Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2006-002814-37	
Name of active ingredient: BIBW 2992 MA		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 5 AUG 2013	**Trial No. / U No.:** 1200.5 / U10-2018-02	**Dates of trial:** 30 MAY 2007 – 04 JAN 2010	**Date of revision:** dd MON yyyy

Title of trial:	A phase II study of BIBW 2992 added to letrozole in patients with ER+ve hormone refractory metastatic breast cancer progressing on letrozole
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, 5 sites in France
Publication (reference):	Data of this study have not been published
Clinical phase:	II
Objectives:	The primary objective of the trial was to determine the progression-free rate at or after 16 weeks of BIBW 2992 administration with the standard aromatase inhibitor letrozole, in patients with estrogen receptor (ER)-positive, letrozole-refractory metastatic breast cancer.
Methodology:	This was a non-randomised, open-label, 1-stage, single-arm design trial in patients with metastatic breast cancer, with a diagnosis of acquired hormone-resistance. Patients were initially entered into the trial at a BIBW 2992 starting dose of 50 mg daily administered continuously over 28-day treatment cycles, with 2.5 mg letrozole daily; however the first few patients showed compromised tolerability. Protocol amendments were consequently implemented specifying reductions in the starting dose to 40 mg and then 30 mg BIBW 2992. An interim safety analysis was performed after the first 15 patients had completed 1 month of treatment in the trial; data from the interim report indicated a need for a reduction in BIBW 2992 starting dose from 40 mg to 30 mg per day. At each BIBW 2992 starting dose, the trial protocol specified a tolerability-guided dose reduction scheme for patients experiencing drug-related adverse events (AEs).
No. of patients:	
planned:	entered: 30 to 40
actual:	enrolled: 30 entered: 28 treated: 28 analysed (for primary endpoint): 28

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Diagnosis and main criteria for inclusion:	Postmenopausal female patients with metastatic, histologically-proven breast adenocarcinoma that was ER-positive, who had received letrozole and developed acquired resistance and had experienced disease progression within the 6 weeks prior to study entry.
Test product:	BIBW 2992 tablets Letrozole tablets
dose:	BIBW 2992 starting doses of: 50 mg/day with the option to dose reduce to 40 and 30 mg/day; 40 mg/day with the option to dose reduce to 30 and 20 mg/day (protocol amendment 2); and 30 mg/day with the option to dose reduce to 20 mg/day (protocol amendment 4 and the interim safety report). Letrozole: 2.5 mg/day
mode of admin.:	Oral
batch no.:	BIBW 2992: B061000422, B061000376, B061000903, B061001815, B071001147, B071001102, B081002924, and B081002939 Letrozole S0176
Reference therapy:	Not applicable
Duration of treatment:	Patients received continuous daily dosing with BIBW 2992 therapy with letrozole over 28-day treatment cycles until further disease progression.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Efficacy was assessed in terms of the progression-free rate at or after 16 weeks of treatment. For assessment of the primary endpoint progression was defined as the occurrence of 1 of the following: new bone lesion(s); progression or new lesion(s), according to the Response Evaluation Criteria In Solid Tumours (RECIST); an increase in CA 15.3 of more than 20% from baseline in 2 consecutive exams; disease-related skeletal events; or withdrawal from the study due to clinical deterioration amounting to progressive disease, according to the Investigator's judgement. Standard pharmacokinetic (PK) parameters were determined for BIBW 2992 and letrozole. The relationships between BIBW 2992 and letrozole PK parameters and selected AEs were to be assessed using exploratory analyses.

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Safety:	Safety was assessed in terms of the incidence and intensity of AEs, laboratory evaluations, vital signs, cardiac function, and patient performance status.
Statistical methods:	Analyses used descriptive statistics with Kaplan-Meier curves and Greenwood's estimates of variance. PK profiles and PK parameters were assessed at steady state.

SUMMARY – CONCLUSIONS:

Overall, 28 patients were treated with BIBW 2992 and letrozole with 7 patients treated at the 50 mg BIBW 2992 starting dose, 13 patients treated at the 40 mg starting dose, and 8 patients treated at the 30 mg starting dose. Six of 7 patients (85.7%) who received the 50 mg BIBW 2992 starting dose underwent protocol-specified dose reduction to 40 mg and 2 patients subsequently dose-reduced to 30 mg. Eight of 13 patients (61.5%) who received the 40 mg BIBW 2992 starting dose underwent dose reduction to 30 mg. None of the 8 patients who received the 30 mg BIBW 2992 starting dose required dose reduction.

As a result, 15 of 28 patients continued treatment at 40 mg BIBW 2992 and 13 of 28 patients continued treatment at 30 mg BIBW 2992.

Efficacy results: The treated set comprised all 28 patients. Fifteen patients (53.6%) withdrew from the study as a result of disease progression, 11 patients (39.3%) withdrew due to AEs, and 2 patients (7.1%) were withdrawn for other reasons.

All patients (100.0%) entered into the trial were white, and the median age was 64.0 (range: 40 to 82 years). All patients (100.0%) had metastatic disease on entry into the study (range 1 to 4 sites). A total of 27 patients (96.4%) were confirmed as ER-positive, 20 patients (71.4%) were progesterone receptor (PgR)-positive, and 3 patients (10.7%) were human epidermal growth factor receptor-2 (HER-2)-positive.

Efficacy results (continued):

The primary endpoint comprised the progression-free rate at or after 16 weeks of treatment; 8 patients completed 16 weeks of treatment, of whom 4 were considered progression-free based on the protocol-defined criteria. The other 4 patients treated for 16 weeks were not considered progression-free: 2 patients completed 16 weeks of treatment but were found to have undergone disease progression at the 16-week assessment; 1 patient was suspected to have RECIST progression before 16 weeks but this was not formally documented as it could not be demonstrated by computed tomography (CT); and 1 patient experienced a >20% increase in CA 15.3 levels though remaining progression-free based on RECIST. The progression-free rate according to the protocol-defined criteria is summarised in the table below.

	50 mg BIBW 2992	40 mg BIBW 2992	30 mg BIBW 2992	All BIBW 2992 doses
Number of patients N (%)	7 (100.0)	13 (100.0)	8 (100.0)	28 (100.0)
Progression-free rate N (%) [95% CI]	2 (28.57) [3.67, 70.96]	0 (0.00) [0.00, 24.71]	2 (25.00) [3.19, 65.09]	4 (14.29) [4.03, 32.67]

The progression-free rate at or after 16 weeks, as determined based on RECIST criteria alone was 5 patients (17.9%). The additional patient experienced a >20% increase in CA 15.3 levels and so was not considered progression-free based on the protocol definition.

No patients (0 of 28) experienced an objective RECIST response; the best tumour response was stable disease, which was experienced by 15 patients (53.6%). Overall, 6 patients (21.4%) experienced clinical benefit (a RECIST response of complete response, partial response or stable disease) at 16 weeks; this comprised the 4 patients who were classified as progression free according to the primary endpoint, the additional patient who was considered progression free by RECIST but had elevated CA 15.3 levels, and 1 patient who had stable disease at week 16 but had discontinued treatment. Four patients (14.3%) experienced clinical benefit at 24 weeks.

Combination treatment with BIBW 2992 and letrozole was associated with an initial reduction in CA 15.3 tumour marker levels over the first treatment cycle of -4.35% (range -28.4% to 41.8%). During the trial, 4 patients (14.3%) experienced a best change from baseline of an improved ECOG score and 6 patients (21.4%) experienced a deterioration in ECOG score.

Pharmacokinetic results:

The geometric mean (gMean) PK parameters for BIBW 2992 are presented in the table below; data were particularly sparse for the 50 mg starting dose group and were not summarised. The BIBW 2992 maximum concentration at steady state ($C_{max,ss}$) and area under the plasma concentration-time curve at steady state ($AUC_{tau,ss}$) appeared to decrease over the dosing interval with decreasing BIBW 2992 dose based on the sparse data available, with a similar tendency being observed for predose values on Days 57 and 85. No deviation from dose proportionality was observed for either parameter. Intersubject variabilities for $C_{max,ss}$, and $AUC_{tau,ss}$ were moderate for the 40 mg dose group and high for the 30 mg dose group. BIBW 2992 PK parameters were within the ranges observed in BIBW 2992 monotherapy studies, suggesting that continuous combination dosing with 2.5 mg letrozole did not influence BIBW 2992 pharmacokinetics.

BIBW 2992	40 mg BIBW 2992			30 mg BIBW 2992		
	N	gMean	gCV[%]	N	gMean	gCV[%]
$AUC_{tau,ss}$ (ng*h/mL)	4	660	41.3	5	579	62.8
$C_{max,ss}$ (ng/ml)	4	43.8	42.0	5	33.9	79.4
$C_{pre,ss,\ 57}$ (ng/mL)	5	21.4	42.3	8	15.8	42.1
$C_{pre,ss,\ 85}$ (ng/mL)	4	16.9	55.7	5	17.3	46.5
$t_{max,ss}$ (hours) [1]	4	2.00	2.00-4.00	5	4.00	0.917-7.67

[1] For $t_{max,ss}$, median and range are given.

The gMean PK parameters for letrozole are presented in the table on the following page, and showed no trend to higher or lower values in conjunction with BIBW 2992 dosing. As a result, the individual patient data were pooled and assessed together for patients from all BIBW 2992 dose groups. Intersubject variabilities were high. The observed letrozole PK parameters were in the ranges reported in the literature, suggesting that BIBW 2992 does not have a relevant effect on letrozole pharmacokinetics. The PK data available for letrozole in this study were also sparse.

Pharmacokinetic results (continued):

Letrozole	All BIBW 2992 dose levels		
	N	gMean	gCV[%]
$AUC_{tau,ss}$ (ng*h/mL)	10	2420	76.2
$C_{max,ss}$ (ng/ml)	10	135	70.0
$t_{max,ss}$ (hours) [1]	10	1.00	0.917-23.8

[1] For $t_{max,ss}$, median and range are given.

Safety results:

All 28 patients who received at least 1 dose of study medication were included in the safety analysis. Eight patients (28.6%) completed 4 treatment cycles, of whom 3 patients were classified as having undergone disease progression either before or at the Week 16 assessment. As a result 5 patients (17.9%) continued treatment after 16 weeks, comprising the 4 patients classified as progression-free based on the primary endpoint and the patient who experienced a >20% increase in CA 15.3 levels and was not considered progression-free based on the protocol definition.

The most frequently reported treatment-emergent AEs were diarrhoea (27 patients; 96.4%), asthenia (17 patients; 60.7%), rash (16 patients; 57.1%), nausea (12 patients; 42.9%), and mucosal inflammation and epistaxis (both 11 patients; 39.3%). A causal relationship with study drug administration was most frequently reported for: diarrhoea (26 patients; 92.9%), asthenia and rash (both 16 patients; 57.1%), and mucosal inflammation (11 patients; 39.3%). The most common grade 3 treatment-emergent AEs were diarrhoea, asthenia and rash (all 5 patients; 17.9%), and mucosal inflammation and acne (both 4 patients; 14.3%). Treatment-emergent grade 4 AEs comprised diarrhoea, depression, and altered mood (all 1 patient; 3.6%); only the grade 4 diarrhoea was considered related to the study treatment. Treatment-emergent grade 5 AEs comprised disseminated intravascular coagulation, malignant neoplasm progression, and neoplasm progression (all 1 patient; 3.6%), none of which were considered related to the study treatment.

As AEs of diarrhoea and skin toxicity are frequently associated with treatment with BIBW 2992 and other EGFR tyrosine kinase inhibitors, these events were subject to more in-depth exploratory analysis. This analysis identified the first onset of treatment-related diarrhoea as usually being within the 7 days after the start of therapy. Most patients required antidiarrhoeal treatment, with approximately 10% to 40% of patients in the different dose groups discontinuing study treatment as a result of diarrhoea.

Safety results (continued):

Adverse events indicative of rash were pooled, to ensure that such events were not underestimated due to consideration under different preferred terms. The analysis identified rash as occurring in more than 80% of patients in the different dose groups, with all cases of treatment emergent rash being drug-related; patients receiving the higher BIBW 2992 starting doses were more likely to experience CTCAE grade 3 rash. The first onset of treatment-related rash was usually within 7 days of the start of therapy for patients in the 50 mg and 40 mg BIBW 2992 dose groups, but for patients in the 30 mg starting dose group the time to first onset was usually 8 to 14 days. Most patients required treatment for rash. Patients in the higher BIBW 2992 starting dose groups were more likely to require dose reduction or to permanently discontinue study treatment as a result of rash.

Fourteen patients (50.0%) experienced treatment-emergent AEs that led to study discontinuation. The most frequent treatment-emergent AEs necessitating treatment discontinuation comprised diarrhoea (8 patients; 28.6%), asthenia (4 patients; 14.3%), and mucosal inflammation and rash (both 3 patients; 10.7%).

Three patients (10.7%) experienced treatment-emergent AEs leading to death, but none were considered drug-related. Nine patients (32.1%) experienced treatment-emergent serious adverse events (SAEs), with the most common being vomiting and dehydration (both 2 patients, 7.1%). Gastrointestinal SAEs, dehydration, renal failure, mucosal inflammation, asthenia, bacterial arthritis, and pneumococcal sepsis were considered related to the study treatment. Two patients experienced SAEs during the post-study period comprising febrile bone marrow aplasia with general physical health deterioration and breast cancer with dyspnoea; none of the events were considered related to the study drug but the general physical health deterioration and breast cancer were fatal.

Treatment-emergent other significant AEs were observed in 12 patients (42.9%), and were associated with either treatment discontinuation or dose reduction; the most common other significant AEs comprised diarrhoea (8 patients; 28.6%), asthenia (4 patients 14.3%), and rash (3 patients; 10.7%).

Safety results (continued):	Grade 3 or 4 changes in laboratory parameters were only seen for potassium and sodium levels, and occurred in the 50 mg and/or 40 mg BIBW 2992 starting dose groups. Clinical laboratory evaluations showed some patients to experience potentially clinically significant changes in laboratory parameters, with the most common being decreased haematocrit and red blood cell count (both 4 of 24 patients), increased blood urea nitrogen and decreased potassium (both 3 of 24 patients), and decreased haemoglobin (2 of 24 patients). No clinically relevant changes in vital sign parameters or left ventricular function were seen during the trial.
Conclusions:	BIBW 2992 administered with letrozole showed the ability to induce disease stabilisation when treating patients with estrogen receptor-positive metastatic breast cancer who had previously progressed on letrozole monotherapy; 14.29% of patients were progression-free at or after 16 weeks of treatment. There was no indication of a drug-drug interaction between BIBW 2992 and letrozole (when compared with the literature data). BIBW 2992 pharmacokinetic parameters showed dose proportionality during concomitant administration with letrozole and were comparable to those seen during BIBW 2992 monotherapy. The safety profile of BIBW 2992 with letrozole was consistent with that seen in phase I BIBW 2992 monotherapy studies, with toxicity primarily comprising diarrhoea and skin events; however, during BIBW 2992 combination therapy with letrozole skin events appeared to occur with greater intensity. Administration of 30 mg BIBW 2992 daily with daily letrozole minimised the impact of cutaneous adverse events and allowed patients to remain on treatment for as long as they experienced clinical benefit.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide the results of additional secondary endpoints, as summarised below.

Results for	**presented in**
Progression-free survival	Table 15.2.4: 1
Time to death (overall survival)	Table 15.2.4: 1
Time to and duration of objective response	Not presented, because results could not be calculated (none of the patients had objective response)

Table 15.2.4: 1 Time to event - treated set

	BIBW 50mg	BIBW 40mg	BIBW 30mg
Number of patients	7	13	8
Progression free survival* [days]			
Number of patients at risk	7	13	8
Number of censored patients [N(%)]	2 (28.6)	6 (46.2)	1 (12.5)
Median (95% CI)	60.00 (51.0, 443.0)	107.00 (44.0, 163.0)	79.00 (21.0, 230.0)
(P25, P75)	(51.00, 274.00)	(65.00, 116.00)	(51.00, 230.00)
Time to death [days]			
Number of patients at risk	7	13	8
Number of censored patients [N(%)]	6 (85.7)	11 (84.6)	6 (75.0)
Median (95% CI)	(208.0,)	(288.0,)	(137.0,)
(P25, P75)			(414.00,)

* According to RECIST criteria