Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.:** 2011-001804-37	
Name of active ingredient: Afatinib (BIBW 2992)		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 07 FEB 2012	**Trial No. / U No.:** 1200.152 / U12-1140-01	**Dates of trial:** 20 JUL 2011 – 30 AUG 2011	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of a single oral dose of 40 mg afatinib given alone and after multiple doses of rifampicin – an open-label, two-period, fixed sequence clinical phase I trial in healthy male volunteers
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre/Translational Medicine Birkendorfer Strasse 65 Biberach, Germany
Publication (reference):	Data from this trial have not been published
Clinical phase:	I
Objectives:	To investigate whether multiple oral administration of the P-gp inducer rifampicin prior to single oral administration of afatinib affected the pharmacokinetics (PK) of afatinib
Methodology:	Open-label, 2-period, fixed-sequence design
No. of subjects:	
planned:	entered: 22
actual:	Reference treatment: single dose afatinib (40 mg) entered: 22 treated: 22 analysed (for primary endpoint): 22
	Test treatment: rifampicin (7 days, 600 mg per day), single dose afatinib (40 mg) entered: 22 treated: 22 analysed (for primary endpoint): 22
Diagnosis and main criteria for inclusion:	Healthy male volunteers aged 18 to 55 years with a BMI from ≥18.5 to ≤29.9 kg/m^2 were eligible to participate.

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Test treatment:	Afatinib (film-coated tablet) and rifampicin (Eremfat® 600; film-coated tablet)
dose:	600 mg rifampicin per day on evenings of Days -7 to -1; single morning dose of 40 mg afatinib on Day 1
mode of admin.:	Rifampicin: oral, with 240 mL water Afatinib: oral, with 240 mL water after an overnight fast
batch no.:	B003011 (rifampicin); B907817 (afatinib)
Reference treatment:	Afatinib (film-coated tablet)
dose:	Single dose of 40 mg afatinib
mode of admin.:	Oral, with 240 mL water after an overnight fast
batch no.:	B907817
Duration of treatment:	Period 1 (reference treatment): single dose of afatinib on Day 1, with PK sampling on Days 1 to 6 (total duration of 6 days) Period 2 (test treatment): 7 days of rifampicin on Days -7 to -1, and single dose of afatinib on Day 1. PK sampling was performed from Days 1 to 6 (total duration of 13 days). A washout period of at least 21 days separated administration of afatinib in the 2 trial periods.
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints were $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} for afatinib administered alone and after multiple doses of rifampicin. Secondary endpoints were AUC_{0-24}, $\%AUC_{tz-\infty}$, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, and V_z/F for afatinib administered alone and after multiple doses of rifampicin.
Safety:	Safety was assessed by physical examination, blood pressure, pulse rate, 12-lead ECG, laboratory tests, adverse events (AEs), and global tolerability.
Statistical methods:	$AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} were log-transformed prior to fitting an ANOVA model that included effects for 'treatment' and 'subject'. The 90% confidence intervals (CIs) were computed for the primary endpoints, then back-transformed to the original scale to give the point and interval estimates for the geometric mean (gMean) ratio of the test to reference treatment. Descriptive statistics were calculated for all other parameters.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

In total, 22 healthy male subjects were entered and treated. All subjects received all doses of trial medication, and all but 1 subject (who withdrew consent) completed the planned observation time. All subjects were of white race and the mean age was 32.7 years (range 22 to 48 years). Data from all 22 subjects were included in the PK analysis.

For administration of single-dose afatinib (reference treatment), gMean values of $AUC_{0-\infty}$ and AUC_{0-tz} were 912 and 860 ng·h/ml, respectively, and gMean C_{max} was 38.3 ng/mL. Interindividual variability was moderate (gCV values of approximately 40%). After 7 days of rifampicin treatment, assessment of the gMean ratio in urine of 6β-hydroxycortisol to cortisol (a marker of CYP3A4 activity and a surrogate for P-gp induction) indicated that induction had been achieved. Compared with the reference treatment, administration of single-dose afatinib after rifampicin treatment (test treatment) resulted in decreased exposure to afatinib: gMean values of $AUC_{0-\infty}$ and AUC_{0-tz} were 610 and 575 ng·h/ml, respectively, and gMean C_{max} was 30.0 ng/mL. Interindividual variability was moderate (gCV values of approximately 30%). For secondary endpoints, values of apparent oral clearance and apparent volume of distribution were higher for the test treatment, and AUC_{0-24} was lower. Other PK parameters were similar between the treatments (see table below).

Parameter[a]	Unit	Reference		Test	
		gMean	gCV [%]	gMean	gCV [%]
$AUC_{0-\infty}$	[ng·h/mL]	912	38.3	610	32.1
AUC_{0-tz}	[ng·h/mL]	860	39.8	575	32.3
C_{max}	[ng/mL]	38.3	38.4	30.0	34.1
t_{max}[b]	[h]	6.00	5.00–7.00	6.00	3.00–8.00
$t_{1/2}$	[h]	32.8	18.4	36.0	15.1
AUC_{0-24}	[ng·h/mL]	491	41.4	353	35.0
$\%AUC_{tz-\infty}$	[%]	5.25	44.8	5.48	31.1
MRT_{po}	[h]	36.9	14.3	35.1	14.0
CL/F	[mL/min]	731	38.3	1090	32.1
V_z/F	[L]	2080	53.2	3410	34.7

[a]For the reference treatment, N=22; for the test treatment, N=22 for C_{max} and t_{max} and N=21 for all other PK parameters

[b]Median and range are presented

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Clinical pharmacology results (continued)

Statistical comparison of primary endpoints for the treatments yielded adjusted gMean ratios (test/reference) of 66.20% for $AUC_{0-\infty}$, 66.18% for AUC_{0-tz}, and 78.41% for C_{max}. The 90% CIs for both AUC parameters were below 80.00%; for C_{max}, the 90% CI was below 85.00% (see table below).

Parameter[a]	Adj. gMean ratio (test/reference) [%]	2-sided 90% CI [%] Lower limit	Upper limit	Intra-individual gCV [%]
$AUC_{0-\infty}$ [ng·h/mL]	66.20	60.82	72.06	16.1
AUC_{0-tz} [ng·h/mL]	66.18	60.66	72.21	16.5
C_{max} [ng/mL]	78.41	72.36	84.97	15.6

[a]For the reference treatment, N=22; for the test treatment, N=22 for C_{max} and N=21 for $AUC_{0-\infty}$ and AUC_{0-tz}

Safety results:

All 22 subjects received both planned doses of afatinib (40 mg per dose; 80 mg total) and all 7 planned doses of rifampicin (600 mg per dose; 4200 mg total).

Of the 22 treated subjects, 8 (36.4%) reported any AE in any trial period. Including both trial periods, the most frequent AEs by system organ class were nervous system disorders and infections and infestations, each reported for 4 subjects (18.2%). The most frequent preferred terms were headache, for 4 subjects (18.2%), and nasopharyngitis, for 3 subjects (13.6%). Including the entire trial duration, all AEs reported were of CTCAE grade 1 or 2. There were no deaths or other serious AEs, and no AEs leading to discontinuation of trial medication. All AEs had resolved by the end-of-study examination.

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Safety results (continued):

In the first trial period, in which single dose afatinib was administered, 4 of 22 subjects (18.2%) reported any AE: Nasopharyngitis, headache, laceration (a cut on the right hand), and diarrhoea were each reported for 1 subject. One AE (diarrhoea) was considered by the investigator as related to trial treatment. In the second trial period, in which rifampicin and single dose afatinib were administered, 5 of 22 subjects (22.7%) reported any AE during the 7 days of rifampicin treatment. Headache was reported for 3 subjects, and influenza, dyspepsia, vomiting, nasopharyngitis, and muscle tightness were each reported for 1 subject. For single dose afatinib after rifampicin, AEs were reported for 2 subjects (9.1%): 1 subject reported nasopharyngitis and oral herpes, and 1 subject reported myalgia. In the second trial period, no AE was considered by the investigator as related to trial treatment. All AEs had resolved by the end of the trial.

Clinical laboratory assessment demonstrated no relevant mean changes in any parameter. A total of 3 subjects had on-treatment changes in laboratory parameters that were classified as CTCAE grade 3 or higher: For Subject [redacted], increased CK, AST, ALT, and glucose were likely caused by the concurrent AE influenza; for Subject [redacted], decreases in absolute lymphocytes and neutrophils were reported at the same time as 2 AEs (vomiting and headache), but the relationship to these AEs is unclear; and for Subject [redacted] no clinical signs or symptoms or AEs were reported in association with increases in lipase and amylase. All abnormalities had resolved to CTCAE grade 1 or 0 at the last assessment.

Overall tolerability was assessed as good for all 22 subjects.

Conclusions:

Induction of P-gp expression by multiple dose administration of rifampicin resulted in moderately decreased exposure to single-dose afatinib: Values of AUC parameters decreased by 34%, and C_{max} decreased by 22%. The median t_{max} of afatinib was 6.00 h for both treatments and the terminal half-life of afatinib was comparable between treatments (36.0 h for the test treatment vs. 32.8 h for the reference treatment), indicating no substantial alteration in absorption or elimination kinetics.

No safety issues arose in this trial to indicate that administration of single dose afatinib (with or without rifampicin) was unsafe for healthy male volunteers.