Boehringer Ingelheim

# 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:** | | **EudraCT No.:** 2005-005255-18 | |
| **Name of active ingredient:** BI 2536 | | **Page:** 1 of 5 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:** 21 APR 2009 | **Trial No. / U No.:** 1216.19 / U09-1357-01 | **Dates of trial:** 09 JAN 2007 – 14 FEB 2008 | **Date of revision:** Not applicable |



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| **Title of trial:** | A single arm phase II study to investigate the efficacy, safety and pharmacokinetics of a single dose of 200 mg of i.v. BI 2536, administered once every 3 weeks in patients with advanced metastatic hormone-refractory prostate cancer |
| **Coordinating Investigator:** | [redacted] |
| **Trial sites:** | Multicentre study, conducted at 6 sites in the UK |
| **Publication (reference):** | Pandha HS, Protheroe A, Wylie J, et al. JCO 2008; 26(Suppl): abstract 14547 [P08-08017]; |
| **Clinical phase:** | II |
| **Objectives:** | The primary objective of the trial was to evaluate the response rate for BI 2536 in terms of prostate specific antigen (PSA) and Response Evaluation Criteria In Solid Tumours (RECIST) responses in patients with advanced metastatic hormone-refractory prostate cancer (HRPC) as determined by radiographic, bone and PSA criteria. |
| **Methodology:** | Uncontrolled, open label, single arm, two-stage design trial. |
| **No. of patients:** | |
| **planned:** | entered: stage 1: 15 evaluable patients; stage 2: 35 additional evaluable patients |
| **actual:** | enrolled: 35<br>entered: 20 patients treated: 20 analysed (for primary endpoint): 20 |
| **Diagnosis and main criteria for inclusion:** | Patients with documented metastatic adenocarcinoma of the prostate that was clinically refractory or resistant to hormone therapy, following progression on at least one hormonal therapy. |
| **Test product:** | BI 2536 |
| **dose:** | Starting dose of 200 mg administered once every 3 weeks, with the option for dose escalation to 250 mg or a 50 mg dose reduction. |
| **mode of admin.:** | Intravenous (i.v.) |
| **batch nos.:** | 6DB02, B071000232 and B071002627 |

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| **Reference therapy:** | Not applicable |
| **dose:** | - |
| **mode of admin.:** | - |
| **batch no.:** | - |
| **Duration of treatment:** | BI 2536 was administered on Day 1 of each 3-week treatment cycle over a maximum of 8 cycles (24 weeks). |
| **Criteria for evaluation:** | |
| **Efficacy / clinical pharmacology:** | The primary endpoint was evaluation of the PSA response rate, according to Prostate Specific Antigen Working Group (PSAWG) criteria, after 12 weeks (4 cycles) treatment with BI 2536, for all patients. Secondary endpoints considered: duration of PSA response, time to PSA progression, overall objective response using RECIST criteria in patients with measurable disease, time to death, time to overall progression, progression free survival, overall survival and duration of overall response.<br>Standard pharmacokinetic parameters for BI 2536 in plasma were determined. |
| **Safety:** | Safety was assessed in terms of the incidence and intensity of adverse events (AEs), changes in laboratory safety and vital signs parameters, physical examination findings and the occurrence of dose limiting toxicity. |
| **Statistical methods:** | Descriptive statistics and Kaplan-Meier analyses. |
| **SUMMARY – CONCLUSIONS:** | |
| **Efficacy / clinical pharmacology results:** | Overall, 20 patients were treated with i.v. BI 2536. The analysis population comprised 20 patients, with no patients being excluded due to protocol violations. All randomised patients were treated with BI 2536 and were included in both the safety and efficacy analyses. Fifteen patients (75%) withdrew from the study as a result of disease progression, 4 patients (20%) withdrew due to AEs and 1 patient (5%) was withdrawn for other reasons.<br>Most patients (95%) enrolled into the trial were Caucasian, 1 patient (5%) was black. The median age was 70.5 (range: 56-76 years). All patients had a baseline ECOG of 0 (60%) or 1 (40%). Nineteen patients (95%) had metastatic disease; all of these (100%) had distant metastases, 63% had lymphatic and |

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| | 37% local metastases. Eighteen patients (90%) had bone metastases at baseline.<br><br>The primary endpoint comprised PSA response rate, with response defined as a ≥50% decrease in PSA level from baseline. Though some patients achieved a reduction in PSA level during BI 2536 treatment, none experienced a ≥50% reduction. As a result, no patients were classified as achieving a PSA response and recruitment into the trial was stopped after stage 1.<br><br>No patients (0 of 12 with measurable disease) experienced an objective RECIST response. The best tumour response was stable disease, which was experienced by 10 patients (50%). Kaplan-Meier analysis estimated the median: time to PSA progression as 44.5 days ($25^{th}$ percentile 42.5 days, $75^{th}$ percentile 107.0 days); time to RECIST progression as 121.0 days ($25^{th}$ percentile 78.0 days, $75^{th}$ percentile 147.0 days); and progression-free survival as 43.5 days ($25^{th}$ percentile 36.0 days, $75^{th}$ percentile 70.5 days).<br><br>Four patients (20%) experienced some improvement in ECOG score during the trial. Four patients (20%) had new bone lesions reported during the study, though none experienced skeletal-related events. |
| **Pharmacokinetic results:** | BI 2536 showed multi-compartmental pharmacokinetic behaviour. In most patients the plasma concentration increased until the end of infusion (1 hour). After the end of infusion the plasma concentrations decreased rapidly, indicating a rapid distribution phase. Plasma BI 2536 concentrations during Course 1 decreased over the 3 hours after the end of infusion to, on average, less than 15% of the concentration seen at the end of infusion. At 168 hours plasma BI 2536 was still detectable but at less than 0.5% of the level at the end of infusion. The inter-patient variability in plasma concentrations was low (gCV: 24.8-37.1%). |
| **Safety results:** | All 20 patients who received at least one dose of BI 2536 were included in the safety analysis.<br><br>The most frequently reported AEs during treatment were general disorders and administration site conditions, blood and lymphatic disorders, gastrointestinal disorders and nervous system disorders. The most common AEs were: neutropenia (55% of patients), fatigue (50%), nausea (40%), constipation (35%), diarrhoea (25%), leukopenia (20%), headache (20%), lethargy (20%), back pain (20%), pain in the extremities (20%) and anorexia (20%). AEs of |

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maximal severity of grade 3 were reported for 10 patients (50%) and of grade 4 severity were reported for 7 patients (35%). No grade 5 AEs were reported during the trial. The most common CTCAE grade 3 events seen during treatment comprised neutropenia (25% of patients). Grade 4 AEs comprised neutropenia (30% of patients) and leukopenia, thrombocytopenia and petechiae (all 5%).

Pooling of AEs considered indicative of haematological toxicity or infectious complications was also performed, to ensure that such events were not underestimated due to consideration under different system organ classes. This analysis identified neutropenia and associated events as occurring in 70% of patients (65% experienced drug-related events); infection was seen in 35% of patients (20% drug-related); anaemia and associated events were seen in 20% of patients (15% drug-related); thrombocytopenia and associated events were seen in 15% of patients (15% drug-related); individual patients experienced events of bleeding, local tissue damage at the injection site and mucosal damage.

A causal relationship with study drug administration was frequently reported for: neutropenia (55% of patients), fatigue (50%), nausea (30%), leukopenia (20%), lethargy (20%), thrombocytopenia (15%), constipation (15%), diarrhoea (15%) and alopecia (15%). Dose limiting toxicity was observed in 8 patients (40%) and consisted of neutropenia (30% of patients), febrile neutropenia (5%), pruritis (5%) and pyrexia (5%) of grade 3 or 4.

Six patients (30%) experienced AEs that led to discontinuation of BI 2536 treatment and 1 patient (5%) experienced a post-study AE that would have necessitated treatment discontinuation. Drug-related AEs necessitating BI 2536 discontinuation comprised myocardial ischaemia, angina pectoris, thrombocytopenia/low platelet levels with petechiae and skin rash.

No deaths occurred during this trial. Overall, 35% of patients experienced serious adverse events (SAEs) during treatment comprising neutropenic sepsis, febrile neutropenia, urinary tract infection, thrombocytopenia, pyrexia, cervical cord compression, muscular weakness, petechiae, malignant neoplasm progression and myocardial ischaemia (all 1 patient, 5%). One patient experienced post-study SAEs of hydronephrosis and increased blood creatinine levels. Haematological- and infection-associated SAEs, myocardial ischaemia and petechiae were considered study-drug related. Significant non-serious AEs

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| | consisted of drug-related events of neutropenia and pruritis. Other events considered significant consisted of angina pectoris, reduced platelet count and rash.<br><br>Clinical laboratory evaluations showed changes in haematological parameters that were consistent with the toxicities identified during AE assessment.<br><br>Overall i.v. BI 2536 showed an acceptable safety profile at doses of up to 250 mg when administered to patients with hormone-refractory prostate cancer. The AE profile of BI 2536 was predominantly characterised by haematological toxicity, in particular neutropenia. |
| **Conclusions:** | BI 2536 did not show efficacy in treating patients with advanced metastatic HRPC, when assessed in terms of PSA or RECIST tumour response rates. The median time to PSA progression was 44.5 days, the median time to RECIST progression was 121.0 days and the median progression-free survival time/time to overall progression was 43.5 days. BI 2536 pharmacokinetic parameters were consistent with those seen in phase I dose-escalation trials. The safety profile of BI 2536 was consistent with that seen in other phase I monotherapy studies, with toxicity primarily being associated with haematological events. |