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.

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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.:** 2005-005253-22	
Name of active ingredient: BI 2536		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 NOV 2009	**Trial No. / U No.:** 1216.10 / U09-1690-01	**Dates of trial:** 01 SEP 2006 – 14 OCT 2008	**Date of revision:** Not applicable

Title of trial:	An open, randomised, clinical phase II trial in patients with unresectable advanced pancreatic cancer investigating the efficacy, safety, and pharmacokinetics of BI 2536 administered in repeated 3-week cycles as a single IV dose of 200 mg on Day 1 or as 60 mg doses on Days 1, 2, and 3
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study with 9 centres in Germany and 1 in Austria
Publication (reference):	Mross K, Dittrich C, Aulitzky W, et al. 33rd Ann Cong of the European Society for Medical Oncology (ESMO), Stockholm, 12 - 16 Sep 2008. Ann Oncol 2008;19(Suppl 8):VIII163 (P09-05916)
Clinical phase:	II
Objectives:	The primary aim of the trial was to evaluate the efficacy, safety and pharmacokinetics of BI 2536 in the treatment of unresectable advanced pancreatic cancer as first line or second line therapy. A secondary aim was to identify the most suitable dosage regimen for the further phase II and III clinical programme of BI 2536.
Methodology:	Open-label, randomised, 2-stage, parallel group comparison of 2 dosing schedules of BI 2536 (first line patients); the second stage open-label, single arm treatment in second line patients was dependent on the outcome in first line patients (regimen was to be selected after an interim analysis of the respective tumour control rates and response rates in both treatment arms in first line patients). Note: no second line patients were recruited.

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No. of subjects:	
planned:	entered: up to 105 (70 first line patients; 35 second line patients)
actual:	enrolled: 90 first line patients 200 mg BI 2536 IV on Day 1: entered: 45; treated: 43; analysed (for primary endpoint): 43 60 mg BI 2536 IV on Days 1, 2, and 3: entered: 44; treated: 43; analysed (for primary endpoint): 43 No second line patients were enrolled.
Diagnosis and main criteria for inclusion:	Patients aged ≥18 years with advanced, unresectable pancreatic cancer: chemonaïve (first line treatment arms); after failure of gemcitabine-based first line chemotherapy (second line treatment arm)
Test product:	BI 2536
dose:	200 mg once daily on Day 1 of each 3-week cycle 60 mg once daily on Days 1, 2, and 3 of each 3-week cycle
mode of admin.:	IV infusion
batch no.:	6DB01, 6DB04, 899710
Reference therapy:	Not applicable to this study
dose:	
mode of admin.:	
batch no.:	
Duration of treatment:	At least 2 treatment cycles, and while a patient had at least stable disease and acceptable tolerability

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Criteria for evaluation:

Efficacy / clinical pharmacology: Efficacy endpoints were objective tumour response according to the Response Evaluation Criteria in Solid Tumours (RECIST), tumour control, progression-free survival (PFS), overall survival, and CA19-9 response. The primary endpoint was best objective tumour response evaluated according to the RECIST criteria (by independent review of tumour images).

BI 2536 plasma concentrations were measured.

Safety: Incidence and intensity of adverse events (AEs) graded according to Common Terminology Criteria for Adverse Events (CTCAE, version 3.0), including dose limiting toxicity (DLT) events, laboratory investigations, vital signs, body weight, physical examination, Karnofsky performance score, and electrocardiogram

Statistical methods: Analyses were descriptive and exploratory. No formal statistical inferences were planned. Confidence intervals (CIs), Simon's ranking and selection methods, logistic regression, and Kaplan-Meier estimation were used for efficacy analyses. BI 2536 plasma concentrations were summarised; no pharmacokinetic variables were derived.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: All patients were white, the median age was 64.5 years (range: 35 to 84 years), and 22.1% of the patients were 70 years or older. About two thirds of patients were male (68.6%). A majority of the patients had a Karnofsky performance status of at least 90 (79.1%). Median weight was 75.5 kg.

No patient in either group had a complete response. Three patients had a partial response (PR) as their unconfirmed best overall response according to the independent review (response rate 3.5%), 2 of which were confirmed (response rate 2.3%). Stable disease (SD) was the confirmed best overall response in 24.4% of patients. None of the PRs were reported by the investigator, and the 3 patients with PR by independent review discontinued treatment with BI 2536 after cycle 4 due to clinically progressive disease as per investigator assessment (coinciding with confirmation of PR by independent review).

At the time of the interim analysis (based on investigator assessment), 5 of 18 patients evaluable for the interim analysis (1 day schedule) and 5 of 18 patients evaluable for the interim analysis (3 day schedule) had survived progression-free

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after 3 months of treatment. At the time point that triggered the interim analysis, 41 of 79 recruited patients were considered not evaluable for the interim analysis due to early progression before completion of cycle 2 of treatment. Therefore, even though formally the criteria to proceed to stage II were fulfilled, it was decided not to proceed with recruitment of second line patients (U09-2341-01).

For the whole trial population, regarding the secondary endpoint of tumour control (CR + PR + SD) at 3 months after start of treatment, i.e. after 4 cycles of therapy, as per independent review, tumour control at 3 months was reported for 12.8% of all patients (16.3% of patients on 200 mg Day 1; 9.3% of patients on 60 mg Days 1-3). In 48.8% of patients, tumour control was unknown according to the independent assessment.

For pooled schedules, median PFS was 46 days (95% CI 44, 56). No significant difference was observed between the 2 dosing schedules with an estimated hazard ratio of 1.22 (95% CI 0.78, 1.91) and p=0.38 for the Wald test of the Cox proportional hazard model, with PFS appearing slightly better in the 200 mg treatment arm. None of the following confounding factors influenced PFS between the 2 schedules: age, gender, Karnofsky performance status at screening, clinical stage at screening. For the pooled population, patients with a Karnofsky score of >80 at screening had increased PFS.

Based on data from the independent review of imaging and investigator data on clinical progression, 14 of 43 patients in the 1 day schedule arm and 7 of 43 patients in the 3 day schedule arm remained progression free at 3 months of treatment, corresponding to Kaplan-Meier rates of 31.1% and 15.4%, respectively.

For pooled schedules, median overall survival (OS) was 149 days (95% CI 137, 213). No significant difference was detected between the 2 dosing schedules with a hazard ratio of 1.10 (Day 1 group vs. Days 1-3 group, 95% CI 0.68, 1.78) and p=0.69 for the Wald test of the Cox proportional hazard model. For the pooled population, patients with a Karnofsky score of >80 at screening had an increased OS.

Thirty-four patients in the 200 mg Day 1 group and 33 patients in the 60 mg Days 1-3 group had an elevated CA 19-9 level at baseline and could be included in the analysis of CA 19-9 response. Two evaluable patients in the 200 mg Day 1 group and 2 evaluable patients in the 60 mg Days 1-3 group showed a CA 19-9 response (decrease ≥25% from baseline at 2 consecutive measurements).

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	BI 2536 exhibited multi-compartmental pharmacokinetic behaviour. The plasma concentrations of BI 2536 increased during the infusion period. After the end of infusion, BI 2536 showed a fast disposition phase. The maximum plasma concentrations were observed at 0.5 hours or 1 hour post-dosing in the 200 mg Day 1 (gMean maximum plasma concentration 577 ng/mL) and at 1 hour post-dosing on Day 1 (gMean 129 ng/mL) or 0.5 hours post-dosing on Day 3 (gMean 145 ng/mL) for the 60 mg Days 1-3 treatment group. At 120 hours after the 200 mg dose and 72 hours after the last of three 60 mg doses, BI 2536 plasma concentrations were less than 1.5 % of the maximum plasma concentrations. The inter-patient variability was moderate to high after administration of 200 mg (gCV: 49.3-83.4 %) and 60 mg (gCV: 58.1-165%) of BI 2536. BI 2536 was not detected in pre-dose samples in Cycles 2 to 7, suggesting that no accumulation of BI 2536 occurred following repeated infusions of BI 2536 every 3 weeks.
Safety results:	The most frequently reported AEs by preferred term (PT) were fatigue (48.8%), nausea (38.4%), neutropenia (37.2%), leukopenia (29.1%), constipation and vomiting (each reported by 27.9%), and anorexia (25.6%). Generally, incidences of AEs were similar in both treatment groups, except for fatigue, anorexia, alopecia, and back pain, which were more common in patients treated with 60 mg on Days 1-3 and vomiting, abdominal pain, leukopenia, and hyperhidrosis, which were more common in patients treated with 200 mg on Day 1. Six patients discontinued due to AEs (4 patients on 200 mg on Day 1; 2 patients on 60 mg on Days 1-3); all discontinuations were due to SAEs. The most frequently reported drug-related AEs by PT were neutropenia (37.2%), leukopenia (29.1%), fatigue (29.1%), and nausea (22.1%). Generally, the frequencies of drug-related AEs on the PT level were similar in both treatment groups, but nausea and alopecia were more common for patients on 60 mg on Days 1-3 and neutropenia and leukopenia were more common for patients on 200 mg on Day 1. A total of 46 (53.5%) patients had CTCAE grade 3/4 AEs and 21 (24.4%) had grade 1/2 AEs as their highest grade, while 43 (50.0%) had grade 3/4 drug-related AEs and 23 (26.7%) had grade 1/2 drug-related AEs as their highest grade. The most frequently reported CTCAE grade 4 AEs were blood and lymphatic system disorders (25.6% of patients), including neutropenia (25.6%), leukopenia (5.8%), and thrombocytopenia (4.7%), and most were considered to be drug-related.

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There were 18 fatal AEs during the study; all were unrelated to study medication. The most common cause of death was malignant neoplasm progression (8 patients in the 200 mg Day 1 treatment group; 5 patients in the 60 mg Days 1-3 treatment group). For a further 3 patients with fatal events not coded as malignant neoplasm progression, further information made it apparent that deaths were related to progression of their underlying disease.

There were no fatal drug-related SAEs. Drug-related SAEs were reported for 8 patients on 200 mg on Day 1. The haematological drug-related SAEs were neutropenia (2 patients), leukopenia (2 patients), and thrombocytopenia (1 patient). Non-haematological drug-related SAEs were anal abscess (1 patient), biliary sepsis (1 patient), pneumonia (1 patient), duodenitis (1 patient), nausea (1 patient), vomiting (1 patient), fatigue (1 patient), and pyrexia (1 patient).

Drug-related SAEs were reported for 9 patients on 60 mg on Days 1-3: the haematological drug-related SAEs were febrile neutropenia (3 patients), leukopenia (3 patients), neutropenia (2 patients), and thrombocytopenia (1 patient); non-haematological drug-related SAEs were somnolence (1 patient), constipation (1 patient), diarrhoea (1 patient), fatigue (1 patient), pyrexia (1 patient), vomiting (1 patient), stomatitis (1 patient), and nausea (1 patient).

In total, 26 (30.2%) patients had DLT events; 25.6% of patients on 200 mg on Day 1; 34.9% of patients on 60 mg on Days 1-3. The most common DLT event was neutropenia (16.3% in each treatment group).

Three patients had other significant AEs (ICH E3 definition): 1 patient on 200 mg on Day 1 due to neutropenia and thrombocytopenia; 2 patients on 60 mg on Days 1-3 due to neutropenia and leukopenia (1 patient) and neutropenia and thrombocytopenia (1 patient).

There were no clinically meaningful changes comparing baseline to the last assessment for laboratory safety parameters, vitals signs, or body weight in patients treated with either dosing schedule.

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Conclusions:

In this randomised, open-label, exploratory study, there was no indication that BI 2536 monotherapy exerts any clinically relevant efficacy in the treatment of unresectable advanced pancreatic cancer.

No relevant differences between dosing schedules could be detected.

Sparse blood sampling was done to assess the plasma concentration-time data of BI 2536. The pharmacokinetic behaviour was as expected when compared with data obtained from Phase I dose rising trials with BI 2536.

BI 2536 showed an acceptable safety profile that was consistent with previous findings for BI 2536 and there were no marked differences between the 2 dosing schedules.