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.

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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2006-000613-38	
Name of active ingredient: BI 2536		**Page:** **1 of 6**	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 SEP 2011	**Trial No. / U No.:** 1216.20 / U11-2247-01	**Dates of trial:** 05 OCT 06 – 27 OCT 09	**Date of revision :** Not applicable

Title of trial:	An open, randomised clinical Phase I/IIa trial to investigate the maximum tolerated dose, efficacy, safety and pharmacokinetics of repeated three-week courses of a single dose i.v. BI 2536 on Day 1 in comparison to single doses i.v. BI 2536 on Days 1, 2 and 3 in patients over 60 years of age with refractory or relapsed acute myeloid leukaemia
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial (7 centres in Germany and 2 centres in Austria).
Publication (reference):	Mueller-Tidow C, Bug G, Schlenk R, et al. 50th Ann Mtg of the American Society of Hematology (ASH), San Francisco, 6 - 9 Dec 2008 (Poster) (P09-00486) Mueller-Tidow C, Bug G, Schlenk R, et al.50th Ann Mtg of the American Society of Hematology (ASH), San Francisco, 6 - 9 Dec 2008. Blood 112 (11), 1021, Abstr 2973 (2008) (P09-00077) Lee KH, Mueller-Tidow C, Schlenk R, et al. 50th Ann Mtg of the American Society of Hematology (ASH), San Francisco, 6 - 9 Dec 2008 (Poster) (P09-00485) Lee KH, Schlenk RF, Bug G, et al. 50th Ann Mtg of the American Society of Hematology (ASH), San Francisco, 6 - 9 Dec 2008. Blood 112 (11), 913 - 914, Abstr 2641 (2008) (P09-00073)
Clinical phase:	I/IIa
Objectives:	To investigate the maximum tolerated dose, efficacy, safety and pharmacokinetics of different dosing schedules of BI 2536 in acute myeloid leukaemia patients.
Methodology:	Open, randomised, parallel group comparison of 3 dosing schedules of BI 2536.

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No. of subjects:	
planned:	Entered: 60 patients
actual:	Total: entered: 68 patients; treated: 68, analysed (for primary endpoint): 68 Treatment group A (infusion on Day 1): entered: 32, treated: 32, analysed (for primary endpoint): 32 Treatment group B (infusion on Days 1, 2, and 3) (Note: only valid for patients entered before implementation of protocol amendment 3): entered: 14, treated: 14, analysed (for primary endpoint): 14 Treatment group C (infusions on Days 1 and 8) (Note: only valid for patients entered after implementation of protocol amendment 3): entered: 22, treated: 22, analysed (for primary endpoint): 22
Diagnosis and main criteria for inclusion:	Patients over 60 years of age with relapsed or refractory acute myeloid leukaemia (AML).
Test product:	BI 2536, solution for injection
dose:	Treatment group A (d1): infusion on Day 1 (dose levels 200, 250, 300, 350 and 400 mg) Treatment group B (d1-d3): infusion on Days 1, 2, and 3 (dose levels 50 and 60 mg/day) (Note: only valid for patients entered before implementation of protocol amendment 3) Treatment group C (d1+d8): infusion on Days 1 and 8 (dose levels 100, 150, 200 and 225 mg/day) (Note: only valid for patients entered after implementation of protocol amendment 3)
mode of admin.:	Intravenous infusion over 60 minutes
batch no.:	6DB01, 6DB03 and 916515.
Reference therapy:	Not applicable
Duration of treatment:	Protocol recommendation was for a minimum of one, 21-day course, with courses then being continued until disease progression (note: patients could withdraw from the study at any time due to toxicity).

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Criteria for evaluation:

Safety:	Maximum tolerated dose (MTD), incidence of dose limiting toxicity (DLT), incidence and intensity of adverse events (AEs) graded according to common terminology criteria for adverse events (CTCAE), laboratory assessments, physical examination, electrocardiogram (ECG) and vital signs.
Efficacy / clinical pharmacology:	Objective response, event-free survival, overall survival, remission duration, best overall response, BI 2536 pharmacokinetics (PK) using non-compartmental analysis, pharmacodynamic (PD) monitoring by analysis of effects of BI 2536 on the leukaemia cells, peripheral blood and bone marrow aspirate samples.
Statistical methods:	Exploratory data analyses using confidence intervals for proportions and Kaplan Meier estimations.

SUMMARY – CONCLUSIONS:

Study Population:

The trial was performed in 7 centres in Germany and 2 centres in Austria. A total of 78 patients were enrolled, of which 71 (91.0%) were randomised and 68 (95.8%) were treated with BI 2536. 51 patients discontinued due to disease progression, 7 due to AEs, 4 due to patient refusal to continue treatment, and 8 due to other reasons. All patients were White with a median age overall of 68.5 years. 13 patients (19.1%) had an ECOG score of 0 at baseline, 36 patients (52.9%) had an ECOG score of 1, 17 patients (25.0%) had an ECOG score of 2, and 2 patients (2.9%) had an ECOG score of 3.

The mean number of courses completed for all patients combined was 2.2 (±3.1), however, 1 patient each completed 7, 8 and 9 course, and 1 patient completed 22 courses of treatment.

Safety results:

In the d1 schedule group, 3 out of 5 patients (60.0%) in the 400 mg dose group experienced a DLT during treatment course 1, so the 400 mg dose was classed as above the MTD and the MTD was defined as 350 mg. At the MTD of 350 mg, 1 out of 6 patients (16.7%) experienced a DLT. In the d1+d8 schedule, 2 out of 3 patients (66.7%) at the 225 mg dose level experienced a DLT, so the 225 mg dose was classed as above the MTD and MTD was defined as 200 mg. At the MTD of 200 mg, 1 out of 6 patients (16.7%) experienced a DLT. No determination of the MTD was made in the d1-d3 dose group since this treatment regimen was prematurely discontinued due to the high numbers of patients experiencing disease progression within the first treatment cycle. The

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Safety results (continued):

highest dose tested in the d1-d3 schedule before discontinuation was 60 mg/day.

All but 1 patient had at least one AE during all treatment courses of the study. The most common AEs reported overall during the study were febrile neutropenia and leukopenia (reported in 30.9% and 26.5% of patients, respectively). In the d1 schedule, the most common AEs that were reported at the MTD dose of 350 mg were fatigue (7 patients, 38.9%), sepsis, anaemia, petachiae and peripheral oedema (all reported in 6 patients, 33.3%). In the d1+d8 schedule, the most common AEs that were reported at the MTD of 200 mg dose were leukopenia (6 patients, 46.2%), febrile neutropenia, pyrexia and thrombocytopenia (all reported in 4 patients, 30.8%). In schedule d1, 9 patients (28.1%) had an AE with CTC Grade 5, 9 patients (28.1%) had an AE with CTC Grade 4 and 5 patients (15.6%) had an AE with CTC Grade 3. In schedule d1-d3, 5 patients (35.7%) had an AE with CTC Grade 5, 5 patients (35.7%) had an AE with CTC Grade 4 and 3 patients (21.4%) had an AE with CTC Grade 3. In schedule d1+d8, 2 patients (9.1%) had an AE with a CTC Grade of 5, 12 patients (54.5%) had an AE with CTC Grade 4 and 5 patients (22.7%) had an AE with CTC Grade 3. The remainder of the patients in each dose schedule had AEs with CTC Grade 2 or lower. Overall 6 patients discontinued due to AEs: 2 in the d1 schedule (due to haematuria and lymphadenitis), 1 in the d1-d3 schedule (due to disorientation), and 3 in the d1+d8 schedule (due to leukopenia, hypokalaemia/diarrhoea/muscosal inflammation, and facial bone fracture).

Approximately two thirds of the patients (67.6%) had AEs that were considered drug-related by the investigators, with leukopenia, alopecia, thrombocytopenia, anaemia and neutropenia being reported as drug-related by the investigators in >10% of patients in the total group. Over half the patients (61.8%) had SAEs, with most AEs being considered serious because they resulted in hospitalisation of the patient (51.5%). However, only 3 SAEs were reported in >10% of patients overall, with these events being febrile neutropenia (reported in 29.4% of patients), and sepsis and general physical health deterioration (both reported in 11.8% of patients). Out of the 42 patients with SAEs, 12 (28.6%) had SAEs that were considered treatment-related. A total of 16 patients had SAEs that led to death.

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Efficacy / clinical pharmacology results:

In the d1 schedule, 3 patients (9.4%) achieved an objective response after receiving the MTD dose of 350 mg (1 patient achieved CR at cycle 3 and 2 patients achieved PR – 1 at cycle 1 and 1 at cycle 11). In the d1+d8 schedule, 2 patients (9.1%) achieved an objective response: 1 patient achieved CR at cycle 3 after being dosed with the MTD dose of 200 mg BI 2536, and 1 patient achieved PR at cycle 1 after being dosed with 225 mg BI 2536.

The pharmacokinetic behaviour of BI 2536 can be described as multi-compartmental, with a fast distribution after the end of infusion followed by slower elimination phases. BI 2536 administered intravenously as a 1-hour infusion at doses of 50, 60, 100, 150, 200, 225, 250, 300, 350, and 400 mg in course 1 showed no obvious deviation from dose proportionality (based on $C_{max,norm}$, $AUC_{0\text{-}inf,norm}$ and $AUC_{0\text{-}24,norm}$ values). For the d1 and d1+8 schedules, the volume of distribution was high, with the geometric mean V_{ss} being higher than 1540 L. Terminal elimination half-lives of up to 42 hours were observed. Overall total plasma clearance of BI 2536 was high (geometric means 1080-1530 mL/min). Slightly higher exposure of BI 2536 was observed in female patients than in male patients. However, due to the low number of individuals in each group a definite conclusion cannot be made. There was no obvious influence of age, weight or body surface area on the exposure of BI 2536 (based on $C_{max,norm}$, $AUC_{0\text{-}inf,norm}$ and $AUC_{0\text{-}24,norm}$ values). There were no obvious differences in exposure or PK parameters of BI 2536 between the 3 different treatment schedules.

Conclusions:

The MTDs were determined for the d1 and d1+8 schedules at BI 2536 doses of 350 mg and 200 mg, respectively. No unexpected safety concerns were raised by this study.

Preliminary evidence of efficacy was seen in this study, with 5 out of 68 patients (7.4%) reporting an objective response. In the d1 schedule, 3 patients (9.4%) achieved an objective response after receiving the MTD dose of 350 mg (1 patient achieved CR and 2 patients achieved PR) and in the d1+d8 schedule, 2 patients (9.1%) achieved an objective response: 1 patient achieved CR after being dosed with the MTD dose of 200 mg, and 1 patient achieved PR after being dosed with 225 mg BI 2536. These results indicate some anti-leukaemic effect of BI 2536 at the doses determined to be the MTD.

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Conclusions (continued):	Comparing the 3 different treatment schedules, no difference in pharmacokinetic parameters of BI 2536 was seen. BI 2536 showed a multi-compartmental behaviour with a fast disposition phase after the end of infusion and a high volume of distribution, indicating a high distribution into deep compartments. BI 2536 is a high clearance drug and exhibits a half-life of up to 42 hours.