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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-011996-59	
Name of active ingredient: Afatinib (BIBW 2992)		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 OCT 2012	**Trial No. / U No.:** 1200.74 / U12-2359-01	**Dates of trial:** 19 JUL 2010 – 29 MAR 2012	**Date of revision:** Not applicable

Title of trial:	An open label, partially randomised Phase II trial to investigate the efficacy and safety of BIBW 2992 in patients with metastatic colorectal cancer who never received prior anti-EGFR treatment
Coordinating Investigator:	[redacted]
Trial sites:	Mulitcentre trial (13 centres in the United Kingdom)
Publication (reference):	Data of this study have not been published.
Clinical phase:	II
Objectives:	The objectives of this trial are to compare the efficacy of single agent afatinib with cetuximab in patients with wild-type KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) tumours, and to assess the efficacy of afatinib in patients with KRAS mutated tumours.
Methodology:	Phase II open label, randomised trial for patients with KRAS wild type tumours, and non-randomised for patients with KRAS mutated tumours.
No. of subjects:	
planned:	Enrolled: 100 entered: 88
actual:	Enrolled: 120
	Treatment: afatinib in patients with KRAS wild type metastatic colorectal cancer entered: 36 treated: 36 analysed (for primary endpoint): 36
	Treatment: cetuximab in patients with KRAS wild type metastatic colorectal cancer entered: 15 treated: 14 analysed (for primary endpoint): 15
	Treatment: afatinib in patients with KRAS mutated metastatic colorectal cancer entered: 43 treated: 41 analysed (for primary endpoint): 41
Diagnosis and main criteria for inclusion:	Patients with metastatic colorectal cancer who had failed both oxaliplatin and irinotecan-based regimens. Patients with both wild-type KRAS and KRAS mutated tumours were included. No prior anti-EGFR therapy was allowed.

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Test product:	Afatinib tablets
dose:	50 mg daily (starting dose: 40 mg daily, which could be increased to 50 mg daily after 4 weeks in the event of no or minimal drug-related adverse events [AEs] or reduced in steps of 10 mg in the event of pre-defined drug-related AEs to a minimum of 20 mg)
mode of admin.:	Oral
batch no.:	20 mg – 808920; 30 mg – 809167 and 001004; 40 mg – 809170 and 001002; 50 mg – 809169 and 907816
Reference therapy:	Cetuximab
dose:	400 mg/m^2 on Day 1, then 250 mg/m^2 once a week
mode of admin.:	Intravenous
batch no.:	Commercial stock
Duration of treatment:	Continuous treatment until progression of disease, intolerability of the trial drug or availability of potentially curative treatment options. Median duration of treatment was estimated to be approximately 8 weeks.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was objective response (complete response [CR], partial response [PR]) in the KRAS wild type subgroup, and disease control (CR, PR, stable disease [SD]) in the KRAS mutated subgroup. Other endpoints included progression-free survival (PFS), overall survival (OS) based on RECIST 1.1 criteria, exploratory analysis of biomarkers, and pharmacokinetic (PK) parameters of afatinib.
Safety:	Incidence and intensity of AEs graded according to the Common Terminology Criteria for AEs (CTCAE, Version 3.0), and laboratory parameters.

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Statistical methods:	Exploratory data analyses. The primary analysis estimated the proportion of patients who achieved objective response in each treatment group using Wald logistic regression and 90% confidence intervals (CIs) for the KRAS wild-type tumour subgroup, and Clopper -Pearson exact binomial 90% CI for the KRAS mutated tumour subgroup. PFS and OS were summarised descriptively, and Kaplan-Meier plots were produced. Analyses in the wild-type group were based on the randomised set and analyses in the mutated group were based on the treated set.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Disposition: Investigators screened 120 patients, of whom 94 went on to be included in the study: 51 patients with KRAS wild type tumours who were randomised to either afatinib (36 patients) or cetuximab (15 patients) and 43 patients with KRAS mutated tumours who all received afatinib. All patients discontinued treatment since the protocol allowed patients to be treated until disease progression or intolerable AEs. The most common reason for treatment discontinuation was progressive disease: in the KRAS wild-type tumour group, 75% of patients in the afatinib group and 93% of patients in the cetuximab group withdrew for this reason, as did 78% of patients in the KRAS mutated tumour group.

Demography and baseline characteristics: In the KRAS wild-type tumour group, the demographic and baseline characteristics were generally similar between the 2 treatment groups. Overall, 72% of patients were male, 96% were White, and the mean age was 62.5 years. The mean time since first oncological diagnosis was 2.72 years. In 72% of patients the tumour was moderately differentiated and the most common primary sites were the rectum (36%) and sigmoid colon (28%).

In the KRAS mutated tumour group, 54% of patients were female, 95% were White and the mean age was 60.0 years. The mean time since first oncological diagnosis was 2.44 years. In the majority of patients the tumour was moderately differentiated (76%) and the most common primary sites were the rectum (32%) and sigmoid colon (29%).

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Efficacy / clinical pharmacology results (cont.):	Efficacy results: In the KRAS wild-type tumour group, more patients had an unconfirmed objective response (CR or PR) in the cetuximab group compared to the afatinib group (3 patients [20%] compared to 1 patient [3%]), although the difference was not statistically significant (p=0.0735). When using confirmed responses, 0 patients in the afatinib group and 2 patients (13%) in the cetuximab group achieved a confirmed objective response. PFS was longer in the cetuximab-treated group (median 144.5 days) compared to the afatinib-treated group (46.0 days). However, this difference did not translate into a notably shorter OS time based on Kaplan-Meier plots. In the KRAS mutated tumour group, no objective responses were reported and disease control (CR, PR, SD) with confirmation criteria applied was seen in 5 patients (12%) (p=0.6394). The same findings were seen using unconfirmed responses. Median PFS was similar when testing for a difference from 10% to that seen in wild-type patients (41.0 days), although the median OS was shorter (173.0 days). Pharmacokinetics: There were no significant differences between afatinib plasma concentrations in KRAS wild-type and mutated metastatic colorectal cancer patients. At the day of the first PK sampling on Day 8, afatinib trough plasma concentrations were at steady state. There was no sign of a systematic change in steady state trough plasma concentrations over the PK observation period. Overall, the variability in afatinib plasma concentrations was high.
Safety results:	In the KRAS wild-type tumour group, all patients had at least one AE during the treatment period or within 28 days post-treatment (i.e. treatment-emergent AEs) and all patients in the cetuximab group and 97% of patients in the afatinib group had at least 1 drug-related AE during this period. The most common AEs in the afatinib group were diarrhoea (reported by 81% of patients) and rash (reported by 56% of patients), followed by nausea (44%), fatigue (36%), decreased appetite (33%), and vomiting (31%). In the cetuximab group the most common AEs were rash (71%), decreased appetite (43%), constipation (36%), and diarrhoea, fatigue, urinary tract infection, headache, and hypomagnesaemia (all reported in 29% of patients).

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Safety results (cont.):

The only difference of note between the groups was the higher incidence of diarrhoea in the afatinib group. In both treatment groups, severe AEs (maximum CTCAE Grade 3) were reported in 42% and 43% of patients in the afatinib and cetuximab groups, respectively. All 7 patients that discontinued study treatment due to an AE were in the afatinib group (19%). Similar numbers of patients had SAEs (42% in the afatinib group and 36% in the cetuximab group), with the majority of the events being considered serious because they resulted in hospitalisation of the patient (39% in the afatinib group and 36% in the cetuximab group). Five patients in total had an SAE that resulted in death: 3 in the afatinib group and 2 in the cetuximab group. None of the deaths were considered drug-related by the investigators. No changes indicative of an adverse effect of afatinib were seen in any laboratory parameter, vital sign or other safety parameter.

In the KRAS mutated tumour group, all of the patients had at least one AE during the treatment period or within 28 days post-treatment and the majority (95%) had at least 1 drug-related AE during this period. The most common AEs were diarrhoea (reported by 71% of patients) and rash (reported by 61% of patients), followed by nausea (54%), vomiting (41%), fatigue (39%), and decreased appetite (32%). Severe AEs (maximum CTCAE Grade 3) were reported in 37% of patients. A total of 9 patients (22%) discontinued study treatment due to an AE. Eighteen patients (44%) had SAEs, with the majority of the events being considered serious because they resulted in hospitalisation of the patient (41%), and 8 patients had an SAE that resulted in death (none of the deaths were considered drug-related by the investigators). No changes indicative of an adverse effect of afatinib were seen in any laboratory parameter, vital sign or other safety parameter.

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Conclusions:

Treatment with afatinib showed no notable benefit compared to cetuximab in patients with KRAS wild-type colorectal cancer. Only limited benefit was observed in patients with KRAS mutated tumours.

There were no significant differences between afatinib plasma concentrations in KRAS wild-type and mutated metastatic colorectal cancer patients.

Afatinib showed an acceptable safety profile in this trial that was consistent with EGFR inhibition. In the KRAS wild-type tumour group, the safety profile was similar between patients treated with afatinib and those treated with cetuximab, with the exception of diarrhoea that occurred in a higher frequency in the afatinib group. In patients with KRAS mutated tumours, the safety profile was similar to that seen in patients treated with afatinib in the KRAS wild-type tumour group.

Trial Synopsis - Appendix

The result table on the following page supplements the trial results presented in the Trial Synopsis. The appended table provides the results for an additional secondary endpoint, as summarised below.

Results for	presented in
Overall survival	Table 15.2.2.2: 1

Table 15.2.2.2: 1 Analysis of overall survival [days]

KRAS mutation status: wild-type tumours - randomised set

	Afatinib	Cetuximab
Number of patients [N (%)]	36 (100)	15 (100)
Patients at risk [N (%)]	36 (100)	15 (100)
Median [95% CI]	355.0 [211.0, 449.0)	NE [204.0, NE)
(Q1, Q3)	(179.0, 449.0)	(256.0, NE)
Patients censored [N (%)]	20 (56)	10 (67)

Median, lower and upper quartiles are based on Kaplan-Meier estimates.

Source data: Appendix 16.2.6, Listing 9 ctr\tte.sas 16JUL2012