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.

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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.:** 2008-006288-36	
Name of active ingredient: Afatinib (BIBW 2992)		**Page:** 1 of 9	**Synopsis No.:**
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Title of trial:	Phase II open label trial to assess the efficacy and the impact on QTcF of continuous oral BIBW 2992 at a daily dose of 50 mg in patients with relapsed or refractory solid tumours including patients with brain metastases and those with glioblastoma not amenable to other therapy
Coordinating Investigator:	[redacted]
Trial sites:	4 hospitals in the UK: Royal Marsden, Sutton; Guy's and St. Bartholomew's, London; and Royal County Surrey, Guildford
Publication (reference):	Data of this study has not been published.
Clinical phase:	II
Objectives:	To investigate the efficacy and safety of afatinib (BIBW 2992) monotherapy in patients with epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor (HER) 2-positive tumours with and without brain metastases, and in patients with recurrent glioblastoma.
Methodology:	Open label, single arm, multi-centre study consisting of a screening period (14 days to 1 day before start of study medication), followed by a treatment period, an end-of-treatment (EOT) visit (within 5 days after termination of trial drug), and a follow-up visit (28 ± 4 days after the EOT visit). During the treatment period, afatinib was to be administered continuously in courses each lasting 28 days. NOTE: Interim analyses were performed when electrocardiogram (ECG) data from the first 2 weeks of treatment were available for the last patient entered. Results for ECG (QTcF), adverse events (AEs), and pharmacokinetics (PK) using various database snapshots were included in an interim report dated 16 Sep 2010. This final report contains the results for ECG-related safety endpoints, results for efficacy based on tumour response, molecular determinants of response (biomarkers), fully updated PK and AE data, and other safety results.

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No. of subjects:		
planned:	entered:	60
actual:	enrolled:	71
	entered/treated: with afatinib:	60
	analysed:	49 (primary safety endpoint) 60 (all other safety endpoints and all efficacy endpoints) 60/44 (Day 1/14, Course 1), 17 (Day 14, Course 2), 5 (Day 14, Course 3) (PK) 59 (PK/QT analysis)
Diagnosis and main criteria for inclusion:		Patients with a confirmed diagnosis of a malignant solid tumour refractory or not amenable to standard therapies, preferentially patients with tumours, historically known to express HER2-and/or EGFR, patients with brain metastases, and glioblastomas
Test product:		Afatinib film-coated tablets
dose:		50 mg daily (morning dose, 1 h before food intake) with reduction to 40 or 30 mg daily in case of drug-related AEs
mode of admin.:		Oral
batch nos. (expiry):		50 mg: B081000220 (Jan 2010), 809169 (30 Sep 2010), 809168 (31 Mar 2011), 907816 (31 Mar 2012) 40 mg: B071003955 (Nov 2009), 809170 (30 Sep 2010), 809170 (31 Mar 2011) 30 mg: B071003954 (Nov 2009), 809167 (30 Sep 2010), 809167 (31 Mar 2011)
Reference therapy:		Not applicable
Duration of treatment:		Treatment with study medication was to be continued until progression of disease or undue AEs, whichever occurred first.

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Criteria for evaluation:

Efficacy / clinical pharmacology:

Primary efficacy endpoint:

- Objective tumour response according to Macdonald criteria for glioblastoma (GBM) patients and patients with brain metastases; Response Evaluation Criteria In Solid Tumours (RECIST, version 1.0) for other patients. Objective tumour response was defined as confirmed complete response (CR) or partial response (PR).

Secondary efficacy endpoints:

- Disease control rate: CR, PR, or stable disease (SD)
- Progression-free survival (PFS)
- Molecular determinants of response

Other efficacy assessments: Eastern Cooperative Oncology Group (ECOG) performance status

PK characteristics of afatinib after single dose (Day 1) and at steady state (Day 14): area under the curve over the dosing interval τ (24 h) following the first dose of uniform intervals (AUC_{0-24}) and the last dose at steady state ($AUC_{\tau,ss}$); maximum measured plasma concentration following the first dose (C_{max}) and at steady state ($C_{max,ss}$); time from dosing to maximum measured plasma concentration (t_{max}, $t_{max,ss}$); accumulation ratio of AUC or C_{max} values after multiple dose administration over a uniform dosing interval *t* ($R_{A,AUC}$, $R_{A,Cmax}$), peak trough fluctuation (PTF).

Safety:

Primary safety endpoint:

- QTcF interval (corrected by the Fridericia formula): average time-matched QTcF change from baseline to Day 14 of Course 1 over 1 to 24 h following administration of afatinib

Secondary safety endpoints:

- QTcF: Average time-matched change from baseline to Day 1 of Course 1, averaged over 1 to 24 h
- QT, heart rate (HR): Average time-matched change from baseline to Day 1 and to Day 14 over 1 to 24 h

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Criteria for evaluation: **Safety (continued):**	• QTcF, QT, HR: Time-matched change from baseline at each sampling time from 1 to 24 h on Day 1 and Day 14 • Marked prolongation of QT: any time-matched change from screening in QTcF >30 and >60 ms and any QTcF >450, >480, and >500 ms excluding patients with any prolonged value during screening • Cardiac safety parameters: abnormalities in PR and QRS intervals, HR, T wave and U wave morphology • Incidence and intensity of AEs, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 Other safety assessments: Laboratory investigations, physical examination including vital signs, and left ventricular ejection fraction (LVEF).
Statistical methods:	For the analysis of ECG, PK, and AEs, descriptive statistics were calculated. Average (mean) time-matched changes from baseline to Day 1 and to Day 14 for QTcF, QT, and HR were calculated together with the associated 2-sided 90% confidence intervals (CIs) using the t-distribution. For the analyses at each time point, a linear mixed-effects model for repeated measures was used assuming a special parametric structure of the covariance matrix. The model included "time" as a fixed categorical effect and the time-matched baseline value as a covariate. The analyses of changes from baseline to Days 1 and 14 were also performed for other QT correction modes (QTcN and QTcB) as sensitivity analyses. For the subgroup analyses for gender effect, the average time-matched changes from baseline to Days 1 and 14 in QTcF, QT, and HR were analysed using an analysis of variance model including "gender" as fixed effect. The relationship between afatinib plasma concentrations and QTcF change from baseline was explored using a linear mixed model to estimate the QTcF change and its 90% CI at the geometric mean (gMean) of the C_{max}. These analyses were also performed using the corresponding endpoints based on QT and HR.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

A total of 71 patients were enrolled and 60 patients were treated. 49 patients were analysed for the primary safety endpoint and 60 patients were analysed for all other safety endpoints and all efficacy endpoints. For PK analysis in Course 1, 60 patients were analysed on Day 1 and 44 patients on Day 14.

The reasons for discontinuation of trial medication were as follows: 55 patients had progressive disease or an "other" AE, 2 patients refused to continue taking trial medication, 1 patient was considered for stent insertion, 1 patient needed radiotherapy, and 1 patient was unable to tolerate afatinib.

The treated analysis set consisted of 30 men and 30 women and 80.0% were white, 10.0% were Asian, and 10.0% were Black/African American. The mean (s.d.) age of patients was 58.7 (11.9) years. Solid tumours, excluding glioblastomas, occurred in 56 patients and 2 patients had brain metastases. Non-small cell lung cancer was the most common type of solid tumour in 21 patients, followed by cancers of the oesophagus and breast in 6 patients each. Four patients had glioblastomas.

Efficacy results:

None of the patients experienced a confirmed or unconfirmed CR. One patient with a solid tumour experienced a confirmed PR and 2 patients achieved an unconfirmed PR. The confirmed objective response rates were thus 1.7% (1/60 patients) for the treated set overall, 0% for patients with glioblastoma or brain metastasis, and 1.8% (1/56) for patients with solid tumours (excluding glioblastomas).

The confirmed disease control rates (CR, PR, SD) were 53.3% (32/60) for the treated set, 66.7% (4/6) for patients with glioblastoma or brain metastasis, and 53.6% (30/56) for patients with solid tumours (excluding glioblastomas).

The median duration of disease control was 15.3 weeks (95% CI 15.0, 24.0).

The median PFS time in the treated set was 10.6 weeks (95% CI 7.4, 15.0). The median overall survival time was 39.6 weeks (95% CI 23.3, not evaluable).

For molecular determinants of response, few biopsies were available and therefore, no conclusive analysis was possible.

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Efficacy / clinical pharmacology results (continued):

In 45 (75.0%) patients, the best overall assessment of the ECOG performance status was unchanged during treatment, in 7 patients (11.7%) it improved, and in 5 patients (8.3%) it deteriorated. Data were missing in the remaining 3 (5.0%) patients.

Pharmacokinetic results:

After single and multiple administration of 50 mg afatinib once daily in Course 1, similar disposition kinetics were obtained. The plasma concentration-time profiles for afatinib exhibited a bi-exponential shape which was more pronounced in the steady state. A moderate inter-patient variability was observed after a single dose (Day 1) and at steady state (Day 14).

Single oral administration of 50 mg afatinib (BIBW 2992) - Day 1

PK parameter	Unit	No. patients	gMean	gCV%
AUC_{0-24}	[ng·h/mL]	56	482	55.6
C_{max}	[ng/mL]	60	44.7	58.9
t_{max} [1]	[h]	60	3.06	0.900, 6.17

Multiple oral administration of 50 mg afatinib (BIBW 2992) once daily - Day 14

PK parameter	Unit	No. patients	gMean	gCV%
$AUC_{\tau,ss}$	[ng·h/mL]	44	1250	53.3
$C_{max,ss}$	[ng/mL]	44	86.6	55.2
$t_{max,ss}$ [1]	[h]	44	3.07	1.00, 7.05
$R_{A,AUC}$		42	2.67	53.4
$R_{A,Cmax}$		44	2.05	58.5
PTF	[%]	44	97.6	37.8

[1] For t_{max} and $t_{max,ss}$ the median and range (minimum, maximum) are given.

Safety results:

Exposure:

The median duration of treatment with afatinib was 56.5 days (range 1 to 588 days) and 11 patients were treated for more than 6 months. The dose of afatinib was reduced in 27 (45.0%) patients.

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Safety results (continued):

Adverse events:

On-treatment AEs were reported in all of the 60 patients in the treated set. On the system organ class level, the most frequently reported AEs were gastrointestinal disorders (95.0% patients), skin and subcutaneous tissue disorders (80.0%), and general disorders and administrative site conditions (78.3%). The most common preferred terms (PTs) were diarrhoea (85.0% patients), rash (63.3%), nausea (51.7%), and fatigue (50.0%). Drug-related AEs were reported in 58 (96.7%) patients. The most common were diarrhoea (83.3%) and rash (60.0%).

AEs leading to dose reduction were reported in 24 (40.0%) patients and the most common PT was diarrhoea (12 patients). AEs leading to temporary or permanent discontinuation of afatinib were reported in 17 (28.3%) patients; the most common were diarrhoea, rash, and fatigue (in 4 patients each).

In regard to CTCAE grading (highest grade), AEs were assessed by the investigator as Grade 1 in 1 (1.7%) patient and as Grade 2 in 19 (31.7%) patients. Overall, 27 (45.0%) of the patients experienced a Grade 3 AE as the highest grade; the most common Grade 3 AEs were diarrhoea (11 patients) and rash (8 patients). Four (6.7%) patients experienced a Grade 4 AE as the highest grade (anaemia and diarrhoea in 2 patients each; dehydration, pulmonary embolism, and renal failure acute in 1 patient each).

SAEs were reported in 34 (56.7%) patients and diarrhoea was the most common (7 patients); fatal events (Grade 5) were reported in 9 (15.0%) patients. Drug-related SAEs were reported in 12 (20%) patients and diarrhoea was again the most common (7 patients). None of the SAEs with a fatal outcome was considered to be related to the study drug.

Review of findings for special AEs that are already known to be associated with afatinib administration (diarrhoea, nausea/vomiting, rash/acne, stomatitis, and ocular effects) did not reveal any new findings of clinical concern. There was no evidence that afatinib was associated with renal insufficiency or hepatic events. No drug-related cardiac findings of clinical concern were reported.

Overall, the profile of AEs was consistent with the known safety profile of

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	afatinib and the population of patients with advanced cancer; there were no unexpected findings.
Safety results (continued):	<u>ECG-related endpoints:</u> The mean average time-matched QTcF change from baseline to Day 14 of Course 1 over 1 to 24 h (primary safety endpoint) showed a decrease of 0.3 ms (90% CI –2.8, 2.3; N=49). The mean average time-matched QTcF over 1 to 24 h showed a small decrease of 1.0 ms (90% CI –2.2, 0.2) from baseline to Day 1 (N=60). On Day 14, the time courses of the adjusted mean time-matched changes from baseline in QTcF revealed small increases of 1.6 ms (90% CI –2.1, 5.2) at 1 h and 1.2 ms (90% CI –2.4, 4.9) at 2 h. At later time points (3 h to 24 h), changes ranged from -2.5 ms to 0.6 ms. Changes from baseline on Day 1 were minor. The maximum upper limits of the 90% CIs were 3.8 ms on Day 1 (at 7 h) and 5.2 ms on Day 14 (at 1 h). The upper limits of the 2-sided CIs for the average time-matched changes from baseline were thus well below 10 ms indicating that administration of multiple or single 50 mg doses of afatinib did not lead to prolongation of the QTcF. The mean average time-matched HR over 1 to 24 h showed a slight increase from baseline to Day 1 (1.3 bpm) and a minimal increase on Day 14 (0.1 bpm). These findings were reflected by the decreases seen in the mean average time-matched uncorrected QT over 1 to 24 h (decrease of 2.8 ms on Day 1 and 0.4 ms on Day 14); the upper limits of the 90% CIs (–0.7 and 4.0 ms, respectively) were well below 10 ms. Adjusted mean changes from baseline in QT were small at all time points, ranging from –6.6 to 2.5 ms on Day 1 and from –4.6 to 5.4 ms on Day 14. There were no clinically relevant differences in changes of the QTcF interval, HR, or QT interval between men and women. Analyses of categorical endpoints and outlier analyses revealed that there were very few patients with large increases in QTcF or high QT values. None of the patients experienced new onset of an absolute QTcF interval >450 ms or an uncorrected QT interval >500 ms on Day 1 or Day 14. Only 1 patient (440211) had notable findings consisting of time-matched QTcF increases from baseline

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	above the threshold of 60 ms on Days 1 and 14: 67 ms on Day 1 (at 24 h) and 94 ms on Day 14 (at 24 h). The patient had large fluctuations in QTcF on the baseline day (Day –1) with an unusually low value of 321 ms at 24 h and QTcF
Safety results (continued):	values ranging from 369 ms to 403 ms over 0 to 10 h. The low QTcF value at 24 h on the baseline day had a large influence on time-matched increases at 24 h on Days 1 and 14. Moreover, Fridericia's formula did not adequately correct the QT interval for HR and findings for plasma levels of afatinib in this patient were inconspicuous. Review of ECG recordings by an independent board-certified cardiologist did not reveal any clinically relevant cardiac abnormalities with onset during treatment with afatinib. The cardiologist classed abnormalities as 'clinically relevant' in 2 patients at baseline (intermittent atrial fibrillation, prolonged QT interval) and in 1 of these patients during study treatment (prolonged QT interval). None of these 'clinically relevant' findings were reported as AEs by the investigator. Analyses of plasma concentrations of afatinib and the time-matched changes in QTcF, QT, and HR did not indicate any relationship between exposure to afatinib and prolongation of QT. <u>Laboratory and other safety assessments:</u> No clinically relevant post-baseline transitions in laboratory values and post-baseline abnormal findings for physical examinations including vital signs, and LVEF were observed. No other new safety concerns were identified in this study.
Conclusions:	The primary and secondary analyses of ECG endpoints in this trial consistently showed that afatinib at doses of 50 mg daily did not prolong the QT interval or the HR-corrected QT interval (QTcF) and did not affect HR when given either as a single dose or as a daily dose for 14 days to patients with relapsed or refractory solid tumours. No clinically meaningful changes in QTcF or other ECG endpoints were observed during afatinib treatment; no drug-related cardiac safety findings of clinical concern were reported. This trial indicates that during afatinib monotherapy, clinically meaningful changes in QTcF are unlikely. Hence monitoring of ECGs can be performed at baseline and as clinically indicated; routine ECG monitoring may not be necessary in future clinical trials

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	with single-agent afatinib. Afatinib treatment was associated with anti-tumour activity in this patient population. The overall AE profile was consistent with the known safety profile
Conclusions (continued):	of afatinib and there were no unexpected findings. The overall PK profile was consistent with the known PK characteristics of afatinib.