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***.

Name of company: Boehringer Ingelheim		**Clinical Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-003108-37	
Name of active ingredient: BI 44370 TA		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 OCT 2008	**Trial No. / U No.:** 1246.3 / U08-2049-01	**Date of trial:** 06 FEB 2008 – 31 MAR 2008	**Date of revision** (if applicable)**:**

Title of trial:	Effects of 100 mg and 500 mg BI 44370 TA orally applied as 50 mg tablets on the pharmacokinetics of 2 mg orally administered midazolam solution. An open-label, randomised, parallel group, fixed-sequence study with intra-individual comparison of midazolam pharmacokinetics with and without BI 44370 TA.
Principal/Coordinating Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	none
Clinical phase:	I
Objectives:	Evaluation of the long-term (48 h) and short-term (1 h) effects of BI 44370 BS on the pharmacokinetics of midazolam as marker of a possible inhibition of CYP 3A4; safety and tolerability
Methodology:	Open-label, randomised, parallel group, fixed-sequence study with intra-individual comparison of midazolam pharmacokinetics with and without BI 44370 TA
No. of subjects:	
planned:	entered: 48 (24 male and 24 female subjects), 12 per treatment
actual:	randomised: 48 Drop-out after randomisation: 2 Completed: 46 Dose Group 1: entered: 12 (6 males, 6 females) treated: 12, analysed for primary endpoint: 12 Dose Group 2: entered: 12 (6 males, 6 females) treated: 12, analysed for primary endpoint: 12

Name of company: Boehringer Ingelheim		**Clinical Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:**	
Name of active ingredient: BI 44370 TA		**Page:** 2 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 OCT 2008	**Trial No. / U No.:** 1246.3 / U08-2049-01	**Date of trial:** 06 FEB 2008 – 31 MAR 2008	**Date of revision** (if applicable)**:**

	Dose Group 3: entered: 12 (6 males, 6 females) treated: 12, analysed for primary endpoint: 11 Dose Group 4: entered: 12 (6 males, 6 females) treated: 12, analysed for primary endpoint: 11
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers, age ≥21 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 44370 TA 50 mg tablet/midazolam solution
dose:	2 mg midazolam solution after 100 mg or 500 mg BI 44370 TA **Dose Group 1**: administration of midazolam 1 h after administration of 100 mg BI 44370 TA (the six females of this group will additionally receive a single dose of 300 mg BI 44370 TA at Visit 4) **Dose Group 2**: administration of midazolam 48 h after administration of 500 mg BI 44370 TA **Dose Group 3**: administration of midazolam 24 h after administration of 500 mg BI 44370 TA **Dose Group 4**: administration of midazolam 1 h after administration of 500 mg BI 44370 TA
mode of admin.:	Oral
batch no.:	B071004285, B071004328, B071004327, B071004363, B071004364
Reference therapy:	Midazolam (Dormicum® V 5 mg/5 mL)
dose:	2 mL
mode of admin.:	solution for intravenous application 5 mg/ 5 mL
batch no.:	F023311
Duration of treatment:	one single dose of midazolam 2 mg solution for each reference and test treatment, one single dose of 100 mg or 500 mg BI 44370 BS at 1h, one single dose of 500 mg BI 44370 BS at 24 or 48 h before the midazolam dose (test treatment), one single dose of 300 mg BI 44370 BS at visit 4 for the six females of dose group 1

Name of company: Boehringer Ingelheim		**Clinical Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:**	
Name of active ingredient: BI 44370 TA		**Page:** 3 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 OCT 2008	**Trial No. / U No.:** 1246.3 / U08-2049-01	**Date of trial:** 06 FEB 2008 – 31 MAR 2008	**Date of revision** (if applicable)**:**

Criteria for evaluation:

Efficacy / clinical pharmacology:

Pharmacokinetic parameters:
C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, $MRT_{p.o.}$, CL/F, V_z/F, AUC_{0-tz}, AUC_{t1-t2} of midazolam and BI 44370 BS (free base)

C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, $MRT_{p.o.}$, AUC_{0-tz}, AUC_{t1-t2} of α-hydroxymidazolam (1-OH- midazolam)

Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$; of BI 44370 BS

ratio of $AUC_{0-\infty}$ and AUC_{0-tz} 1-OH-midazoalm / $AUC_{0-\infty}$ and AUC_{0-tz} midazolam

Safety:

Physical examination, blood pressure, pulse rate, 12-lead ECG, laboratory tests, adverse events (AEs) and tolerability

Statistical methods:

Descriptive statistics for safety and pharmacokinetic endpoints were calculated. The statistical model for the analysis of relative bioavailability of midazolam was an ANOVA on the log scale.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Co-administration of a single oral dose of 2 mg midazolam given as solution and a single oral dose of 100 or 500 mg BI 44370 BS given as tablet significantly affected the PK of midazolam. BI 44370 BS increased the oral bioavailability of midazolam by about:

- 2.5-fold at a dose of 100 mg BI 44370 BS given 1 h before midazolam
- 9.3-fold at a dose of 500 mg BI 44370 BS given 1 h before midazolam
- 1.9-fold at a dose of 500 mg BI 44370 BS given 24 h before midazolam
- 1.3-fold at a dose of 500 mg BI 44370 BS given 48 h before midazolam

The metabolic ratio was decreased by about the same extent as shown for the increase in AUC after the co-administration of 100 and 500 mg BI 44370 BS, respectively. In contrast, $t_{1/2}$ of midazolam remained unaffected by the co-administration of 100 mg BI 44370 BS and when the higher dose of BI 44370 BS was administered 24 or 48 h before midazolam. The median t_{max} was delayed from 0.5 to 0.75 h when either 100 or 500 mg BI 44370 BS was given 1 h before midazolam.

Name of company: Boehringer Ingelheim		**Clinical Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:**	
Name of active ingredient: BI 44370 TA		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 OCT 2008	**Trial No. / U No.:** 1246.3 / U08-2049-01	**Date of trial:** 06 FEB 2008 – 31 MAR 2008	**Date of revision** (if applicable)**:**

The study confirmed the over dose-proportional increase in exposure of BI 44370 BS. At a dose of 500 mg BI 44370 BS, female subjects had on average a 56 % higher $AUC_{0-\infty}$ and 84 % higher C_{max} compared with male subjects. The gender difference remained even after adjustment of the exposure measure on body weight or BMI. Accordingly, the percent of dose excreted into urine (fe_{0-24}) was about 50 % higher in females compared with males.

Safety results:

Study 1246.3 was an open-label, randomised, parallel group fixed sequence study to evaluate the short-term and long-term effects of 100 mg and 500 mg orally applied BI 44370 TA tablets on the pharmacokinetics of 2 mg orally administered midazolam. Before proceeding to the higher dose of 500 mg BI 44370 TA, the 6 female subjects in the first dose group received a single oral dose of 300 mg BI 44370 TA to investigate the safety of BI 44370 TA in women. Before this study, no female subjects had been exposed to BI 44370 TA.

In total, 48 subjects (24 males, 24 females) were randomised to the 4 dose groups, and all 48 subjects were treated as planned with a single dose midazolam at Visit 2 (reference treatment). The entire course of the study was completed by 46 subjects. Two subjects had discontinued before administration of BI 44370 TA at Visit 3 (one female in Dose Group 3 due to a SAE, and one female in Dose Group 4 withdrew consent due to personal reasons).

No deaths and no drug-related serious or other significant AEs (acc. to ICH E3) were observed during the study. None of the drug-related AEs was severe. The AEs with a relationship to the study drugs, i.e., headache, dizziness, fatigue, and papular rash, were all mild in intensity and resolved completely by the end of the trial. None of the drug-related AEs required therapy.

One episode of fatigue was observed at screening.

Name of company: Boehringer Ingelheim		**Clinical Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:**	
Name of active ingredient: BI 44370 TA		**Page:** 5 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 OCT 2008	**Trial No. / U No.:** 1246.3 / U08-2049-01	**Date of trial:** 06 FEB 2008 – 31 MAR 2008	**Date of revision** (if applicable)**:**

In summary, the rate and intensity of AEs was low, altogether 21 drug-related AEs were observed.
Five (5) events related to the study drug (headache, fatigue, dizziness) were observed under midazolam alone.

Six (6) events related to the study drug (headache, fatigue, papular rash) were observed under BI 44370 BS alone. One AE (fatigue) was observed after administration of 100 mg BI 44370 BS alone, two AEs (papular rash (2)) after administration of 500 mg alone, and 3 AEs were observed after 300 mg BI 44370 BS alone (headache (2), papular rash).
Papular rash was reported three times as papules face, in one case, under 100 mg BI 44370 BS alone, it was reported as papular exanthema on back and abdomen.

The majority of adverse events with relation to the study drug were observed after administration of both BI 44370 BS and midazolam, i.e., 10 events related to the study drug (headache, fatigue, and papular rash). Five (5) of these were observed after the combination treatment midazolam 1 h after 500 mg BI 44370 BS administration. Three (3) events (papular rash, fatigue (2)) were observed after co-administration of midazolam 1 h after administration of 100 mg BI 44370 BS, 1 event (fatigue) after co-administration of midazolam 48 h after administration of 500 mg BI 44370 BS, and 1 event (headache) after co-administration of midazolam 24 h after administration of 500 mg BI 44370 BS.

A possible relationship to BI 44370 BS was assumed for 9 AEs: 1 event of fatigue, 4 events of headache and the 4 events of papular rash. The single occurrence of mild fatigue is not considered a signal for a kind of AE that can be expected with BI 44370 BS.

The majority of AEs assessed as possibly related to BI 44370 BS (8 of 9) were observed in female subjects. As these AEs were distributed over all dose groups and the exposure differences between doses are much larger than the gender differences, the difference in AE rate between genders, if it should be confirmed in larger studies, cannot be explained by the slightly higher exposure in females.

Name of company: Boehringer Ingelheim		**Clinical Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:**	
Name of active ingredient: BI 44370 TA		**Page:** 6 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 17 OCT 2008	**Trial No. / U No.:** 1246.3 / U08-2049-01	**Date of trial:** 06 FEB 2008 – 31 MAR 2008	**Date of revision** (if applicable)**:**

Conclusions:

The study confirmed previous in vitro findings that depending on the given dose BI 44370 BS must be regarded as a moderate to strong inhibitor of CYP3A4. Based on the generally accepted classification, BI 44370 BS at a dose of 500 mg must be considered as a strong CYP3A4 inhibitor while at a single oral dose of 100 mg BI 44370 BS, could be classified as moderate CYP3A4 inhibitor. For the presumed therapeutic dose of 200 mg a >500 % increase in midazolam oral bioavailability is to be expected, which would in turn refer to BI 44370 BS being a strong CYP3A4 inhibitor.
The observed gender difference in exposure seems to be due to a higher oral bioavailability / higher absorption of BI 44370 BS in female subjects.

Due to the low number of AE episodes, the absence of a placebo group and the open label design, the conclusions that can be drawn are limited.
In general, all treatments investigated were safe and tolerated well, independent of the doses applied. From the AEs observed in this trial, there is no concern for further clinical investigations of BI 44370 BS in the doses tested in males and females, given that all related events were of mild intensity and resolved completely without therapy. In future clinical trials, the kind of AEs that were assessed as possibly related to BI 44370 BS in this trial (headache and papular rash) may need special attention.