Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2006-002018-36	
Name of active ingredient: BIBW 2992		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis Date: 31 JUL 2013	**Trial No. / U No.:** 1200.10/U10-1598-01	**Dates of trial:** 01 DEC 2006 – 20 MAY 2009	**Date of revision:** Not applicable

Title of trial:	An open-label phase II trial to assess the efficacy and safety of a once daily oral dose of 50 mg BIBW 2992 in two cohorts of patients with HER2-negative metastatic breast cancer after failure of no more than two chemotherapy regimen
Coordinating Investigators:	[redacted]
Trial sites:	Multicentre trial: 13 centres in Germany and Belgium.
Publication (reference):	Harbeck N, Schmidt M, Harter P, et al. 32nd CTRC-AACR San Antonio Breast Cancer Symp, San Antonio, 9 - 13 Dec 2009 (Poster) (P10-01992) Schuler MH, Uttenreuther-Fischer MM, Piccart-Gebhart MJ, Harbeck N. 46th Ann Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 4 - 8 Jun 2010. J Clin Oncol 28 (Suppl), 130S, Abstr 1065 (2010) (P10-07071)
Clinical phase:	II
Objectives:	To evaluate objective response (complete response [CR], partial response [PR]) (Cohort B only), clinical benefit (CR, PR, stable disease [SD] for a minimum of 4 months) (Cohort A only), time to objective response, duration of objective response, time to progression, progression-free survival, overall survival, safety and pharmacokinetics (PK).
Methodology:	Open-label study, conducted in two cohorts: **Cohort A**: Patients with human epidermal growth factor 2- (HER2-) negative, oestrogen receptor- (ER-) negative, progesterone- (PgR-) negative tumours (triple negative tumours) **Cohort B**: Patients with HER2-negative, ER-positive and/or PgR-positive tumours
No. of subjects:	
planned:	Approximately 48 enrolled; 40 entered in each cohort.

actual:	Enrolled: 56 patients (entered and treated 50 patients) **Cohort A**: entered and treated: 29; analysed (for primary endpoint): 29 **Cohort B**: entered and treated: 21; analysed (for primary endpoint): 21
Diagnosis and main criteria for inclusion:	Female patients (age ≥18 years) with a confirmed diagnosis of HER2-negative Stage IV metastatic breast cancer who had failed or relapsed after no more than two lines of chemotherapy were to be included. Patients should not have received treatment with trastuzumab, epidermal growth factor receptor- (EGFR-) or EGFR/HER2-inhibitors prior to enrolment. Patients must have recovered from preceding anti-cancer therapy. Additional inclusion criteria for Cohort A: HR-negative patients. ER-status and PgR-status was assessed by immunohistochemistry (IHC). Evaluation of IHC was done by "Allred Score" with a cut off of 2/8, i.e. 3/8 representing a positive score. Patients in Cohort A also had to sign an informed consent form for pharmacogenetic analyses prior to analysis of EGFR and EGFR ligand overexpression on mRNA basis. Additional inclusion criteria for Cohort B: ER-positive and/or PgR-positive patients. ER-status and PgR-status were assessed by IHC. Evaluation of IHC was done by "Allred Score" with a cut off of 2/8, i.e. 3/8 representing a positive score.
Test product:	BIBW 2992 tablets
dose:	Starting dose 50 mg once daily continuously
mode of admin.:	Oral
batch no.:	5 mg: B050205, B061001815, B071001102, B081002924 20 mg: B061000422, B061000905, B071001147, B081002939
Reference therapy:	None
Duration of treatment:	Continuous treatment, in the absence of clinical disease progression or treatment-related toxicity requiring discontinuation from trial, unacceptable non-compliance or withdrawal of consent.

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Criteria for evaluation:

Efficacy/clinical pharmacology:	Objective response (CR, PR) (Cohort B), clinical benefit (CR, PR, or SD for a minimum of 4 months) (Cohort A), time to objective response, duration of objective response, time to progression, progression-free survival (PFS), overall survival, and Eastern Cooperative Oncology Group (ECOG) status. BIBW 2992 plasma concentrations and serum biomarker levels were also evaluated.
Safety:	Adverse Events (AEs) according to common terminology criteria for adverse events (NCI CTCAE v 3.0), laboratory evaluations, vital signs, electrocardiogram (ECG), echocardiography, multigated acquisition scan (MUGA), and cardiac left ventricular function.
Statistical methods:	Descriptive statistics were used for most of the efficacy parameters. Kaplan-Meier estimation and Greenwood's estimate variance were to be used for analysis of PFS. Safety parameters were evaluated descriptively.

SUMMARY – CONCLUSIONS:

Efficacy/clinical pharmacology results:

A stopping rule was built into the protocol that allowed recruitment to be stopped in the respective cohorts if efficacy was not seen. As such, Cohort A was extended to full accrual after clinical benefit (CR + PR + SD) for a minimum of four months was observed in 3 of the initial 20 patients treated, in line with the protocol stopping rules. However, recruitment into Cohort B was stopped early after 21 patients had been treated, as an objective response was not observed in this set of patients (the stopping criteria for Cohort B specified that at least one objective response needed to be documented). Recruitment into Cohort A was eventually stopped early due to poor recruitment and many competing trials, with 29 patients recruited.

Three patients in Cohort A (10.3%) achieved the primary endpoint of a clinical benefit for a minimum of four months. No patients achieved an objective response. Time to and duration of response could therefore not be analysed. Likewise, no patients in Cohort B achieved the primary endpoint of objective response (CR + PR). However, 1 patient (4.8%) experienced clinical benefit for a minimum of four months.

Efficacy/clinical pharmacology results (continued):	In Cohort A, the median PFS for all patients was 52 days (95% CI: 39 to 71 days). For the 3 patients who had clinical benefit the median PFS was 184 days (range 132 to 335 days). In Cohort B, the median PFS for all patients in this group was 54 days (95% CI: 50 to 112 days). The only prognostic factors that were seen to have an effect on PFS in Cohort A were cytokeratin 5_6 and cytokeratin 5_14, with patients with negative results at baseline having longer PFS times, on average, than those with positive results. It should be noted that the difference was not of statistically significance, although it is of note in a trial of this size. In Cohort A during the course of the study, the ECOG performance score improved in 1 patient (3.4%) and deteriorated in 15 patients (51.7%) and in Cohort B, the ECOG performance score did not improve in any patients and deteriorated in 13 patients (61.9%). In the remainder of the patients the scores either remained unchanged or the changes were unknown. There were no obvious differences in BIBW 2992 plasma concentrations between patients in Cohort A and B (both using a 50 mg dose). Plasma concentrations at steady state were increased in comparison to the single dose data, suggesting a slight accumulation after multiple dosing of BIBW 2992. Steady state was reached at the latest by Day 14 at the latest (the first assessment point) and pre-dose plasma concentrations remained stable over the observed treatment periods. The overall variability for the pre-dose plasma concentrations at steady state for patients who received the 50 mg dose was moderate to high, with gCV values of 32% to 173%. BIBW 2992 plasma concentrations decreased with decreasing doses, as indicated by the comparison of the gMean plasma concentration profiles of the 50 mg dose and the patients who were reduced to 40 mg.
Safety results:	BIBW 2992 showed a manageable safety profile in this trial. All of the patients had at least one AE during the study, with most AEs (96.0%) being considered drug-related by the investigators. The main AEs were diarrhoea (reported by 92.0% of patients), nausea and rash (both reported by 40.0% of patients). The most common dose reduction toxicity AE was also diarrhoea, which was reported by 44.0% of patients (44.8% in Cohort A and 42.9% in Cohort B).

Safety results (continued):	Out of all of the patients with AEs, 1 patient (2.0%) had a maximum graded AE of Grade 1, 13 patients (26.0%) had a maximum graded AE of Grade 2, 28 patients (56.0%) had Grade 3, 3 patients (6.0%) had Grade 4, and 5 patients (10.0%) had Grade 5. Twenty patients (40.0%) had at least one SAE, with the SAEs being fatal in 5 patients (4 in Cohort A and 1 in Cohort B). One fatal SAE was considered drug-related: general physical health deterioration (related to drug-related diarrhoea) was reported in Patient [redacted]. In addition, Patient [redacted] developed acute renal failure 29 days after the end of the study which was considered causally related to the study drug by the investigator (patient was on doxorubicin at the time of the event and developed acute renal failure 2 days after the start of the doxorubicin infusion). The patient died from the event. Fifteen patients (51.7%) in Cohort A and 15 patients (71.4%) in Cohort B had dose reduction toxicity AEs, and 23 patients (46.0%) overall discontinued permanently from the study due to AEs. No changes indicative of an adverse effect of BIBW 2992 was seen on any laboratory parameters, vital signs or ECG parameters.
Conclusions:	Some patients achieved a clinical benefit (CR + PR + SD) for a minimum of four months (primary endpoint for Cohort A): 3 (10%) patients with triple negative (Cohort A) and 1 (5%) patient with HER2-negative, HR positive metastatic breast cancer (Cohort B). However, no patients achieved an objective response (primary endpoint for Cohort B). The median PFS in Cohort A was 52 days and the median PFS in Cohort B was 54 days. BIBW 2992 plasma concentrations decreased when dose reductions were performed (as allowed by the protocol). Steady state was reached at the latest at Day 14, and pre-dose plasma concentrations remained stable over the observed treatment periods.

Conclusions (continued): Diarrhoea was the most common toxicity in this study, occurring in 92% of patients and leading to dose reduction in almost half the patients, with 24% of patients permanently discontinued from the study due to diarrhoea. Despite the treatment discontinuations due to diarrhoea, BIBW 2992 side effects overall were manageable. Early implementation of treatment algorithms and timely treatment of BIBW 2992 related AEs may help to prevent AE associated treatment discontinuations in the future.

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**
Time-to-event analyses (PFS and OS)	Table 15.2.3: 1
Significant changes in LVEF values	Table 15.3.4: 3

Table 15.2.3: 1 Summary of time-to-event - treated set

Variable	Cohort A	Cohort B
Number of patients treated	29	21
PFS (investigator + clin. prog.)		
Number of patients evaluated	29	21
Median [days]	52	54
(P25, P75) [days]	(36, 103)	(50, 112)
95% CI [days]	39 to 71	50 to 112
Patients censored [N(%)]	1 (3.45)	3 (14.3)
Overall survival		
Number of patients evaluated	29	21
Median [days]		448
(P25, P75) [days]	(58,)	(310, 537)
95% CI [days]	120 to inf.	310 to 537
Patients censored [N(%)]	20 (69)	15 (71.4)

Table 15.3.4: 3 Patients with a significant change in LVEF values - treated set

Treatment group	Patient	Visit	Date of assessment	Method used for assessment	LVEF [%]		Lower limit of normal [%]
Cohort A	115	Screening	09JUL2008	Echocardiogram	70		50
		EOT	20AUG2008	Echocardiogram	56	*	50
Cohort B	112	Screening	09AUG2007	Echocardiogram	78		50
		C3_V1	08NOV2007	Echocardiogram	53	*	50
	123	Screening	30OCT2007	Echocardiogram	60		50
		C3_V1	27DEC2007	Echocardiogram	61		50
		EOT	22FEB2008	Echocardiogram	45	*	50

* significant change in LVEF values: >=20% decrease from baseline OR to below LLN (50% as LLN if not available)

Source data: Appendix 16.2.8, Listing 14 ch_15\et_lvef.sas 21JUN2010