Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product:				
Name of active ingredient: BIBF 1120		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 11 March 2008	**Number:** U08-1214-03	**Study period (dates):** 31 AUG 05 - 03 JAN 07		**Date of revision:** 28 March 2013

Title of study:	A double-blind, randomised phase II study to determine the efficacy and safety of oral treatment with BIBF 1120 ES 250 mg twice daily versus 150 mg twice daily in patients suffering from advanced non-small-cell lung cancer
Principal investigator:	[redacted]
Study centres:	Multicentre study, cf. Appendix 16.1.4
Publication (reference):	Reck M, Kaiser R, Eschbach C, Stefanic M, Love J, Gatzemeier U, Stopfer P, Pawel J von. A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. Ann Oncol 2011;22(6):1374-1381 [P11-00203
Clinical Phase:	II
Objectives:	The overall purpose of this phase II trial was to evaluate the efficacy of 250 mg BIBF 1120 twice daily (BID) versus 150 mg BIBF 1120 BID in patients with advanced non-small-cell lung cancer (NSCLC) who had failed at least one prior chemotherapy regimen. In addition, safety data for the two different dosages were collected and analysed.
Methodology:	Randomised, double-blind, double-dummy, parallel arm design
No. of patients:	
planned:	entered: 70
actual:	enrolled: 73 250 mg BID BIBF 1120: entered: 36 treated: 36 analysed (for primary endpoint): 36 150 mg BID BIBF 1120: entered: 37 treated: 37 analysed (for primary endpoint): 37
Diagnosis and main criteria for inclusion:	Patients suffering from advanced NSCLC stage IIIB and IV after failure of prior platinum or non-platinum containing chemotherapy
Test product:	BIBF 1120
dose:	250 mg BID or 150 mg BID
mode of admin.:	Oral

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batch no.:	BIBF 1120 200 mg: 1243780001 BIBF 1120 50 mg: 1251910001 BIBF 1120 50 mg (open-label): 1251900001 Placebo 200 mg: 1243790001 Placebo 50 mg: 1243800001
Duration of treatment:	Continuous treatment until disease progression or dose limiting toxicity (DLT)
Reference therapy:	None
dose:	Not applicable
mode of admin.:	Not applicable
batch no.:	Not applicable
Criteria for evaluation:	
Efficacy:	Clinical response assessed by imaging (based on RECIST criteria) and by the investigator, progression-free survival, overall survival and quality of life.
Pharmacokinetics	BIBF 1120 plasma concentrations were determined.
Safety:	Adverse events according to Common Terminology Criteria for Adverse Events (CTCAE version 3.0), changes in safety laboratory parameters, patient performance, and vital signs.
Statistical methods:	Exploratory data analysis, descriptive statistics, hazard ratios, confidence intervals for proportions, logistic regression, Kaplan Meier estimation of times-to-event, Greenwood's variance estimate and log-rank tests. Tumour diameters were compared using ANCOVAR, with Wilcoxon rank-sum tests and waterfall plots. Safety parameters were compared using one-sided Fisher's exact test.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Efficacy

A total of 73 patients with NSCLC were enrolled into the study; 37 patients were treated with 150 mg BID BIBF 1120 and 36 patients were treated with 250 mg BID BIBF 1120. All patients were Caucasian except one Asian patient in the 250 mg BID group. The overall mean age was 62.7 (range: 37 - 81 years). Sixty percent of the patients were male with a substantially greater proportion entered into the 250 mg BID dose group compared with the 150 mg BID dose group (72% vs 49%). Overall, about half of the patients had adenocarcinoma and a quarter had squamous cell carcinoma. Most of the patients had Stage IV disease with a lower percentage of these patients in the higher dose group (78% vs 97%). The majority of patients had metastases; they occurred most frequently in the lung (57%) or lymph nodes (64%). In total, 99% of patients had been previously treated with platinum-containing chemotherapy and more than one-third of patients had received 2 or more prior chemotherapies.

BIBF 1120 at 150 mg BID and 250 mg BIBF 1120 BID were equivalent in terms of median PFS time (48 vs. 53 days). The corresponding overall survival times were 144 days for patients receiving the 150 mg BID dose and 208 days for patients receiving the 250 mg BID dose. When considering patients with a baseline ECOG of 0 or 1, the median PFS was greater compared with all patients; as for all patients, median PFS was independent of dose (150 mg BID 81 days; 250 mg BID 85 days).

In the subgroup with ECOG 0 or 1, clinical benefit was achieved by nearly 60% of patients; one of the 17 patients with baseline ECOG of 2 had stable disease. One patient treated with 250 mg BID sustained a 74% reduction (partial response) in tumor size through 9 months.

Median time to death was 208 for the 250 mg BID and 144 days for the 150 mg BID dose group (HR=0.693, p=0.210). However, after adjusting for tumour size, the superiority of the higher dose declined (HR=0.907, p=0.756). The risk of death was found to be significantly associated with baseline ECOG, baseline tumour size and the presence of liver metastases (p<0.010). The median overall survival for patients with ECOG 0 or 1 was 264 days (150 mg BID: 197 days; 250 mg BID: 361 days).

ECOG performance score improved for 9% of patients; most patients (87%) experienced some stabilisation, with their best ECOG performance score being the same as that seen at baseline. Physical functioning, as measured by the EORTC QLQ-C30, showed results similar to those for ECOG. The majority of patients (58.9%) remained stable for 42 days.

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Pharmacokinetics	The quality of the bioanalytical assay for the determination of BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide was good as the acceptance criteria were met. Steady state for BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide was latest reached by Day 15 after BIBF 1120 BID dosing for both dose groups. The steady state might have been reached at an earlier time point, however no PK sampling was performed between Day 1 and Day 15. In general, pre-dose BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide plasma concentrations remained stable. There was no sign of systematic changes in BIBF 1120 as well as BIBF 1202 and BIBF 1202-glucuronide trough values during long-term treatment with BIBF 1120. For the BIBF 1120 $Cpre_{ss}$ values of both the 150 mg and the 250 mg BIBF 1120 BID dose groups, no deviation from dose-proportionality was detectable. In general, a moderate to high inter-patient variability of BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide pre-dose plasma concentrations was observed.
Safety results:	All patients who were documented to have taken at least one dose of investigational treatment were included in the safety analysis (37 patients in the 150 mg BID group and 36 patients in the 250 mg BID group). Adverse events irrespective of relatedness were seen mainly for the gastrointestinal system. A causal relationship with BIBF 1120 administration was frequently reported for nausea (57.5%), diarrhoea (47.9%), vomiting (42.5%), and anorexia (28.8%). The frequency of the gastrointestinal adverse events was comparable between dose groups. Nausea and/or vomiting necessitated treatment discontinuation in a total of 8 patients (11.0%). Other frequently reported AEs comprised anorexia (39.7%), fatigue (32.9%), weight decrease (23.3%), pyrexia (19.2%), abdominal pain (16.4%), headache (15.1%), increased ALT (15.1%), back pain (13.7%), upper abdominal pain (12.3%), chest pain (11.0%) and increased AST (11.0%). There was no difference in the frequency of most of the AEs when comparing dose groups.

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Safety results:

Drug-related ALT, AST and bilirubin elevations only occurred in the 250 mg BID group. CTCAE grade 3 drug-related AEs were more frequently observed in the 250 mg BID group and comprised nausea (11.1% vs. 2.7%), vomiting (5.6% vs. none), diarrhoea (11.1% vs. 5.4%), ALT (19.4% vs. none) and AST elevations (2.8% vs. none).

Thirty-four (47%) of 73 patients died during the study, with 31 deaths being due to disease progression and none being considered related to BIBF 1120 treatment. Deaths from other causes than NSCLC were due to a general deterioration in physical health in a patient in the 150 mg BID treatment group and haemorrhage and haemoptysis in patients in the 250 mg BID group; the general deterioration in physical health and the haemoptysis was considered related to NSCLC by the investigators.

During the study 41 of 73 patients experienced at least one SAE, with the most frequent being progression of the underlying disease. Non-disease associated SAEs occurred in 22 patients and most frequently consisted of gastrointestinal conditions (12 patients).

Thirty-seven (50.7%) of 73 patients discontinued BIBF 1120 treatment due to AEs; for 20 of these patients, this was due to worsening of NSCLC. Other AEs leading to treatment discontinuation primarily comprised nausea, vomiting and elevated hepatic enzymes.

Significant non-serious AEs primarily consisted of gastrointestinal events and elevations in hepatic enzymes.

Increased levels of liver enzymes based on laboratory values were reported in the 250 mg BID dose group only. Nine patients (25.0%) in this group experienced grade 3 ALT elevation, with 4 patients (11.1%) also experiencing grade 2 elevations in total bilirubin. Most occurrences of elevated liver enzymes resolved during the course of the study. A small proportion of patients experienced possibly clinically significant abnormalities inhaematological or serum electrolyte levels. Lymphopenia and major changes in CD4-cell counts were not apparent during this study.

Median values for vital signs parameters showed no major changes from baseline to the end of the study.

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<tr><td>Conclusions:</td><td colspan="4">BIBF 1120 appeared to show similar signs of efficacy in patients with ECOG 0 to 1 as compared to historical data of other VEGFR inhibitors in a similar patient population. There was no evidence of a difference in efficacy between the two BIBF 1120 dosages. BIBF 1120 pre-dose concentrations at both dose levels showed no deviation from dose-proportionality. BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide pre-dose concentrations remained stable over the observed treatment period in the target NSCLC patient population in both dose groups. Continuous daily treatment with BIBF 1120 was well tolerated. Gastrointestinal AEs were the predominant side effects; elevations in liver enzyme levels were also seen but only at the higher BIBF 1120 dose.</td></tr>
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