# 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:** Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:** Buscopan® | | **EudraCT No.:** 2006-004691-12 | |
| **Name of active ingredient:** Hyoscine butylbromide | | **Page:** **1 of 5** | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:** 16 OCT 2008 | **Trial No. / U No.:** 202.833 / U08-2033-01 | **Date of trial:** 29 MAY 2007–26 JUL 2007 | **Date of revision** (if applicable)**:** |



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| **Title of trial:** | A randomised, double-blind, placebo-controlled study to assess pharmacokinetics, safety and tolerability of single rising oral doses (20 mg, 60 mg, 100 mg, 200 mg and 400 mg) and multiple rising oral doses (3 x 20 mg, 3 x 60 mg and 3 x 100 mg per day) of Buscopan® in healthy male volunteers |
| **Principal/Coordinating Investigator:** | [redacted] |
| **Trial sites:** | [redacted] Germany |
| **Publication (reference):** | None |
| **Clinical phase:** | I |
| **Objectives:** | To investigate pharmacokinetics, safety and tolerability of Buscopan® after single rising dose and after multiple rising doses |
| **Methodology:** | Randomised, double-blind, placebo controlled within dose groups, single rising dose and multiple rising dose, single centre |
| **No. of subjects:** | |
| **planned:** | entered: 60 |
| **actual:** | enrolled: 60 |
| | Treatment 20 mg: entered: 9 treated: 9 analysed for pharmacokinetics: 9<br>Treatment 60 mg: entered: 9 treated: 9 analysed for pharmacokinetics: 9<br>Treatment 100 mg: entered: 9 treated: 9 analysed for pharmacokinetics: 9<br>Treatment 200 mg: entered: 9 treated: 9 analysed for pharmacokinetics: 9<br>Treatment 400 mg: entered: 9 treated: 9 analysed for pharmacokinetics: 9<br>Treatment Placebo: entered: 15 treated: 15 analysed for pharmacokinetics: 15 |
| **Diagnosis and main criteria for inclusion:** | Healthy male volunteers, age ≥ 21 and ≤ 50 years, BMI ≥ 18.5 and < 30 kg/m$^2$ |

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| **Test product:** | Buscopan®, 20 mg film coated tablet |
| **dose:** | 20 mg, 60 mg, 100 mg, 200 mg, 400 mg |
| **mode of admin.:** | Oral |
| **batch no.:** | n.a. |
| **Duration of treatment:** | One day (single dose) of each treatment |
| **Reference therapy:** | Placebo |
| **Test product:** | Buscopan®, 20 mg film coated tablet |
| **dose:** | 20 mg, 60 mg, 100 mg (1 single dose in the single rising dose part, then 3 times a day) |
| **mode of admin.:** | Oral |
| **batch no.:** | n.a. |
| **Duration of treatment** | 10 doses of one dose strength (multiple doses) from day 1 to day 4 |
| **Reference therapy:** | Placebo |
| **Criteria for evaluation:** | |
| **Efficacy / clinical pharmacology:** | Pharmacokinetic parameters:<br>After the single (1st) dose: $C_{max}$, $t_{max}$, $AUC_{0-\infty}$, $AUC_{0-tz}$, $\lambda_z$, $t_{1/2}$, MRTpo, CL/F, Vz/F, $A_{et1-t2}$, $fe_{t1-t2}$, $CL_{R,t1-t2}$; After the last dose of multiple dosing: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{\tau,ss}$, $C_{pre,ss}$, $C_{avg}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $Vz/F_{,ss}$, $Ae_{t1-t2\ ,ss}$, $fe_{t1-t2,,ss}$,$CL_{R,t1-t2,ss}$;<br>Accumulation ratio: $R_{A,AUC,N}$, $R_{A,Cmax,N}$, and linearity index (LI); Attainment of steady state, dose proportionality of pharmacokinetic parameters |
| **Safety:** | Physical examination, vital signs (BP, PR), 12-lead ECG, laboratory tests, adverse events and tolerability |

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**Statistical methods:**

Descriptive statistics for safety and PK parameters were calculated.

Dose proportionality of Buscopan® was analysed using a linear regression model on log-transformed data; 95% confidence intervals for the slope were computed. The linearity index was explored using an ANOVA model. The attainment of steady state was explored using a repeated measures ANOVA model.

**SUMMARY – CONCLUSIONS:**

**Efficacy / clinical pharmacology results:**

*Pharmacokinetics*

Following oral administration of Buscopan® film coated tablets under fasting conditions, peak plasma concentrations were reached at 1-2 hours for both single rising doses and multiple rising doses. A vast majority of the individual plasma concentrations were below 10 ng/mL for all dose groups, suggesting relatively low systemic drug exposure. Mean terminal half life of Buscopan range from approximately 6 to 10 h (only 100 mg dose had 2/3 individual subjects for descriptive statistics) for the single rising doses, and 7 to 14 h for the multiple rising doses. The steady state accumulation ratio of Buscopan is approximately 1.8 for AUC and 1.4 for $C_{max}$. Urinary excretion of Buscopan was less than 0.1% of the dose for both single rising doses and multiple rising doses. Buscopan pharmacokinetics exhibit very high intersubject variability.

*Dose proportionality*

For single rising doses, the slope estimates (power model) were 1.08 (95% CI: 0.80, 1.35) for $C_{max}$, 0.89 (95% CI: 0.54, 1.25) for $AUC_{0-\infty}$ and 1.10 (95% CI: 0.79, 1.42) for $Ae_{0-24}$, indicating that there was not enough evidence to conclude non-proportionality over the dose range of 20 mg to 400 mg. However, the confidence interval widths are large due to the huge amount of intersubject variability: The coefficients of variation for the log-transformed $C_{max}$ are 723% for the 200 mg dose and 333% for the 400 mg dose, for $AUC_{0-\infty}$ it is 211% for the 100 mg dose.

For multiple rising doses, the slope estimates (power model) were 0.75 (95% CI: 0.23, 1.28) for $C_{max,ss}$ and 0.74 (95% CI: 0.20, 1.28) for $AUC_{\tau,ss}$, indicating that there was not enough evidence to conclude non-proportionality over the whole dose range of 20 mg to 100 mg. However, the confidence interval widths are large due to the huge amount of intersubject variability: The coefficients of variation for the log-transformed $AUC_{\tau,ss}$ are -1760% for the 60 mg dose and 210% for the 100 mg dose.

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| | *Attainment of steady state*<br>Attainment of steady state for multiple rising doses could not be rejected. However, the adjusted mean ratios of subsequent time points did not indicate any specific pattern pointing towards attainment of steady state.<br>*Linearity index*<br>The adjusted linearity indices were slightly above 1 for all three doses: 20 mg qd / 20 mg tid: 1.281, 60 mg qd / 60 mg tid: 1.212 and 100 mg qd / 100 mg tid: 1.120. Linearity could not be rejected, i.e. 1 is contained in all 95% CIs; however, the confidence interval widths are rather large. |
| **Safety results:** | Eighteen of 60 subjects experienced adverse events. AEs were mild to moderate in intensity and fully reversible. Tolerability of Buscopan® was good with exception of one subject with satisfactory tolerability at 20 mg single dose and good tolerability at 20 mg multiple dose.<br>Twelve different AEs were observed. The most frequently reported AE was headache 23.3% (14/60). Other AEs were dizziness 5% (3/60), fatigue 5% (3/60), abdominal pain 1.7% (3/60), arthralgia 1.7% (1/60), diarrhoea 1.7% (1/60), malaise 1.7% (1/60), muscle disorder 1.7% (1/60), nasopharyngitis 1.7% (1/60), nausea 1.7% (1/60), rhinitis 1.7% (1/60) and vomiting 1.7 % (1/60).<br>AEs such as abdominal pain, headaches, dizziness, fatigue, malaise, muscular disorder, nausea, vomiting were considered as drug-related by the investigator (listed as percentage by number of subjects per dose group):<br>Single doses: for placebo 26,7% (4/15) (headaches and fatigue), for the 20 mg dose 11.1% (1/9) (headaches and vomiting), for the 60 mg dose 11.1% (1/9) (dizziness), for the 100 mg dose 11.1% (1/9) (headaches), for the 200 mg dose 11.1% (1/9) (nausea) and for the 400 mg dose 33.3% (3/9) (dizziness, headaches and fatigue).<br>Multiple doses: placebo 33.3% (3/9) (headaches), for the 20 mg dose 0% (0/0), for the 60 mg dose 11.1% (1/9) (muscular disorder) and for the 100 mg dose 33.3% (3/9) (headaches, abdominal pain and malaise)<br>No deaths and no serious AEs occurred. No findings of vital signs, ECG or clinical laboratory parameters were considered clinically relevant. |
| **Conclusions:** | *Efficacy / clinical pharmacology*<br>Pharmacokinetic results showed that Buscopan plasma concentrations (mostly < |

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10 ng/mL) and urinary excretion (<0.1% of dose) were low following either a single oral dose (20 to 400 mg) or multiple oral dosing (20 to 100 mg three times a day) for 3 days. Mean terminal half life of Buscopan obtainable mostly at higher doses was approximately 10 hours, and therefore exhibited some accumulation at steady state (approximately 1.8 for AUC and 1.4 for $C_{max}$).. Buscopan pharmacokinetics exhibit very high intersubject variability. In general, higher plasma concentrations were observed with dose, and no dose dependency in Buscopan® pharmacokinetics was apparent.

Summarising the statistical analysis of dose proportionality of Buscopan®, the results did not indicate any specific pattern pointing towards dose proportionality for both single rising doses and multiple rising doses: There was not enough evidence to conclude non-proportionality over the whole dose range, but the wide confidence interval limits for the slope indicate that the estimates for the slope have only low precision.

Attainment of steady state for multiple rising doses could not be rejected. However, the adjusted mean ratios of subsequent time points did not indicate any specific pattern pointing towards attainment of steady state.

Linearity with respect to multiple administration of Buscopan® could not be rejected, however, the confidence interval widths for the linearity index are rather large.

*Safety*

Single and multiple doses of Buscopan® were safe and tolerability was good to satisfactory in healthy male volunteers. AEs like abdominal pain, headaches, dizziness, fatigue, malaise, muscular disorder, nausea, vomiting were considered as drug-related by the investigator.