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..

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.:** 2006-004529-27	
Name of active ingredient: BI 2536		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 JAN 2010	**Trial No. / U No.:** 1216.18 / U10-1098-01	**Dates of trial:** 20 JUL 2007 – 09 FEB 2009	**Date of revision :** Not applicable

Title of trial:	Multicenter parallel phase II trial of BI 2536 administered as a 1 hour i.v. infusion every 3 weeks in defined cohorts of patients with various solid tumours. A new drug screening program of the EORTC network of core institutions (NOCI)
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, 14 sites in 4 countries
Publications (reference):	Schoeffski P, Blay J, de Greve J, et al. ECCO 15 and 34th ESMO Multidisciplinary Congress, Berlin, 20-24 September 2009. Abstract M09-0053. Schoeffski P, Blay J, de Greve J, et al. ECCO 15 and 34th ESMO Multidisciplinary Congress, Berlin, 20-24 September 2009. Abstract M09-0172.
Clinical phase:	II
Objectives:	To investigate whether BI 2536 demonstrates antitumour activity in the selected tumour types, and to further document its safety profile in the treated patient population.
Methodology:	This was a non-randomised, open-label single arm, 2-stage design trial in patients with various tumour types (head and neck carcinoma, breast cancer, ovarian cancer, soft tissue sarcoma, melanoma).
No. of patients:	
planned:	12 per tumour type during stage 1; in case of 1 or more confirmed tumour response for a given tumour type an additional 25 patients with the same indication were to be recruited, to a maximum of 37 eligible patients per tumour type.

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actual:	total enrolled: 76 total treated: 71 total analysed (for the primary endpoint): 59 Head and neck cancer patients enrolled: 16 treated: 14 analysed (for the primary endpoint): 10 Breast cancer patients enrolled: 15 treated: 14 analysed (for the primary endpoint): 11 Ovarian cancer patients enrolled: 15 treated: 15 analysed (for the primary endpoint): 13 Soft tissue sarcoma patients enrolled: 14 treated: 14 analysed (for the primary endpoint): 13 Melanoma patients enrolled: 16 treated: 14 analysed (for the primary endpoint): 12
Diagnosis and main criteria for inclusion:	Patients aged at least 18 years with an ECOG score of 0 to 2, adequate haematological function, without clinical evidence of brain metastases, and suffering from documented progression of head and neck carcinoma, breast cancer, ovarian cancer, soft tissue sarcoma or melanoma. Patients were to have at least 1 measurable tumour lesion.
Test product:	BI 2536
dose:	Starting dose of 200 mg administered once every 3 weeks, with the option for a single dose escalation to 250 mg.
mode of admin.:	Intravenous
batch nos.:	916515 and 1053427
Reference therapy:	Not applicable
dose:	-
mode of admin.:	-
batch no.:	-
Duration of treatment:	Patients were treated until: disease progression, the occurrence of an unacceptable drug-related AE, the occurrence of intercurrent illness that prevented further drug administration, administration of a prohibited medication, or the patient's refusal to continue in the study.

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Criteria for evaluation:

Efficacy / clinical pharmacology

Activity was assessed by evaluation of tumour responses documented according to the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.0.

BI 2536 plasma concentrations were to be assessed for population pharmacokinetic (PK) analysis at Courses 1 and 3, and optionally at 1 additional course from Course 6 or later to assess the long-term PK characteristics of BI 2536.

Safety:

Safety was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical methods:

Descriptive statistics and Kaplan-Meier analyses.

SUMMARY – CONCLUSIONS:

Of the 76 patients who enrolled in the trial, 71 patients were included in the safety set and 59 patients were included in the efficacy set. The median age of patients participating in the trial was 58 years, with other demographic parameters generally being consistent with the characteristics of the particular tumour-type patient group.

Efficacy / clinical pharmacology results:

The primary endpoint of the trial was to document the confirmed response rate as defined by RECIST. No patients treated with BI 2536 study experienced a complete response or partial response. The best overall response to treatment was stable disease, which was experienced by 18 patients (30.5%) based on the Investigator's assessment and by 25 patients (42.4%) based on the Coordinating Investigator's review of patient data. As no patients in any of the tumour-type cohorts experienced a confirmed response, the study was closed after stage I and no patients were enrolled into stage 2.

Clinical benefit was experienced by 42.4% of patients (95% CI 29.6%, 55.9%). The median progression-free survival was 1.41 (95% CI 1.35, 2.53) months, with 3.45% of patients (95% CI 0.64%, 10.57%) estimated as being progression-free at 0.5 years after the start of treatment. The median overall survival was 9.53 (95% CI 6.18, 11.83) months, with 63.79% of patients (95% CI 50.06%, 74.67%) estimated as surviving at 0.5 years and 34.82% (95% CI 21.86%, 48.10%) as surviving 1 year after the start of treatment.

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Efficacy / clinical pharmacology results (continued):	The plasma concentration profiles from 68 patients were analysed during treatment with 200 mg BI 2536, 10 patients were also assessed after Course 1 during treatment with 150 mg BI 2536, and 7 patients were also assessed after Course 1 during treatment with 250 mg BI 2536. BI 2536 exhibited multicompartmental pharmacokinetic behaviour. Plasma concentrations increased for 0.5 to 1 hour after the start of infusion and decreased rapidly after the end of infusion. By 24 hours after administration, the average plasma concentration was 24 ng/mL, less than 3.8% of the average maximum plasma concentration of 636 ng/mL; by 120 hours the plasma concentration had decreased to about 1.85 ng/mL, less than 0.5% of the maximum plasma concentration. The inter-patient variability of plasma concentrations was moderate (gCV: 54.0-75.3%). Low BI 2536 plasma concentrations were detected in some patients before dose administration, indicating that BI 2536 did not accumulate significantly during repeated infusion every 3 weeks.
Safety results:	A total of 71 patients entered the trial and received at least 1 dose of study medication. The median actual dose intensity was 66.7 mg/week and was consistent with the planned dose intensity. Overall 22.5% of patients underwent the planned dose escalation at treatment Course 2; 31.0% of patients required dose reduction. AEs occurring during the trial were collected and assessed according to EORTC analysis rules. The EORTC partially precategorise events that might be likely to be associated with the study treatment; those events that do not coincide with a prespecified AE category are grouped as 'other' event types. All patients (100.0%) experienced at least 1 AE during the course of the study. The most frequently observed AEs were pain (88.7% of patients), fatigue (70.4%), anorexia (32.4%), and hair loss/alopecia (31.0%). The most common grade ≥3 AE was febrile neutropenia (19.7% of patients). Grade 4 AEs seen during the trial comprised febrile neutropenia (4.2%), dyspnoea (1.4%), and other toxicity (1.4%). Five patients (7.0%) experienced grade 5 events described as other toxicity.

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Safety results (continued):

A total of 51 patients (71.3%) experienced at least 1 drug-related AE. The most frequently reported drug-related AEs were fatigue (39.4% of patients), hair loss/alopecia (26.8%), and febrile neutropenia (19.7%). Grade ≥3 drug-related AEs comprised: febrile neutropenia (19.7% of patients), other toxicity (8.5%), fatigue (2.8%), and other haemorrhage/bleeding (1.4%). Grade 4 drug-related AEs comprised: febrile neutropenia (4.2%) and other toxicity (1.4%). One patient (1.4%) experienced drug-related other toxicity at grade 5.

Three patients (4.2%) experienced AEs that led to discontinuation of the study treatment of gastrointestinal fistula and distension, and other shock. Forty-one patients died during or after the study; 39 patients (95.1% of those who died) died due to progressive disease, 1 patient (2.4%) died due to an AE of drug-related shock, and for 1 patient (2.4%) death was classified as being for other reasons (thought to be due to bleeding from brain metastases). Thirty patients (42.3%) experienced 41 SAEs, with the most frequent being febrile neutropenia/neutropenic fever (9.9% of patients).

A total of 70 patients (98.6%) experienced at least 1 laboratory abnormality during the study. The most frequently observed grade ≥3 laboratory parameters seen during treatment were: neutrophil count (81.7% of patients), WBC count (67.6%), platelet count (19.7%), and haemoglobin level (15.5%). One patient experienced a clinically-relevant ECG abnormality during the study

Overall, intravenously administered BI 2536 showed an acceptable safety profile when administered at a starting dose of 200 mg to patients with various solid tumours. The AE profile of BI 2536 was predominantly characterised by haematological toxicity.

Conclusions:

BI 2536 did not show efficacy in treating patients with various advanced solid tumours in this trial, when assessed in terms of RECIST tumour response. However the proportion of patients experiencing disease stabilisation would indicate that further exploration of the use of Polo-like kinase 1 inhibitors is warranted, and should focus on optimising the dose and treatment schedule and on translational research parameters indicative of tumour target modulation. BI 2536 exhibited multicompartmental pharmacokinetic behaviour. The safety profile of BI 2536 was consistent with that seen in other studies, with treatment being associated with fatigue, alopecia, nausea, and haematological events.