state was not well tolerated by healthy subjects.
- Liver enzymes (AST, ALT, GLDH) clearly increased above normal in a total of 22 subjects, 2 days after the combined dosing of 5 mg midazolam/500 mg tolbutamide at steady-state of BI 207127 NA. A slight increase of AST and AL, with the individual values remaining within the normal ranges, could already be assumed at pre-dose of Day 8, i.e. 24 hours after the co-administration of BI 207127 NA, midazolam and tolbutamide.
- The most frequent AEs were related to gastrointestinal disorders, most often attributable to treatment with 800 mg BI 207127 NA t.i.d. alone.
- There were no relevant safety signals for vital signs, ECG and physical examination.
- The primary objectives of the clinical trial were not met due to the premature stop of the trial.

The reason for the delayed final reporting of this clinical trial was that efforts failed to identify validated biomarkers for liver injury that could be used in further exploration of the PK samples.