Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.:** 2007-04805-80	
Name of active ingredient: Afatinib (BIBW 2992)		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: Final – 07 Dec 09	**Trial No. / Doc No.:** 1200.11/ c01950387-07	**Dates of trial:** 06 Nov 2006 – 28 Aug 2009	**Date of revision:** 12 Jun 2014

Title of trial:	Phase II trial of BIBW 2992 in patients with HER2-positive metastatic breast cancer after failure of trastuzumab therapy
Coordinating Investigator:	[redacted]
Trial sites:	Mulitcentre trial (6 centres in US and 6 in UK)
Publication (reference):	Hickish T, Wheatley D, Lin N, Carey L, Houston S, Mendelson D, et al. Use of BIBW 2992, a novel irreversible EGFR/HER1 and HER2 tyrosine kinase inhibitor to treat patients with HER2-positive metastatic breast cancer after failure of treatment with trastuzumab. 45th Ann Mtg of the American Society of Clinical Oncology (ASCO), Orlando, 29 May - 2 Jun 2009 (Poster) (P09-06705)
Clinical phase:	II
Objectives:	To evaluate objective response (complete response [CR], partial response [PR]) and stable disease (SD) rate, time to response, duration of response, time to progression, progression-free survival, overall survival, and safety.
Methodology:	Open-label study.
No. of subjects:	
planned:	Approximately 48 to be enrolled and 40 to be entered.
actual:	enrolled: 52; entered and treated: 41; evaluable: 34
Diagnosis and main criteria for inclusion:	Patients with a confirmed diagnosis of HER2-positive Stage IIIB or IV metastatic breast cancer whose disease progressed after standard treatment, including at least 6 weeks of standard dose trastuzumab. Patients should not have received treatment with chemotherapy, hormone therapy, or immune therapy within the last 4 weeks (2 weeks for trastuzumab) prior to enrolment. Patients must have recovered from preceding anti-cancer therapy.
Test product:	BIBW 2992 tablets
dose:	Starting dose 50 mg once daily continuously
mode of admin.:	Oral

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batch no.:	5mg: B071001102, B081002924, B063000229, B073000759, B073000608, B083001062, B063000334 20mg: B071001145, B081002940, B063000230, B073000760, B073000606, B083001063, B063000333
Reference therapy:	None
Duration of treatment:	Continuous treatment in the absence of clinical disease progression or treatment-related toxicity requiring discontinuation from trial, or withdrawal of consent.
Criteria for evaluation:	
Efficacy/clinical pharmacology:	Objective response (CR, PR), time to response, duration of response, progression-free survival, overall survival, maximum percentage decrease in the sum of tumour diameters, disease control (CR, PR, SD), Eastern Cooperative Oncology Group (ECOG) patient performance score, and quality of life (QOL) assessment. 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), laboratory evaluations, vital signs, cardiac left ventricular function, and electrocardiogram (ECG) assessment.
Statistical methods:	Descriptive statistics, calculation of objective response rate with 95% confidence intervals, Kaplan-Meier estimation.
SUMMARY – CONCLUSIONS:	
Efficacy/clinical pharmacology results:	Disposition and demographics: Of the 41 patients treated in the trial, 30 patients (73.2%) discontinued due to progression of disease, 9 patients (22.0%) discontinued due to other AEs, and 2 patients (4.9%) discontinued due to other reasons. All of the patients were female, the mean age was 54.1 years (sd 13.5 years), and 39 patients (95.1%) were White. Efficacy results: Four patients in the treated set (10%) met the primary endpoint of an objective response (all patients achieving PR; no patients achieved CR). In addition, 15 patients (37%) maintained stable disease, with 9 patients (22%) having a decrease in tumour size that did not meet the 30% threshold for PR. The mean duration of objective response was 153.3 days and the mean duration of clinical benefit was 156.6 days. The median progression-free survival was

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Efficacy/clinical pharmacology results (continued):	106 days and median overall survival was 427 days. The mean time to response was not calculated since only 4 patients had objective response. There was no clear association between most baseline biomarkers and subsequent response to BIBW 2992, with the exception that patients who achieved PR showed a smaller mean increase from baseline in CA 15-3 compared to patients whose best response was SD or PD, and patients who achieved PR showed a larger mean increase from baseline in HER2/neu via ELISA from compared to patients whose best response was SD or PD. ECOG status improved during the study in 24 patients (60.0%), remained stable in 15 patients (37.5%) and only deteriorated in 1 patient (2.5%). Assessment of overall QOL showed an improvement in 15 patients (38.5%), remained stable in 18 patients (46.2%) and deteriorated in 5 patients (12.8%). In particular, fatigue, insomnia, and pain were seen to improve following treatment with BIBW 2992, although diarrhoea was noted to have deteriorated. QOL assessed using the more specific breast cancer BR-23 questionnaire showed improvements in future perspective, arm symptoms, and sexual functioning, although the category 'systematic therapy' was noted to have deteriorated. Pharmacokinetic results: BIBW 2992 plasma concentrations slightly accumulated after multiple dosing. Steady state seemed to be reached at latest at Day 15 and pre-dose plasma concentrations appeared to remain stable over the observed treatment periods. The overall variability was moderate to high, with gCV values of 67.9 to 138%. BIBW 2992 plasma concentrations increased with increasing doses, as indicated by the comparison of the gMean plasma concentration profiles of the 40 mg and 50 mg dose groups.
Safety results:	BIBW 2992 showed an acceptable safety profile in this trial. All of the patients had at least one AE during the study, with all but one patient having AEs that were considered drug-related by the investigators. The main toxicities were diarrhoea (reported by 90.2% of patients) and skin disorders, primarily rash (reported by 85.4% of patients), reflecting the known safety profile of other EGFR inhibitors where gastrointestinal effects and skin rash have been noted. Further preferred terms that were reported for more than one third of patients were fatigue and nausea (46.3% for each event), vomiting (41.5%), and stomatitis (36.6%). All the drug-related AEs were Grade 3 or lower; no Grade 4 or 5 drug-related AEs were reported.

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Safety results (continued):	Details of the deaths of 14 patients were recorded. None of the patients died during treatment with the study drug and one patient died during the 28-day follow-up period after the end of treatment. For 6 patients disease progression was documented at last contact prior to death, and for 8 patients no progression or no status of disease was documented at last contact. No reports of BIBW 2992-related deaths were received. Eight patients (19.5%) had at least one SAE during the study or within the 28-day follow-up period, with the SAE being fatal in 1 patient during the 28-day follow-up period (recorded as malignant neoplasm progression). The most common SAE was vomiting, which was reported in 3 patients. Five patients (12.2%) had SAEs that were considered drug-related by the investigators, with the only drug-related SAEs to be reported in >1 patient being vomiting (reported in 3 patients) and dehydration (reported in 2 patients). All patients started on a 50 mg dose but 20 patients (48.8%) had their dose reduced to 40 mg (primarily due to gastrointestinal AEs), and 6 patients (14.6%) had a further reduction from 40 mg to 30 mg. Only 10 patients discontinued treatment permanently due to an AE, indicating that most AEs could be managed by dose reductions. The only AEs that led to discontinuation in > 1 patient were diarrhoea (4 patients) and rash (2 patients). No changes indicative of an adverse effect of BIBW 2992 was seen on any laboratory parameters, vital signs or ECG parameters, although it should be noted the variability was high.
Conclusions:	In this proof-of concept study in patients with HER2-positive metastatic breast cancer after failure of trastuzumab therapy, BIBW 2992 showed promising efficacy. Overall 46% of patients obtained some clinical benefit, and 4 patients (10%) achieved a partial response. Some improvements in quality of life were also seen. BIBW 2992 plasma concentrations increased with increasing doses, steady state seemed to be reached at latest at Day 15 and pre-dose plasma concentrations appeared to remain stable over the observed treatment periods. Approximately half the patients experienced drug-related diarrhoea or skin disorders at the starting dose of 50 mg that required dosage reduction, in line with the known safety profile of other EGFR inhibitors. However, most patients were able to continue BIBW 2992 treatment at a reduced dosage, with only 6 patients (15%) permanently discontinuing treatment due to diarrhoea or skin disorders.