Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2011-001803-11	
Name of active ingredient: Afatinib (BIBW 2992)		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 MAY 2012	**Trial No. / U No.:** 1200.151 / U12-1170-01	**Dates of trial:** 24 AUG 2011 – 22 DEC 2011	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of a single oral dose of 40 mg afatinib given alone compared to concomitant and timed administration of multiple oral doses of ritonavir – an open-label, randomised, three-way crossover trial in healthy male volunteers
Principal Investigator:	[redacted]
Trial site:	Human Pharmacology Centre Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Straße 65 Biberach, Germany
Publication (reference):	Data of this trial have not been published
Clinical phase:	I
Objectives:	To investigate the effect of ritonavir (200 mg twice daily for 3 days) on the pharmacokinetic (PK) parameters $AUC_{0-\infty}$, AUC_{0-tz} and C_{max} of a single oral dose of 40 mg afatinib, when the third dose of ritonavir was administered either simultaneously with afatinib or 6 h after afatinib
Methodology:	Randomised, open-label, 3-way crossover trial. The reference treatment (Treatment A) consisted of 40 mg afatinib administered as single oral dose in the morning. The test treatments consisted of ritonavir (200 mg) administered twice-daily on Days -1, 1, and 2 with the third dose given simultaneously with a single oral dose of 40 mg afatinib in the morning of study Day 1 (Treatment B, concomitant ritonavir) or with the third dose given 6 h after a single oral dose of 40 mg afatinib in the morning of Day 1 (Treatment C, timed ritonavir). A washout period of at least 21 days separated administration of afatinib in each trial period.

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No. of subjects:	
planned:	entered: 24
actual:	entered: 24 Treatment A: single dose of afatinib entered: 23 treated: 23 analysed (for primary endpoint): 22 Treatment B : single dose of afatinib administered simultaneously with ritonavir entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment C: single dose of afatinib administered 6 h prior to ritonavir entered: 23 treated: 23 analysed (for primary endpoint): 22
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 55 years, with body mass index (BMI) in the range from 18.5 to 29.9 kg/m^2
Test treatment:	Afatinib film-coated tablet and ritonavir film-coated tablet (Norvir®)
dose:	Afatinib: 40 mg single dose on Day 1; ritonavir: 2x100 mg administered twice daily (400 mg per day) on Days -1, 1 and 2
mode of admin.:	Oral administration with 240 mL water
batch no.:	Afatinib: 907817; ritonavir: 027038D Abbott
Reference treatment	Afatinib film-coated tablet
dose:	40 mg single dose on Day 1
mode of admin.:	Oral administration with 240 mL water
batch no.:	907817
Duration of treatment:	Treatment A: single dose of afatinib Treatment B (concomitant ritonavir): 3 days of ritonavir (Days -1, 1, 2), single dose of afatinib on Day 1 with third ritonavir dose Treatment C (timed ritonavir): 3 days of ritonavir (Days -1, 1, 2), single dose of afatinib on Day 1 6 h prior to third ritonavir dose A washout period of at least 21 days separated administration of afatinib in each trial period.

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Criteria for evaluation:

Clinical pharmacology: Primary endpoints were $AUC_{0-\infty,}$ AUC_{0-tz}, and C_{max} for afatinib in all trial periods.

Other PK parameters of interest were AUC_{0-24}, $\%AUC_{tz-\infty}$, t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, $RAUC_{0-\infty, T/R}$, $RAUC_{0-tz, T/R}$, and $RC_{max, T/R}$ for afatinib in all trial periods.

Safety: Safety was evaluated by physical examination, blood pressure, pulse rate, 12-lead ECG, laboratory tests, adverse events, and assessment of global tolerability by the investigator.

Statistical methods: $AUC_{0-\infty}$, $AUC_{0-tz,}$ and C_{max} of afatinib for the reference treatment (Treatment A) and for the test treatments (Treatment B or Treatment C) were log-transformed prior to fitting an ANOVA model which included effects for 'sequence', 'subjects nested within sequence', 'period', and 'treatment'. For each primary PK endpoint, the difference between test and reference treatment and the corresponding 90% confidence intervals (CIs) were computed on the log scale, then back-transformed to the original scale to give the point estimator and interval estimates for the geometric mean (gMean) ratio of test/reference treatment.

Descriptive statistics were calculated for all other parameters.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results: In total, 24 healthy male subjects were entered and treated; 22 subjects (91.7%) received all doses of trial medication and completed the planned observation time. Two subjects (8.3%) discontinued treatment with trial medication due to adverse events. All subjects were of white race and the mean age was 38.0 years (range 18 to 51 years). Data from all 24 subjects were included in the PK analysis.

Plasma concentration-time profiles of afatinib alone (Treatment A) were similar to afatinib with concomitant ritonavir (Treatment B) or afatinib with timed ritonavir (Treatment C). For all 3 treatments, afatinib concentrations peaked 6 h after afatinib administration. For concomitant treatment with ritonavir only, during the absorption phase (up to 6 h after administration), afatinib plasma concentrations were slightly higher than those for afatinib alone.

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Clinical pharmacology results (continued):

Noncompartmental PK analysis indicated that gMean exposure parameters (AUC and C_{max}) were similar for the 3 treatments, as were terminal half-life, mean residence time, and apparent volume of distribution (see table below).

Pharmacokinetic parameters for afatinib

Parameter	Treatment A[1] gMean (gCV%)	Treatment B[2] gMean (gCV%)	Treatment C[3] gMean (gCV%)
$AUC_{0-\infty}$ [ng·h/mL]	426 (22.8)	515 (27.5)	475 (19.4)
AUC_{0-tz} [ng·h/mL]	392 (26.2)	478 (27.9)	438 (20.3)
C_{max} [ng/mL]	19.5 (33.5)	20.7 (29.4)	20.7 (24.4)
t_{max} [h]	6.00 (4.00 to 8.00)[4]	6.00 (3.00 to 8.00)[4]	6.00 (0.500 to 8.00)[4]
$t_{1/2}$ [h]	33.0 (25.8)	32.5 (18.2)	33.9 (24.5)
MRT_{po} [h]	37.9 (23.7)	37.5 (17.5)	38.4 (18.3)
CL/F [mL/min]	1570 (22.8)	1300 (27.5)	1400 (19.4)
V_z/F [L]	4480 (39.6)	3640 (29.4)	4120 (25.4)

[1]N=22 for all parameters except for AUC_{0-tz} (N= 21)
[2]N=24 for all parameters
[3]N=22 for all parameters
[4]Median and range

Statistical assessment indicated that afatinib exposure for Treatments B and C was similar to Treatment A. For C_{max}, 90% CIs for both test treatments were within the standard bioequivalence range of 80.00% to 125.00%. For AUC parameters, the 90% CI was within this range for timed ritonavir, and was only slightly outside this range for concomitant ritonavir compared with afatinib alone (see table below). Therefore, there was no relevant drug-drug interaction between 40 mg afatinib and ritonavir for either concomitant or timed treatments.

Bioavailability of afatinib for Treatments B and C compared with Treatment A

Afatinib Parameter[1]	Trt B/A[2] adj. gMean ratio (%)	90% CI (%)	Trt C/A[3] adj. gMean ratio (%)	90% CI (%)
$AUC_{0-\infty}$ [ng·h/mL]	118.56	111.71 to 125.82	110.76	104.94 to 116.91
AUC_{0-tz} [ng·h/mL]	119.30	112.24 to 126.81	110.23	103.84 to 117.01
C_{max} [ng/mL]	104.06	96.68 to 112.00	105.09	96.43 to 114.53

[1]Intraindividual gCV was 16.1% or less for all parameters
[2]For Treatment B, N=24 for all parameters; for Treatment A, N=21 for AUC_{0-tz} and N=22 for $AUC_{0-\infty}$ and C_{max}
[3]For treatment C, N=22 for all parameters

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Safety results:

Of the 24 subjects, 22 (91.7%) received all afatinib and ritonavir doses in each treatment (cumulative doses of 120 mg afatinib and 2400 mg ritonavir). For the 2 subjects who discontinued trial treatment, cumulative doses were 80 mg afatinib and 1400 mg ritonavir (Subject [redacted]) and 40 mg afatinib and 1200 mg ritonavir (Subject [redacted]).

Including all 24 subjects and all trial treatments, 20 subjects (83.3%) reported 1 or more adverse events. Including all treatments, the most frequently reported adverse events on the system organ class (SOC) were gastrointestinal disorders, in 9 of 24 subjects (37.5%). The most frequently reported preferred term (PT) was diarrhoea, in 7 of 24 subjects (29.2%). In 2 of 24 subjects (8.3%), Subject [redacted], lipase increases of up to 8- and 11-fold the upper limit of normal (ULN) led to discontinuation of trial treatment.

For 11 of 24 subjects (45.8%), adverse events were reported that were considered by the investigator as related to trial treatment: these included diarrhoea (CTCAE grade 1) in 7 of 24 subjects, lipase increase (grade 4) in 2 of 24 subjects, and dizziness (grade 1), headache (grade 2), nausea (grade 1), vomiting (grade 1), rash (grade 1), and GGT increase (<grade 1), each in 1 of 24 subjects.

For the 2 subjects with lipase increases (Subject [redacted]; see above), the severity was CTCAE grade 4. For 2 subjects, adverse events of grade 3 severity (influenza) were reported. All other adverse events were of CTCAE grade 1 or 2 severity. There were no deaths or other serious adverse events.

For Subject [redacted], fluctuations of lipase and amylase levels above the normal limits continued after discontinuation of trial treatment, and ranged from 180 U/L (3.5·ULN) to 582 U/L (11.4·ULN) for lipase, and from 118 U/L (1.1·ULN) to 283 U/L (2.6·ULN) for amylase. C-reactive protein and leukocyte count remained normal, and the subject did not show any signs or symptoms of pancreatitis during the trial. An ultrasond of the pancreas showed no abnormalities, and the adverse event was considered by the investigator to be sufficiently characterised. For Subject [redacted], again, the lipase increase was accompanied neither by elevations in C-reactive protein or leukocyte count, nor by any clinical signs or symptoms. Amylase was 113 U/L (1.0·ULN). The lipase elevation in Subject [redacted] resolved promptly after discontinuation of trial treatment.

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Safety results (continued):	Laboratory assessments demonstrated no relevant mean change in any parameter. For individual subjects, increases in CTCAE grade were occasionally observed. Other than in Subject [redacted] (see above), these were of grade 2 or less. Assessment of vital signs did not indicate relevant changes in systolic or diastolic blood pressure or pulse rate for any subject. Overall tolerability was assessed by the investigator as 'good' or 'satisfactory' for almost all subjects in almost all trial periods. Due to grade 1 and 2 treatment-related adverse events, tolerability was rated as 'not satisfactory' in 1 trial period for 1 subject (Subject [redacted] with treatment-related headache and rash), and as 'bad' in 1 trial period for 1 subject (Subject [redacted], with treatment-related nausea, vomiting, dizziness, and headache).
Conclusions:	There was no clinically relevant effect on the pharmacokinetics of a single dose of 40 mg afatinib when the P-gp inhibitor ritonavir was administered either at the same time as afatinib or 6 h after afatinib. In 2 subjects, during combined administration of ritonavir and afatinib, asymptomatic lipase increases of up to 11 times the upper limit of normal were observed. No further safety issues were identified during the trial. Overall, tolerability was acceptable for administration of single doses of 40 mg afatinib combined with multiple doses of ritonavir.