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**.

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| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:**<br>Not applicable | | **EudraCT No.:**<br>2008-001546-67 | |
| **Name of active ingredient:**<br>Afatinib (BIBW 2992) | | **Page:**<br>1 of 13 | **Synopsis No.:** |
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| **Disclosure synopsis date:**<br>27 SEP 2013 | **Trial No. / U No.:**<br>1200.41 / U13-3576-01 | **Date of trial:**<br>16 JUN 2008 – 19 JUN 2012 | **Date of revision:**<br>Not applicable |



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| **Title of trial:** | A Phase II single-arm trial of BIBW 2992 in demographically and genotypically selected non-small cell lung cancer patients |
| **Coordinating Investigator:** | [redacted] |
| **Trial sites:** | Six investigative sites in Belgium and one investigative site in Spain enrolled patients. |
| **Publication (reference):** | Greve J de, Teugels E, Mey J de, in 'tveld P, Decoster L, Schallier D, et al. Clinical activity of BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2 in adenocarcinoma of the lung with mutations in the kinase domain of HER2neu. 13th World Conf on Lung Cancer, San Francisco, 31 Jul - 4 Aug 2009 (Oral Presentation).<br><br>Greve J de, Teugels E, Mey J de, in 'tVeld P, Decoster L, Schallier D, et al. Clinical activity of BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2 in adenocarcinoma of the lung with mutations in the kinase domain of HER2/neu. Joint ECCO 15 - 34th ESMO, Biennial Multidisciplinary Cong of the European Cancer Organisation and European Society for Medical Oncology, Berlin, 20 - 24 Sep 2009 (Poster)<br><br>Greve J de, Teugels E, Geers C, Mey J de, in 'tveld P, Decoster L, et al. Activity of BIBW 2992, an irreversible inhibitor of EGFR and HER2, in adenocarcinoma of the lung with HER2neu kinase domain mutations. Eur J Cancer. 45(7), 555 - 6, Abstr 9166 (2009).<br><br>Greve JL de, Teugels E, Mey J de, Geers C, Galdermans D, Decoster L, et al. Clinical activity of BIBW 2992, an irreversible inhibitor of EGFR and HER2 in adenocarcinoma of the lung with mutations in the kinase domain of HER2neu. 13th World Conf on Lung Cancer, San Francisco, 31 Jul - 4 Aug 2009. J Thorac Oncol. 4(9)(Suppl 1), S307, Abstr A6.7 (2009).<br><br>Greve J de, Decoster L, Mey J de, in't Veld P, Geers C, Taton M, et al. Clinical activity of BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2 in adenocarcinoma of the lung with mutations in the kinase domain of HER2/neu. 2nd Eur Lung Cancer Conf, Geneva, 28 Apr - 1 May 2010 (Poster). |

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| **Publication (reference): (continued)** | De Grève J, Teugels E, Geers C, Decoster L, Galdermans D, Mey J de, et al. Clinical activity of afatinib (BIBW 2992), an irreversible inhibitor of EGFR/HER1 and HER2 in adenocarcinoma of the lung with mutations in the kinase domain of HER2/neu.<br>De Grève J, Teugels E, Geers C, Decoster L, Galdermans D, De Mey J, et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer 2012;76(1):123-7. Fourth Latin American Conference on Lung Cancer, 28–30 July 2010, Buenos Aires, Argentina. Abstract PD.8 and poster. |
| **Clinical phase:** | II |
| **Objectives:** | The primary objective of this open-label, single arm Phase II trial was to explore the efficacy of afatinib defined by the objective response rate (complete response [CR] or partial response [PR]) as determined by the RECIST criteria (version 1.0) in patients with advanced NSCLC Stage IIIB or IV whose tumours harboured activating mutations within exon 18 to exon 21 of the epidermal growth factor receptor (EGFR), in patients with mutations in the HER2/neu receptor, and in patients with EGFR FISH positive tumours with no EGFR mutations. |

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**Methodology:**

This was a multicentre, open-label, single-arm clinical trial designed to investigate the efficacy of afatinib in the treatment of patients with pathologically confirmed diagnosis of NSCLC Stage IIIB or IV with the histology of adenocarcinoma or bronchoalveolar carcinoma whose tumours were genotypically defined as harbouring exon 18 to exon 21 EGFR mutations, were fluorescent *in-situ* hybridization (FISH) positive with no mutation, or had HER2 mutations. All patients were to have biopsy samples available and the EGFR mutation and/or FISH status and/or HER2 mutation was determined, as applicable, in all patients prior to start of treatment with afatinib. This trial included 3 cohorts of patients:

Cohort 1: Patients with EGFR mutation positive tumours who had failed treatment (disease progression, no response) with a reversible EGFR tyrosine kinase inhibitor (TKI)

Cohort 2: Patients with EGFR FISH positive and EGFR mutation negative tumours who had received up to three lines of chemotherapy (including adjuvant) and were EGFR TKI naive

Cohort 3: Patients with HER2 mutation positive tumours, independent of the nature and extent of prior treatments

Patients with both an EGFR or HER2 mutation and EGFR FISH positive tumour were included in the respective mutation positive cohort.

It was planned to obtain at least one Response Evaluation Criteria in Solid Tumours (RECIST) assessment for all patients who received at least one course of therapy. This included patients who discontinued treatment because of adverse events (AEs), disease progression, or for any other reason. The assessment was to be performed as closely as possible to four weeks, but not earlier than three weeks, after the start of treatment. Patients were treated with afatinib monotherapy until disease progression of intolerance.

The patients attended visits at the investigative sites according to the protocol-specified schedule for determination of safety laboratory parameters, recording of AEs, and additional investigations. Tumour evaluation was performed at screening and thereafter every eight weeks (i.e., every two courses of treatment) and at end of treatment. Tumour response was assessed using RECIST, version 1.0. Patients benefiting from afatinib monotherapy were eligible to receive combination therapy comprised of afatinib plus paclitaxel chemotherapy upon progression, at the discretion of investigator.

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**No. of subjects:**

**planned:** entered: Up to 40 patients (approximately 35 total in Cohorts 1 and 2; approximately 5 in Cohort 3)

**actual:** Total screened (enrolled): 82

Total entered: 41

Total treated:

Afatinib monotherapy - 50 mg afatinib starting dose: entered/treated/ analyzed (efficacy and safety): 41

- EGFR mutation positive cohort - entered/treated/ analyzed: 32
- EGFR FISH positive cohort - entered/treated/ analyzed: 2
- HER2 mutation positive cohort - entered/treated/ analyzed: 7

Combination therapy - : entered/treated/ analyzed (efficacy and safety): 8

**Diagnosis and main criteria for inclusion:** Patients with confirmed NSCLC Stage IIIB or Stage IV (adenocarcinoma or bronchoalveolar carcinoma) and at least 1 measurable lesion whose tumours harboured exon 18 to exon 21 EGFR mutations (Cohort 1) or EGFR FISH positive with no EGFR mutation (Cohort 2) or HER2-neu mutations (Cohort 3) were eligible for participation. Patients who had both an EGFR FISH positive tumour and either an EGFR or HER2 mutation were to be included in the respective Cohort 1 or 3. All patients may have had up to 3 prior cytotoxic chemotherapy regimens for treatment of relapsed or metastatic NSCLC. In addition, patients in Cohort 1 must have had progressive disease following treatment with a reversible EGFR TKI and patients in Cohort 2 must not have received prior treatment with an EGFR TKI; no restrictions on prior TKI use were specified for Cohort 3. Patients with active brain metastasis were excluded. All patients must have had biopsy samples available for mutation and FISH analysis prior to start of treatment with afatinib; local results were also acceptable.

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| **Test product:** | Afatinib, supplied as 30-mg and 20-mg film-coated tablets. |
| **dose:** | Starting dose of afatinib 50 mg once daily as monotherapy or afatinib 40 mg once daily in combination with paclitaxel. Dose reductions based on protocol-specified adverse-event (AE) management criteria were permitted. Patients may have been administered reduced doses of 40 mg, 30 mg, or 20 mg for monotherapy or 30 mg or 20 mg in combination with paclitaxel. Dose reductions to 20 mg were only permitted in patients having clinical benefit from the treatment but for whom a reduction to 20 mg due to AEs was deemed necessary by the investigator and was done so in agreement with the Boehringer Ingelheim Clinical Monitor. |
| **mode of admin.:** | Oral, once daily continuous dose afatinib |
| **batch no.:** | Multiple batch numbers were assigned |
| **Reference therapy:** | Paclitaxel concentrate for intravenous administration (6 mg/mL unit strength); as sourced by the investigator. |
| **dose:** | 80 mg/m² in combination with afatinib. Dose reduction to 70 mg/m² were permitted for management of paclitaxel-associated AEs |
| **mode of admin.:** | Intravenous; weekly x 3 (Days 1, 8, 15) in a 4-week course. |
| **batch no.:** | Source as used by investigator |
| **Duration of treatment:** | For afatinib as monotherapy or combination therapy, continuous daily dosing, one course consisted of 28 days. For afatinib monotherapy, patients were eligible for repeated treatment courses in the absence of disease progression and intolerance. Patients with disease progression experiencing clinical benefit were offered the option to continue afatinib in combination with paclitaxel. For combination therapy, duration of the treatment was at the investigator's discretion in the absence of clinical disease progression and undue AEs. |

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| **Criteria for evaluation:** | |
| **Efficacy / clinical pharmacology:** | **Efficacy**<br>Primary: Confirmed objective response according to RECIST (version 1.0).<br>Secondary: Disease control rate (DCR), and progression-free survival (PFS).<br>**Pharmacokinetics**<br>Evaluation of afatinib plasma concentrations during afatinib monotherapy. |
| **Safety:** | Incidence of AEs, graded according to National Cancer Institute (NCI) common terminology criteria for AEs (CTCAE; Version 3.0)<br>AEs of special interest (diarrhoea, grouped terms of rash/acne+, fatigue+, stomatitis+, nail effect+, ocular effect+, and lip effect+, indicated as "term(s)+")<br>Laboratory evaluations, left ventricular ejection fraction (LVEF), and 12- lead electrocardiogram (ECG), and vital signs |
| **Statistical methods:** | Calculated objective response rate with exact 95% confidence interval (CI), display of maximum percent change in target lesion, Kaplan-Meier estimate of PFS; descriptive statistics for all other endpoints during afatinib monotherapy and combination therapy. The PK analysis performed for this study was descriptive. |

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**SUMMARY – CONCLUSIONS:**

**Efficacy / clinical pharmacology results:**

*Efficacy*

Due to the small sample size overall and in two of the three tumour cohorts, meaningful comparisons of DCRs, PFS, or other clinical measures between cohorts are difficult.

Of the 41 patients treated with afatinib, 63% were female and 98% were White. The median age of patients was 63.0 years (min 29; max 81). Patients were either never smokers (68%) or ex-smokers (32%). All but one patient had adenocarcinoma as the predominant NSCLC histology, and, at the time of diagnosis, most patients had Stage IIIb (nonmetastatic, 17%) or IV (metastatic, 63%) disease. By the time patients were screened for the study, 98% of the patients had metastases. The median time since diagnosis was 20.37 (range: 2.4 to 92.9) months.

EGFR mutations (mutations in exons 18 through 21) were identified in 35 tumour samples; gene amplification or high polysomy of the EGFR gene (i.e., FISH positive) was present in 7 tumour samples, and HER2 mutations were identified in 7 tumour samples. Considering both the tumour status and the patient's previous chemotherapy history, patients who qualified for the FISH positive cohort but who also had a mutation in EGFR or HER2 would be entered in the respective EGFR or HER2 cohort. Patients were assigned to the respective cohorts by the investigators as follows: 32 patients in the EGFR mutation positive cohort, two patients in the EGFR FISH positive cohort, and seven patients in the HER2 cohort.

Efficacy analyses included the three separate cohorts as described previously. For the primary endpoint, objective response rate for the entire trial population (representing the three distinct cohorts) was 2% based on 1/41 patients achieving a confirmed PR. In addition 23/41 (56%) patients achieved stable disease (SD; confirmed). No CRs were observed in any cohort.

**Efficacy / clinical pharmacology results (continued):**

In the EGFR mutation positive cohort, responses were seen, 53% of patients (17/32) achieved SD (16 confirmed and 1 unconfirmed). In the EGFR FISH positive cohort, 1 of the 2 patients achieved a confirmed PR by week 8. Duration of response was 40.1 weeks. Tumour genomic testing confirmed that this patient's tumour was negative for both EGFR and HER2 mutations and FISH positive for EGFR. This patient had a best prior response of SD on cisplatin/gemcitabine, which was the only previous systemic therapy this patient had received. In the HER2 positive cohort, 5/7 (71%) patients had SD. Although no ORs were observed in this cohort, one patient [redacted] had an unconfirmed PR (target tumour shrinkage of 31.7%), and three other patients had meaningful target tumour shrinkage (20.3%, 15.3% and 13.4%). Three of the patients with an HER2 mutation in their tumour had major transient tumour responses that however did not fully qualify as confirmed partial remissions as defined by RECIST.

The best objective response rate (CR or PR) in the overall trial population regardless of confirmation was 7% based on three patients (one patient who with confirmed PR [as previously noted] and two patients with unconfirmed PR). The one patient who achieved confirmed PR was appropriately assigned to the EGFR FISH positive cohort. The two patients with unconfirmed PRs were one patient who was assigned to the HER2 mutation positive cohort and one patient who was assigned to the EGFR mutation positive cohort.

The DCR using best confirmed RECIST tumour assessments for the overall trial population was 59% (24/41 patients). Within the three cohorts, DCR (also confirmed) was achieved in 53% of patients (17/32) in the EGFR mutation positive cohort, 100% of patients (2/2) in the EGFR FISH positive cohort, and 71% of patients (5/7) in the HER2 mutation positive cohort. The mean (StD) duration of disease control was 25.6 (19.1) weeks and ranged from 9.1 to 97.3 weeks.

Baseline and post-baseline tumour measurement data for target lesions were available for 31/41 (76%) patients in the afatinib monotherapy treated set. The majority of those patients (18/31 [58%)] had reductions in tumour size.

**Efficacy / clinical pharmacology results (continued):**

In the overall trial population, 39/41 (95%) patients experienced a PFS event and the median PFS was 15.86 weeks (95% CI: 8.14 to 19.14 weeks), i.e., 3.65 months. The probability of being alive and progression-free was 47% at Week 16, 18% at Week 24, and 3% at Weeks 56 through 96 (approximately one to two years). By assigned cohort, median PFS times in weeks (in months; patients meeting progressive disease criteria) were 14.57 (3.35; n = 31) in the EGFR mutation positive cohort, 34.36 (7.90; n = 2) in the EGFR FISH positive cohort, and 17.00 (3.91; n = 6) in the HER2 mutation positive cohort. Despite the relatively large differences in median PFS, no meaningful conclusions can be made due to the relatively low number of patients in each cohort.

Following disease progression on afatinib monotherapy, eight patients received combination therapy with afatinib and paclitaxel. Of those, one patient achieved confirmed PR (duration of response was 41.9 weeks) and two patients had confirmed SD (including one patient with unconfirmed PR). The DCR based on confirmed CR, PR, or SD was 38%.

All eight patients in the combination therapy group had a PFS event (median duration 6.71 weeks). Although the median PFS appears to be short, it is worth noting that this uncontrolled arm reflects a heavily pretreated population of patients with terminal cancer, and the sample size is too small to make definitive conclusions.

*Pharmacokinetics*

For the 50 mg dose group there was enough reliable data for calculation of the geometric mean (gMean) $C_{pre}$ values. Individual patient $C_{pre}$ values appeared to remain stable over the treatment periods. The inter-subject variability on $C_{pre}$ was high.

**Safety results:**

All 41 patients administered at least one dose of afatinib monotherapy were included in the analysis of safety. The median (range) overall duration of treatment with afatinib (all dose levels) was 11.29 weeks (0.7 - 94.9 weeks). The median (range) duration of afatinib monotherapy at the starting dose of 50 mg was 7.57 (0.7 to 94.9) weeks.

The AE profile was consistent with AEs observed in previous afatinib studies and the mechanistic effects of EGFR inhibitors. Adverse events marked with "+" indicate group terms. The most frequently reported AEs were diarrhoea (95%), rash/acne+ (83%), decreased appetite (56%), fatigue+ (51%), stomatitis+ (46%), nail effect+ (39%), cough (32%), dyspnoea and vomiting (29% for each event), nausea and ocular effect+ (27% for each event), and constipation, epistaxis, pruritus, and pyrexia (20% for each event). The majority of patients had AEs with a maximum grade of 3 or lower during afatinib monotherapy. Grade 3 events occurring in ≥ 10% of patients were diarrhoea (34%), fatigue+ (12%), and rash/acne+ (10%).

Although the incidence of Grade 3 diarrhoea appeared somewhat higher when compared to previous studies of afatinib monotherapy in NSCLC patients pre-treated with an EGFR TKI, most such events were non-serious and resolved with either dose reduction or discontinuation of afatinib. While other certain events were frequently reported (e.g., stomatitis+, other gastrointestinal events, and rash/acne+), patients were typically able to continue treatment. Besides diarrhoea, events under the grouped term of rash/acne+ were the only events that resulted in dose reduction of > 10% of patients (15%).

**Safety results (continued):**

Four of 41 (10%) patients in the afatinib monotherapy group had an AE leading to death that was consistent with malignant neoplasm progression and considered not related to study drug, which seems to be typical in this population with advanced and heavily pretreated NSCLC. Diarrhoea and concurrent dehydration were the only drug-related SAEs that occurred in two or more patients.

Laboratory findings were unremarkable for most patients with worst on-treatment values of Grade 3 reported infrequently and no Grade 4 laboratory values reported. Though there was a higher percentage of patients (27.5%) in this study who had possibly clinically significant abnormalities (PCSAs) of lymphopenia compared with previous studies, abnormal haematology values overall were rarely associated with a haematological AE (one patient had Grade 2 anaemia, and one patient each had Grade 1 anaemia and thrombocytopenia). None of the PCSAs for liver enzymes were AEs and none of them resulted in discontinuing the patients from treatment. All shifts in other biochemistry parameters (sodium, potassium, creatinine, creatinine clearance, and creatine kinase) were consistent with consequences of the GI side effects of afatinib.

No clinically important vital signs or cardiac (LVEF or ECG) findings were observed during the study.

Eight patients were administered at least 1 dose of afatinib in combination with paclitaxel and were included in the analysis of safety for combination therapy. While the sample size was too small to make definitive conclusions, no clinically important differences in safety findings were noted based on review of the safety findings during combination therapy as compared with safety findings during afatinib monotherapy.

**Conclusions:**

In this exploratory study evaluating the efficacy of afatinib in patients with distinct molecular profiles pertaining to EGFR and/or HER2, 32/41 patients were assigned to the cohort with EGFR mutation positive tumours, 2/41 to the cohort with EGFR FISH positive tumours, and 7/41 patients to the cohort with HER2 mutation positive tumours. Patients assigned to the EGFR mutation cohort were required to have been pretreated with an EGFR TKI, those in the EGFR FISH cohort though were required be have been EGFR TKI naive. Patients in the HER2 mutation cohort could have been treated with afatinib regardless of prior EGFR TKI use.

In this population of patients with advanced and heavily pretreated NSCLC, the small sample sizes, molecular heterogeneity, lack of a comparator, and differences in requirements for prior EGFR TKI treatment precludes comparison and definitive conclusions.

While in the overall trial population only one patient (2%) achieved a confirmed PR during afatinib monotherapy, a majority of patients (56%) achieved SD and the DCR for the overall trial population was 59% (confirmed). In the EGFR mutation positive cohort, although no objective responses were seen, 17/32 achieved SD for a DCR of 53%. In the EGFR FISH positive cohort, 1 of 2 patients achieved a confirmed PR and the second patient assigned to this cohort achieved SD for a DCR of 100%. In the HER2-positive cohort, although no objective RECIST responses were seen, 5/7 patients achieved SD for a DCR of 71%. Three of those patients achieved major transient tumour regressions amounting to partial remissions, but not fully qualifying as a partial RECIST response because of the duration of the responses. Overall, eighteen of 31 patients (58%) with tumour measurements had reductions in tumour size and 39/41 patients (95%) experienced a PFS event. All of these results were based on confirmed RECIST tumour assessments for best overall tumour response.

Median PFS for the overall population was 15.86 weeks (95% CI: 8.14 to 19.14 weeks), i.e., 3.65 months. The probability of being alive was 47% at week 16, 18% at week 24, and 3% at weeks 56 through 96. By assigned cohort, median PFS times in weeks (in months; patients meeting progressive disease criteria) were 14.57 (3.35; n=31) in the EGFR mutation positive cohort, 34.36 (7.90; n=2) in the EGFR FISH positive cohort, and 17.00 (3.91; n=6) in the HER2 mutation positive cohort. Despite the relatively large differences in median PFS, no meaningful conclusions can be made due to the relatively low number of patients in each cohort.

**Conclusion: (continued)**

Median PFS and disease stabilization observed in the EGFR TKI pretreated, EGFR mutation positive cohort in this trial are consistent with the results observed in previous Phase I to III studies and reiterate the role of afatinib in this refractory population. Patients in the HER2 mutation positive cohort represent a unique population with limited reported literature. Evidence of disease stabilization, transient response, and PFS observed in this study suggests that presence of HER2 mutations may characterize a subgroup of NSCLC patients whose tumours may constitutively be dependent on the HER2 pathway and worthy of further evaluation. Similarly, observation of a confirmed PR in the EGFR FISH positive cohort is notable for further consideration.

The safety data and the adverse event profile of afatinib in this trial are consistent with previous studies of the 50 mg starting dose of afatinib. Although the incidence of Grade 3 diarrhoea and the number of patients who discontinued treatment in this study due to diarrhoea appears higher when compared to previous studies with afatinib, it is worth noting that this trial included patients who were EGFR TKI naive. These events reiterate the importance of proactive medical management with appropriate concomitant therapies and dose reductions in reducing the incidence of Grade 3 events and treatment discontinuation.

Following disease progression on afatinib monotherapy, eight patients received combination therapy with afatinib and paclitaxel. Of these, one achieved confirmed PR and two had confirmed SD (including one patient with unconfirmed PR). The DCR based on confirmed CR, PR, or SD was 38%. All eight patients in the combination therapy group had a PFS event and the median PFS was 6.71 weeks. Although the median PFS appears to be short, it is worth noting that this uncontrolled arm reflects a heavily pretreated population of patients with terminal cancer, and the sample size is too small to make definitive conclusions. Moreover, one of these patients in the HER2 positive cohort had a prolonged disease control of several months and was on afatinib for a total of 15 months (4 months on monotherapy and 11 months in combination with paclitaxel).