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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** Not applicable	
Name of active ingredient: BI 201335 NA		**Page:** 1 of 5	**Synopsis No.:** Not applicable
Module: Not applicable		**Volume:** Not applicable	
Report date: 21 DEC 2010	**Trial No. / U No.:** 1220.33 / U10-4071-01	**Date of trial:** 24 JUN 2009 – 30 JUL 2009	**Date of revision:** Not applicable

Title of trial:	Metabolism and pharmacokinetics of a single dose of 240 mg [^{14}C]-BI 201335 given as oral solution to healthy male volunteers at steady state of BI 201335 NA maintained with oral capsules of 240 mg BI 201335, a phase I, single-arm, open-label trial
Principal/Coordinating Investigator:	[redacted]
Trial sites:	[redacted] USA
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	To determine the pharmacokinetics (PK) of BI 201335 and total radioactivity including excretion mass balance, excretion pathways and metabolism following the oral administration of [^{14}C]-BI 201335 at steady state.
Methodology:	Open-label, multiple-dosing design in healthy male volunteers
No. of subjects:	
planned:	entered: 8
actual:	entered: 8
	Treatment: [^{14}C]-BI 201335 entered: 8 treated: 8 analysed (for primary endpoint): 7
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 55 years inclusive, body mass index (BMI) 18.5 to 29.9 kg/m^2 inclusive, non-smokers
Test product:	[^{14}C]-BI 201335 NA as oral solution
dose:	240 mg BI 201335 labelled with 100 µCi [^{14}C]
mode of admin.:	Oral
batch no.:	BL-101607-005-1

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** Not applicable	
Name of active ingredient: BI 201335 NA		**Page:** 2 of 5	**Synopsis No.:** Not applicable
Module: Not applicable		**Volume:** Not applicable	
Report date: 21 DEC 2010	**Trial No. / U No.:** 1220.33 / U10-4071-01	**Date of trial:** 24 JUN 2009 – 30 JUL 2009	**Date of revision:** Not applicable

Reference therapy:	BI 201335 NA soft gelatin capsule
dose:	240 mg q.d. + loading dose on Day 1
mode of admin.:	Oral
batch no.:	B093000487
Duration of treatment:	15 days – multiple oral administration of BI 201335 NA, intermitted by a single dose of 240 mg [^{14}C]-BI 201335 NA on Day 9.
Criteria for evaluation:	
Pharmacokinetics:	• Individual concentration-time profiles of [^{14}C] radioactivity in whole blood, plasma, saliva, urine, and faeces • Individual concentration-time profiles of BI 201335 in plasma, and amount excreted-time in urine. • Rate and extent of excretion mass balance based on the [^{14}C] radioactivity in urine and faeces • Elucidation of metabolite structures and identification of major metabolites in urine, faeces, and plasma (if feasible) in comparison with various animal species (to be reported separately by the sponsor) • C_{blood} cell/C_{plasma} ratio of [^{14}C]-radioactivity. • Plasma protein binding of [^{14}C]-radioactivity in human plasma samples *ex vivo* • Estimation of PK parameters from: o the plasma concentration and urinary excretion of BI 201335 o the [^{14}C]-radioactivity concentrations in whole blood, plasma, saliva, urine and faeces
Safety:	Tolerability, adverse events (AEs), physical examination, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG), and laboratory tests
Statistical methods:	Descriptive statistics and graphical summaries

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** Not applicable	
Name of active ingredient: BI 201335 NA		**Page:** 3 of 5	**Synopsis No.:** Not applicable
Module: Not applicable		**Volume:** Not applicable	
Report date: 21 DEC 2010	**Trial No. / U No.:** 1220.33 / U10-4071-01	**Date of trial:** 24 JUN 2009 – 30 JUL 2009	**Date of revision:** Not applicable

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Steady state was maintained starting from Day 2 until Day 16 though daily dosing of BI 201335 NA as shown from the daily mean trough plasma concentrations of BI 201335 ZW. Following a single dose oral administration of [^{14}C]-BI 201335 on Day 9, the total radioactivity exposure in blood was much lower compared to plasma. Single dose mean [^{14}C]-radioactivity $AUC_{0-\infty}$ was 92,100 ng Eq·h/mL, which is slightly higher (5%) than the steady state cold drug $AUC_{\tau,ss}$ (87,700 ng·h/mL), whereas the $t_{1/2}$ of the radioactivity was approximately 20% lower. BI 201335 ZW (cold drug) exhibited a mean steady state $C_{max,ss}$ of 7,960 ng/mL at mean $t_{max,ss}$ of 2.58 h. The mean terminal elimination $t_{1/2}$ was 30.4 h. A vast majority (98.7%) of the radioactive [^{14}C]-BI 201335 dose was excreted in faeces, and negligibly (0.113%) excreted in urine.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** Not applicable	
Name of active ingredient: BI 201335 NA		**Page:** 4 of 5	**Synopsis No.:** Not applicable
Module: Not applicable		**Volume:** Not applicable	
Report date: 21 DEC 2010	**Trial No. / U No.:** 1220.33 / U10-4071-01	**Date of trial:** 24 JUN 2009 – 30 JUL 2009	**Date of revision:** Not applicable

Safety results:

Of the eight subjects who entered the study, one (12.5%) subject reported an AE at Screening, six (75.0%) subjects reported AEs following administration of BI 201335 NA, and no subject reported an AE post-study. Three (37.5%) subjects reported AEs post-treatment. There were no subjects with severe or significant AEs, and no deaths or SAEs occurred during this study.

Six (75.0%) subjects had drug-related AEs, including increased appetite, dizziness, headache, vision blurred, abdominal discomfort, abdominal pain, abdominal pain upper, constipation, diarrhoea, dyspepsia, nausea, vomiting, muscle spasms, and chills. Two (25.0%) subjects had other significant AEs that were considered drug related and discontinued the study (moderate vomiting) and/or trial medication (mild constipation, mild nausea, and moderate abdominal pain). One subject reported an AE of mild application site pruritus at the ECG patch site during Screening. Three subjects reported drug-related AEs post-treatment (abdominal discomfort, abdominal pain, chills, constipation, nausea, and vomiting). The most commonly reported AEs were nausea, diarrhoea, and constipation, all of which were considered related to study drug and consistent with AEs reported in previous studies.

There were clinically significant changes noted for high, out-of-range potassium (two subjects) and bilirubin, total (two subjects) values post baseline. No clinically significant changes or findings were noted for vital sign measurements, weight measurement, or 12-lead ECGs for this study. The tolerability to study drug was assessed as follows: two subjects were good, five subjects were satisfactory, and one subject was not satisfactory.

Overall, the changes in the clinical safety assessments were unremarkable.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** Not applicable	
Name of active ingredient: BI 201335 NA		**Page:** 5 of 5	**Synopsis No.:** Not applicable
Module: Not applicable		**Volume:** Not applicable	
Report date: 21 DEC 2010	**Trial No. / U No.:** 1220.33 / U10-4071-01	**Date of trial:** 24 JUN 2009 – 30 JUL 2009	**Date of revision:** Not applicable

Conclusions:

A vast majority of the radioactive [^{14}C]-BI 201335 dose was excreted in faeces, and negligibly excreted in urine. Single dose mean [^{14}C]-radioactivity $AUC_{0-\infty}$ was slightly higher (5%) than the steady state cold drug $AUC_{\tau,ss.}$ Total radioactivity exposure in blood was much lower compared to plasma.

Except for one subject discontinuing from the study on Day 1 due to an AE of moderate, drug-related vomiting, and one subject discontinuing from trial medication following dosing on Day 11 due to the drug-related AEs of mild constipation, mild nausea, and moderate abdominal pain (three days post-treatment), the changes in the clinical safety assessments were unremarkable. Overall, administration over 15 days of multiple oral doses of BI 201335 NA, intermitted by a single dose of 240 mg [^{14}C]-BI 201335 NA on Day 9, appeared to be well tolerated. Results of the study do not have any implication on the safety profile of BI 201335.