Clinical Study Synopsis for Public Disclosure

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Title of trial: A Phase I open label study of continuous oral treatment with BIBF 1120 together with pemetrexed in previously treated patients with non-small cell lung cancer

Coordinating Investigator: [Redacted]

Trial sites: 2 (1 Canada, 1 United States)


Nasser Hanna, Peter Ellis, Peter Stopfer, David Shapiro and Steve Gyorffy. A Phase I study of continuous oral treatment with the triple angiokinase inhibitor BIBF 1120 together with pemetrexed in previously treated patients with non-small cell lung cancer. International Association for the Study of Lung Cancer. Seoul, South Korea, September 2-6 2007. Abstract P3-091

Clinical phase: I

Objectives: The primary objective was to determine the safety, tolerability and maximum tolerate dose (MTD) of BIBF 1120 in combination with pemetrexed. Secondary objectives were to characterize the pharmacokinetic profiles of BIBF 1120 and pemetrexed and to obtain preliminary anti-tumour efficacy information.

Methodology: Uncontrolled, open-label, dose escalation study

No. of subjects: planned: entered: 24-30 actural: enrolled: 31 entered: 26

Treatment A: 100 mg BIBF 1120
<table>
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<tr>
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<th>Boehringer Ingelheim</th>
<th>Tabulated Trial Report</th>
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<tr>
<td>Name of finished product:</td>
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<tr>
<td>Name of active ingredient:</td>
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<tr>
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<tr>
<td>Date of revision:</td>
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<table>
<thead>
<tr>
<th>entered: 6  treated: 6  analyzed</th>
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<tbody>
<tr>
<td>Treatment B: 150 mg BIBF 1120</td>
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<tr>
<td>Treatment C: 200 mg BIBF 1120</td>
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<tr>
<td>Treatment D: 250 mg BIBF 1120</td>
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<tr>
<th>Diagnosis and main criteria for inclusion:</th>
<th>Patients with a confirmed diagnoses of recurrent Stage IIIb or IV non-small cell lung cancer who have failed one prior platinum regimen for advanced disease.</th>
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<tr>
<td>Test product: BIBF 1120</td>
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<td>mode of admin.: P.O.</td>
<td>batch no.: PD-2572, PD-2615</td>
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| Test product: Pemetrexed (Alimta®)     | dose: $500$ mg/m² mg |
| mode of admin.: IV                      | batch no.: PD-2616 (Canada only, United States investigational site used commercial supply and did not retain batch numbers) |

| Reference therapy: Not applicable | |

| Duration of treatment: Minimum of four and a maximum of six repeating 21-day cycles of combination therapy in the absence of disease progression with the option for BIBF 1120 monotherapy extension until disease progression or LPO is reached in the trial. |
### Criteria for evaluation:

- **Efficacy / clinical pharmacology:** Objective tumor response (based on RECIST), plasma concentration-time profiles and pharmacokinetic characteristics of BIBF 1120 and pemetrexed
- **Safety:** Adverse events, according to NCI common terminology criteria (CTC), laboratory evaluation, patient performance

### Statistical methods:

Descriptive statistics

### SUMMARY – CONCLUSIONS:

#### Efficacy / clinical pharmacology results:

- **Efficacy:**

Twenty-six patients were treated at 100, 150, 200 and 250 mg doses of BIBF 1120 bid in combination with standard dose pemetrexed (500 mg/m²). The MTD of BIBF 1120 when given twice a day for 21 days in combination with standard dose pemetrexed given as an infusion on day 1 of the 21-day cycle was determined to be 200 mg.

The majority of the 26 treated patients were of clinical stage IV at screening (80.8%), had at least one prior chemotherapy treatment (100.0%), had two or more prior anti-cancer therapies (including prior surgery, radiotherapy, and chemotherapy), (88.5%), and treated with BIBF 1120 as the second line therapy (92.3%).

All 26 treated patients had RECIST measurable lesions at screening and tumor responses were evaluated according to RECIST criteria for all 26 treated patients. One patient experienced a confirmed complete response: patient 1826 in the pemetrexed 500 mg/m² plus BIBF 1120 100 mg bid group had complete response (CR) after treated with the trial medication for 44 days, and this patient’s CR status was sustained until the interim last-patient-out date (07 May 2007). This patient had a sustained CR and continued on monotherapy treatment with BIBF 1120 100 mg bid for 1415 days until 06 January 2010. Half of the 26 treated patients had stable disease (SD) as the best overall response. The median progression free-survival time for all 26 treated patients was approximately 5.4 months as evaluated on 07 May 2007.
Twenty-one patients who completed the initial 21-day treatment cycle were eligible to continue in the second treatment cycle and beyond. Nine patients completed four cycles of treatment with combination regimen (e.g., pemetrexed 500 mg/m² plus BIBF 1120), and seven patients were treated with monotherapy of BIBF 1120. Five patients participated in this phase I trial for more than six months: four patients were in the pemetrexed 500 mg/m² plus BIBF 1120 100 mg bid group (patient for 1500 days; patient for 286 days; patient for 210 days, and patient for 204 days) and one patient was in the pemetrexed 500 mg plus BIBF 1120 250 mg bid group (patient for 189 days).
**Pharmacokinetics:**

The aim was to investigate PK characteristics of BIBF 1120 and BIBF 1202 (on Day 2 of TC 2) one day after dosing of pemetrexed. For the investigation of an influence of pemetrexed together with dexamethasone on the respective PK characteristics of BIBF 1120 and BIBF 1202, only the MTD dose group of 200 mg BIBF 1120 bid was considered. Moreover, the pemetrexed PK characteristics on Day 1 of TC 2 were to be evaluated after a preceding dosing interval from Day 2 to Day 21 of TC 1 with BIBF 1120 bid.

**BIBF 1120:**

BIBF 1120 was moderately fast absorbed following oral administration of 200 mg BIBF 1120 with maximum plasma concentrations (C_{max}) reached 2 hours post dose (median t_{max} value) on Day 2 of TC 2. The gMean BIBF 1120 C_{max} value was 50.4 ng/mL (gCV% 81.2) on Day 2 of TC 2. The gMean BIBF 1120 AUC_{0-24} value was 308 ng h/mL. The gMean terminal half-life (t_{1/2}) following oral dosing was 12.1 hours on Day 2 of TC 2. Since plasma samples were taken only up to 24 hours after BIBF 1120 administration, the determination of the terminal half-life may have been underestimated in this trial. A relatively high apparent total body clearance (CL/F) for BIBF 1120 was determined with a gMean value of 8180 mL/min on Day 2 of TC 2. BIBF 1120 exhibited a high gMean apparent volume of distribution during the terminal phase, which might indicate a high tissue distribution of the drug. The gMean value for the volume of distribution (V_{z}/F) was 8580 L and on Day 2 of TC 2. The apparent values obtained for total body clearance and volume of distribution should be treated with caution as the absolute bioavailability (F) of BIBF 1120 in humans is unknown.

In general, BIBF 1120 predose (trough) plasma concentrations within the respective TCs remained stable. There was no sign of a systematic increase or decrease of BIBF 1120 trough plasma concentrations during long-term treatment with BIBF 1120 in combination with pemetrexed, although high inter- and intra-individual variability was observed.

There was no deviation of dose proportionality (found through visual inspection) of BIBF 1120 PK characteristics of all tested dose groups in combination with pemetrexed combination therapy. A patient suffering from Gilbert’s syndrome did not show deviating BIBF 1120 PK characteristics compared to the rest of the
200 mg BIBF 1120 bid dose group.

**BIBF 1202:**

Following oral administration of BIBF 1120, BIBF 1202 maximum plasma concentrations (C_{max}) were reached 3 hours post dose (median t_{max} value) on Day 2 of TP 2. The gMean C_{max} value was 49.1 ng/mL (gCV% 130) on Day 2 of TC 2. The gMean BIBF 1202 AUC_{0-24} value was 377 ng⋅h/mL. The gMean terminal half-life (t_{1/2}) following oral dosing ranged around 9.35 hours on Day 2 of TC 2. Since plasma samples were taken only up to 24 hours after BIBF 1202 administration, the determination of the terminal half-life may have been underestimated in this trial.

The rate of metabolism from BIBF 1120 to BIBF 1202 remained constant for all tested dose groups in combination with pemetrexed combination therapy. There was no sign of a systematic increase or decrease in BIBF 1202 trough plasma concentrations during long term treatment with BIBF 1202 in combination with pemetrexed. However, a high inter-patient variability of predose plasma concentrations of BIBF 1202 was observed. A patient suffering from Gilbert’s syndrome did not show deviating BIBF 1202 PK characteristics compared to the rest of the 200 mg BIBF 1120 bid dose group.

There was no deviation of dose proportionality (found through visual inspection) of BIBF 1202 PK characteristics of all tested dose groups in combination with pemetrexed combination therapy.

**Pemetrexed:**

The individual and gMean drug plasma concentration-time profiles of pemetrexed after IV administration of 500 mg/m^2 on Day 1 of TC 2 of the MTD dose group (200 mg BIBF 1120 bid) displayed at least triexponential disposition kinetics. For the MTD dose group the gMean C_{max} value of pemetrexed was 98.0 µg/mL (gCV% 21.8) on Day 1 of TC 2. The gMean exposure (expressed as AUC_{0-24}, AUC_{0-48} and AUC_{0-∞}) to pemetrexed was 200 µg⋅h/mL, 201 µg⋅h/mL and 201 µg⋅h/mL on Day 1 of TC 2, indicating that the main exposure to pemetrexed occurred during the 24 h after the IV administration. The median t_{max} values for IV dosing of pemetrexed was 0.275 hours (range 0.016 to 0.500 hours) on Day 1 of TC 2. The gMean terminal half-life (t_{1/2}) following IV dosing of pemetrexed
was 3.71 hours on Day 1 of TC 2. The gMean total body clearance (CL) for pemetrexed on Day 1 of TC 2 was 4.78 L/h. The volume of distribution during the terminal phase (V₂) was 25.6 L and the volume of distribution at steady-state (Vₚₚ) was 15.4 L.

The pemetrexed pharmacokinetic characteristics from this trial are comparable with the ones found for pemetrexed in the literature (R05-1082, P06-05279, R07-4217, R07-4218).

Safety results: Twenty-six patients were treated at 100, 150, 200 and 250 mg doses of BIBF 1120 bid in combination with standard dose pemetrexed (500 mg/m²). The MTD of BIBF 1120 when given twice a day for 21 days in combination with standard dose pemetrexed given as an infusion on day 1 of the 21-day cycle, was determined to be 200 mg.

Gastrointestinal disorders (mainly nausea, vomiting, abdominal pain and diarrhea) and general disorders and administrative site conditions (predominantly rash) were the most frequently reported drug-related AEs. However none of the reported rashes exceeded a severity of CTC Grade 2. The most common individual AEs were nausea (69.2%) and fatigue (65.4%).

During the first treatment cycle (TC1), 7 patients (26.9%) developed a DLT: 1 out of 6 patients at 100 mg BIBF 1120 bid, 1 out of 6 patients at 150 mg BIBF 1120 bid, 3 out of 12 patients at 200 mg BIBF 1120 bid, and 2 out of 2 patients at the 250 mg BIBF 1120 bid. These DLTs included elevated liver enzymes, gastrointestinal events including vomiting and nausea, fatigue and confusion and were of CTC Grade 3. A second patient at the 150 mg BIBF 1120 also developed a DLT of CTC Grade 3 fatigue in TC1, but was in the follow-up period and not on study drug. Two other patients experienced DLTs in TC 2 and TC 3 respectively: one patient had CTC Grade 3 fatigue on study drug followed with ALT elevation in the follow-up period in the 200 mg BIBF 1120 bid dose, and the other patient developed CTC Grade 3 diarrhea in the 200 mg BIBF 1120 bid cohort. In total 3 patients developed DLT below the MTD dose, 5 patients developed a DLT at the MTD dose and 2 patients developed a DLT above the MTD dose.

At the MTD dose of 200 mg, a total of 12 patients were treated with the combination of BIBF1120 and standard dose pemetrexed. The side effect
profile at this dose was subject to CTC Grade 3 levels of fatigue (4 patients out of 12), with 7 patients in total having reported fatigue of CTC Grade 1-3. Three patients had DLTs related to fatigue, while four patients discontinued due to fatigue. In some cases, the fatigue reported may have been associated with co-medications given during the therapy. The fatigue reported here is comparable to recently published data with single agent SU11248 (similar class of compound as BIBF 1120) where 24% of second-line NSCLC patients reported CTC Grade 3 fatigue with a further 5% reporting Grade 4 fatigue (R08-0470). Overall 70% of treated patients reported fatigue of CTC Grades 1-4 (R08-0470). Gastrointestinal toxicity was observed in 9 of 12 patients, but only two cases were of CTC Grade 3, and only one DLT. Liver enzyme increases (ALT and/or AST) was observed in three patients at the MTD, only one of which was a DLT. At the MTD dose, two patients required dose reductions of study medications while a further three patients discontinued medications due to AEs.

A total of 5 patients (19.2%) experienced one or more serious adverse events; the most frequent SAE was pneumonia reported in 2 patients. During the conduct of the study, one patient died in the post-treatment follow-up due to disease progression. A sixth SAE was reported in the extended access monotherapy section of the study for patient after the initial data cut-off date of 07 May 2007.

Conclusions:
In general, the AEs observed in this trial were consistent with safety profile of BIBF 1120 and those reported for pemetrexed. The MTD dose was found to be 200 mg BIBF 1120 bid in combination with standard dose pemetrexed (500 mg/m²).

Based on the results of this study, a daily oral dose of 200 mg BIBF 1120 bid, in combination with standard dose pemetrexed given on Day 1 of a 21 day cycle is the MTD and this dose should be used in future trials in patients with advanced NSCLC who have failed prior treatment with platinum-based chemotherapy. Overall, the study medications were generally well tolerated, however at the MTD manageable tolerability was observed. The pharmacokinetic characteristics of pemetrexed in combination with BIBF 1120 were comparable with the ones found in the literature. Therefore, there was no clinically relevant influence of BIBF 1120 treatment on the PK of pemetrexed.