Clinical Study Synopsis for Public Disclosure

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**Title of trial:**
A Phase I open-label dose escalation study of single oral daily doses of BIBW 2992 for three days after administration of docetaxel, in patients with advanced solid tumors

**Coordinating Investigators:**

**Trial sites:**
Belgium

**Publication (reference):**


**Clinical phase:**
I

**Objectives:**
Maximum tolerated dose (MTD), safety, pharmacokinetic and pharmacodynamic parameters, and efficacy of pulsatile administration of BIBW 2992 in combination with docetaxel (Taxotere®)

**Methodology:**
Open-label, dose escalation study
Name of company: Boehringer Ingelheim

Name of finished product: Not applicable

Name of active ingredients: BIBW 2992 + Docetaxel

Module: Volume:

Report date: 25 FEB 2010

Trial No. / U No.: 1200.20 / U10-1339-02


Date of revision: 10 JUL 2012

Synopsis No.:

No. of subjects:

planned: Randomised: up to 42 (3 to 6 patients at each dose level, maximum 18 patients at MTD)

actual: Randomised: 45
Treated: 40
Analysed (for primary endpoint): 39

Docetaxel 60 mg/m² + BIBW 2992 10 mg
Randomised: 3  Treated: 3  Analysed (for primary endpoint): 3

Docetaxel 75 mg/m² + BIBW 2992 10 mg
Randomised: 3  Treated: 3  Analysed (for primary endpoint): 3

Docetaxel 75 mg/m² + BIBW 2992 20 mg
Randomised: 3  Treated: 3  Analysed (for primary endpoint): 3

Docetaxel 75 mg/m² + BIBW 2992 40 mg
Randomised: 6  Treated: 6  Analysed (for primary endpoint): 6

Docetaxel 75 mg/m² + BIBW 2992 60 mg
Randomised: 4  Treated: 4  Analysed (for primary endpoint): 4

Docetaxel 75 mg/m² + BIBW 2992 90 mg
Randomised: 13  Treated: 13  Analysed (for primary endpoint): 12

Docetaxel 75 mg/m² + BIBW 2992 120 mg
Randomised: 5  Treated: 5  Analysed (for primary endpoint): 5

Docetaxel 75 mg/m² + BIBW 2992 160 mg
Randomised: 3  Treated: 3  Analysed (for primary endpoint): 3

Diagnosis and main criteria for inclusion:

Patients with a confirmed diagnosis of a malignant solid tumour refractory or not amenable to standard therapies, preferably patients with breast, prostate, or ovarian cancer. In addition, patients with an oncological disease amenable to standard treatment with docetaxel.
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<th>Boehringer Ingelheim</th>
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<td>EudraCT No.: 2005-000034-20</td>
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<td><strong>Name of active ingredients:</strong></td>
<td>BIBW 2992 + Docetaxel</td>
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<td><strong>Dates of trial:</strong></td>
<td>Dates of trial: 23 MAY 2005 – 7 MAR 2008</td>
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<td><strong>Date of revision:</strong></td>
<td>10 JUL 2012</td>
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**Test product:** BIBW 2992 tablets

**dose:**
- Starting dose: BIBW 2992 10 mg (and docetaxel 60 mg/m²)
- Subsequent cohorts: BIBW 2992 10, 20, 40, 60, 90, 120, or 160 mg (and docetaxel 75 mg/m²)

**mode of admin.:** Oral

**batch no.:**
- BIBW 2992 5 mg tablets: B050205
- BIBW 2992 20 mg tablets: B050206
- BIBW 2992 100 mg tablets: B050101

**Test product:** Docetaxel injectable

**dose:**
- Starting dose: 60 mg/m² every 21 days
- Subsequent cohorts: 75 mg/m² every 21 days

**mode of admin.:** Intravenous infusion

**batch no.:** Commercial product (Taxotere®)

**Reference therapy:** No reference therapy was investigated.

**dose:** Not applicable

**mode of admin.:** Not applicable

**batch no.:** Not applicable

**Duration of treatment:**
In each 21-day treatment period (TP), docetaxel was administered as a single dose (Day 1) and BIBW 2992 was administered as 3 single daily doses (Days 2 to 4, pulsatile administration).

In the absence of clinical disease progression or undue toxicity, patients were to be treated for a maximum of 8 TPs in order to limit development of taxotere-related toxicities. However, the investigators decided to administer more than 8 TPs to some patients who did not experience such toxicities.
Criteria for evaluation:

**Efficacy / clinical pharmacokinetics:**

*Secondary endpoints*

Pharmacokinetics of BIBW 2992 and docetaxel following administration in Treatment Period 1 (TP 1) and Treatment Period 2 (TP 2)

Efficacy: Objective tumour responses after administration of BIBW 2992 and docetaxel

*Additional secondary endpoints*

Modulation of biomarkers (EGFR, p-EGFR, p-MAPK, p-Akt, Ki 67, p27Kip1) in skin biopsies prior to administration of BIBW 2992 and on Day 4

Modulation of biomarkers (EGFR, p-EGFR, HER2, p-MAPK, p-Akt, Ki 67, p27Kip1) in tumour biopsies prior to administration of BIBW 2992 and on Day 4 in 6 or more patients treated at the MTD

**Safety:**

*Primary endpoint*

The safety of the treatment schedule of BIBW 2992 with docetaxel, as characterised by

Dose-limiting toxicities (DLTs) of BIBW 2992 in combination with docetaxel to determine the MTD for the treatment schedule

The incidence and the intensity of adverse events (AEs) assessed according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

*Secondary safety endpoint*

The safety of BIBW 2992 and docetaxel following administration in TP 1

**Statistical methods:**

Descriptive statistics
SUMMARY – CONCLUSIONS:

Efficacy: In this trial, 40 patients (17 males and 23 females) with solid tumours were treated with BIBW 2992 and docetaxel. The median age was 51.5 years. The most frequent tumour types were pancreatic cancer (15%), breast cancer (13%), skin cancer including melanoma (13%), cervical, vaginal, or vulvar cancer (13%), and bladder cancer (10%).

The secondary efficacy endpoint was objective tumour responses according to RECIST. Tumour measurements were performed by radiographs, computed tomography, or magnetic resonance imaging at screening and at the end of every other TP. End of treatment (EOT) and follow-up assessments were optional. The investigator evaluated the tumour responses as complete response, partial response, stable disease, or progressive disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Progression-free survival and the ECOG performance score were also analysed as indicators of efficacy.

Five patients had an objective response. A complete response was observed in one patient with breast cancer. Partial responses were observed in 4 patients – one patient with oesophageal cancer, one patient with thymoma, and 2 patients with breast cancer. Stable disease was the best overall response in 17 patients and 12 patients did not show any response.

Thirty-three patients (83%) showed progression of their disease at some point during the study. Progression-free survival time for patients with progressive disease ranged from 29 days to 288 days. In the MTD cohort (docetaxel 75 mg/m² and BIBW 2992 90 mg), the progression-free survival time ranged from 33 days to 288 days. Patients could remain on treatment as long as they received clinical benefit and did not experience undue toxicities. Six patients were on treatment through TP 8 and 5 patients were on treatment through TP 10, 12, or 14. These patients had lung cancer, ovarian cancer, oesophageal cancer, bladder cancer, gastric cancer, breast cancer, cervical carcinoma, renal carcinoid, and malignant melanoma. Progression-free survival in these patients ranged from 178 days to 288 days.

At EOT, ECOG performance scores over treatment deteriorated in 18 patients (45%), were unchanged in 17 patients (43%), and improved in only one patient (3%).
**Pharmacokinetics:**

*BIBW 2992*

The pharmacokinetic parameters of BIBW 2992 in the MTD group (docetaxel 75 mg/m² and BIBW 2992 90 mg) are shown in the table below. Absorption of BIBW 2992 was moderately fast. Maximum plasma concentrations and exposure of BIBW 2992 on Day 2 of TP 1 and TP 2 to 4 increased with the given dose. No deviation from dose-linearity was apparent on visual inspection. The gMean terminal half-life following oral dosing was suitable for once daily dosing. Since plasma samples were taken only up to 24 h after BIBW 2992 administration, the terminal half-life of BIBW 2992 may have been underestimated. BIBW 2992 was detectable after the 18-day wash-out phase in the pre-dose plasma samples on Day 2 of TP 2 to 4 in half of the patients.

For the MTD group, the apparent total body clearance and the apparent volume of distribution of BIBW 2992 were high, which might indicate high tissue distribution of the drug; however, as the absolute bioavailability (F) of BIBW 2992 in humans is unknown, these values should be interpreted with caution. In general, during repeated dosing periods, no systematic increases or decreases in BIBW 2992 plasma concentrations were observed during long term treatment of BIBW 2992 in combination with docetaxel.

<table>
<thead>
<tr>
<th>Parameter [unit]</th>
<th>TP 1 (N=13)</th>
<th>TP 2 to 4 (N=10)</th>
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<tbody>
<tr>
<td>AUC₀–₂₄ [ng·h/mL]</td>
<td>879 (62.6)</td>
<td>995 (48.3)</td>
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<tr>
<td>Cₘₐₓ [ng/mL]</td>
<td>71.4 (69.5)</td>
<td>81.2 (56.7)</td>
</tr>
<tr>
<td>tₘₐₓ [h]</td>
<td>3.00 (1.00 to 5.00)</td>
<td>4.03 (1.00 to 5.00)</td>
</tr>
<tr>
<td>t₁/₂ [h]</td>
<td>16.7 (29.3)</td>
<td>17.5 (32.0)</td>
</tr>
<tr>
<td>CL/F [mL/min]</td>
<td>1040 (57.5)</td>
<td>888 (52.5)</td>
</tr>
<tr>
<td>Vₙ/F [L]</td>
<td>1500 (70.5)</td>
<td>1340 (50.0)</td>
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¹ median (minimum to maximum)
**Docetaxel**

The pharmacokinetic parameters of docetaxel in the MTD group (docetaxel 75 mg/m² and BIBW 2992 90 mg) are shown in the table below. Plasma concentration-time profiles of docetaxel (75 mg/m²) were comparable before (TP 1) and after (TP 2) administration of BIBW 2992 on Days 2 to 4 of TP 1. There was no clinically significant difference in docetaxel exposure between TP 1 and TP 2 as indicated by $C_{\text{max}}$ and AUC levels. In TP 1 and TP 2, essentially the same values were observed for terminal half-life, total body clearance, and volume of distribution of docetaxel.

<table>
<thead>
<tr>
<th>Parameter [unit]</th>
<th>TP 1 (N=13) gMean (gCV)</th>
<th>TP 2 (N=8) gMean (gCV)</th>
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<tr>
<td>$AUC_{0-\infty}$ [ng·h/mL]</td>
<td>3160 (58.1)</td>
<td>3260 (57.7)</td>
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<tr>
<td>$C_{\text{max}}$ [ng/mL]</td>
<td>2070 (63.4)</td>
<td>2200 (42.1)</td>
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<tr>
<td>$t_{\text{max}}$ [h]</td>
<td>1.00 (0.933 to 1.08)</td>
<td>1.00 (0.983 to 1.05)</td>
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<tr>
<td>$t_{1/2}$ [h]</td>
<td>20.9 (26.0)</td>
<td>21.1 (33.7)</td>
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<tr>
<td>CL [mL/min]</td>
<td>712 (61.0)</td>
<td>682 (65.5)</td>
</tr>
<tr>
<td>$V_z$ [mL/min]</td>
<td>1290 (81.3)</td>
<td>1250 (107)</td>
</tr>
<tr>
<td>$V_{ss}$ [L]</td>
<td>488 (87.6)</td>
<td>487 (83.9)</td>
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$^1$median (minimum to maximum)
Safety results:

All 40 patients completed at least TP 1. Three patients completed TP 1, 1 patient completed TP 3, 4 patients completed TP 4, 3 patients completed TP 5, 2 patients completed TP 6, 1 patient completed TP 7, 6 patients completed TP 8, 2 patients completed TP 10, 2 patients completed TP 12, and 1 patient completed TP 14. Median exposure to BIBW 2992 and docetaxel was 95 days (range 13 to 305 days).

The primary objective of this trial was to determine the MTD for BIBW 2992 given in combination with docetaxel, defined as the highest dose at which no more than 1 of 6 patients experienced DLT during TP 1. Three patients were treated in each dose group up to 75 mg/m² and BIBW 2992 160 mg. When 1 of 3 patients treated at this highest dose experienced CTCAE grade 4 neutropenia, the next lower cohort, docetaxel 75 mg/m² and BIBW 2992 120 mg was expanded. In that cohort, 2 of 5 patients experienced DLT (CTCAE grade 4 febrile neutropenia in one patient, CTCAE grade 3 nausea, vomiting, and diarrhea in another patient). Then the next lower dose group, docetaxel 75 mg/m² and BIBW 2992 90 mg, was expanded and no DLT was observed in 13 patients treated. Therefore, the MTD for BIBW 2992 in combination with docetaxel 75 mg/m² was determined to be 90 mg BIBW 2992 daily.

All 40 treated patients experienced at least one AE. The AEs reported in the highest frequency of patients were fatigue (25 patients, 63%) and diarrhea (23 patients, 58%). The frequency of patients with diarrhea increased from 0% in patients treated with BIBW 2992 10 mg and docetaxel 75 mg/m² to 69% in patients at the MTD of BIBW 2992 90 mg and docetaxel 75 mg/m².

Thirty-eight patients (95%) experienced an AE which the investigator considered possibly related to the study medications. The AEs reported as drug-related in the highest frequency of patients were diarrhea, stomatitis, and alopecia (each 20 patients, 50%) and rash (16 patients, 40%). These frequently reported drug-related AEs were highest CTCAE grade 1 or 2 except in 2 patients with highest CTCAE grade 3 diarrhea and one patient with highest CTCAE grade 3 alopecia.

Overall, the only AEs of highest CTCAE grade 4 were neutropenia (4 patients, 10%), febrile neutropenia and pulmonary embolism (one patient each, 3%), all of which were considered possibly drug-related. However, none of the AEs of highest CTCAE grade 5, most frequently general physical health deterioration (11 patients, 28%), were considered possibly drug-related.
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**Safety results (cont’d):**

Serious AEs were reported in 21 patients (53%). The serious AE reported in the highest frequency of patients was general physical health deterioration, a clinical sign of disease progression (13 patients, 33%). Sixteen patients (40%) died during the trial. The causes of death were general physical health deterioration in a total of 11 patients (including one patient who also died of pyrexia and cholangitis), malignant neoplasm progression in a total of 4 patients (including one patient who also died of general physical health deterioration), septic shock and renal failure in one patient, and pleural effusion and dyspnoea in one patient. No deaths were considered related to the study medications.

Other significant AEs according to ICH E3 were reported in 4 patients (neutropenia and nausea in one patient each and fatigue in 2 patients). Adverse events which led to discontinuation of the trial medication were reported in 3 patients (disease progression, syncope, and dizziness in one patient, fatigue in one patient, and general physical health deterioration in one patient). Predefined significant AEs were reported in 3 patients (dyspnoea in 2 patients and renal failure in one patient).

Changes in white blood cell count to CTCAE grades 3 and 4 were reported in 17 patients (43%) and 8 patients (20%), respectively. Changes in neutrophil count to CTCAE grade 3 and 4 were reported in 4 patients (10%) and 22 patients (55%), respectively. Clinical laboratory values reported as AEs were CTCAE grade 1 hypokalaemia (2 patients), CTCAE grade 3 hypercalcaemia (1 patient), CTCAE grade 1 increase in C-reactive protein (1 patient), and CTCAE grade 1 and grade 2 increases in blood creatinine (1 patient each).

**Conclusions:**

The MTD in this study was 90 mg BIBW 2992 administered on Days 2, 3, and 4 after administration of docetaxel 75 mg/m² administered on Day 1 in a 21-day treatment cycle. The most frequently reported AEs were fatigue and diarrhoea. The frequency of patients with diarrhoea increased from 0% in patients treated with BIBW 2992 10 mg and docetaxel 75 mg/m² to 69% in patients at the MTD of BIBW 2992 90 mg and docetaxel 75 mg/m². The current data suggest that, in a 21-day treatment cycle, 3 single daily doses of BIBW 2992 (administered on Days 2, 3, and 4) have no clinically significant effect on the pharmacokinetics of docetaxel (75 mg/m² administered on Day 1).