Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00012
Edition Number	1
Date	5 April 2012
EudraCT Number	2010-024452-28

A Single-blind, Placebo-controlled, 2-period, Fixed Sequence Study to Determine the Effects of Coadministration of Fostamatinib 100 mg Twice Daily on the Pharmacokinetics of an Oral Contraceptive in Healthy Female Volunteers

Study dates: First subject enrolled: 9 March 2011
Last subject last visit: 13 November 2011

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To assess the effect of repeated doses of fostamatinib on the PK of Microgynon, a monophasic oral contraceptive, by assessment of $C_{max,ss}$ and AUC_{ss} of ethinyl estradiol and levonogestrel on Day 21	AUC_{ss} and $C_{max,ss}$ of ethinyl estradiol and levonorgestrel
Secondary	Pharmacodynamic	To characterise the PD of progesterone, LH, FSH, and SHBG, following administration with monophasic oral contraceptive (Microgynon) alone and following coadministration with fostamatinib	AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$, and $t_{max,ss}$ of progesterone, LH, FSH, and SHBG
	Pharmacokinetic	To determine R406 plasma concentration-time profiles and resulting PK parameters (steady state) when fostamatinib is coadministered with an oral contraceptive	AUC_{ss}, $C_{max,ss}$, and $t_{max,ss}$ of R406
	Safety	To examine the safety and tolerability of fostamatinib in combination with an oral contraceptive	Adverse events, laboratory assessments, vital signs, physical examination, and 12-lead electrocardiogram

AUC_{ss}: area under the plasma concentration-time curve from zero to tau at steady state; $C_{max,ss}$: maximum plasma concentration at steady state; $C_{min,ss}$: minimum plasma concentration at steady state; FSH: follicle-stimulating hormone; LH: luteinising hormone; NA: not applicable; PD: pharmacodynamic; PK: pharmacokinetic; R406: analyte in plasma for the dephosphorylated drug; SHBG: sex hormone binding globulin; $t_{max,ss}$: time to maximum plasma concentration at steady state.

Study design

This was a Phase I single-blind (healthy volunteers blinded to treatment), placebo-controlled, single centre, 2-period, fixed sequence study to assess the effect of repeated administrations of fostamatinib on the pharmacokinetics (PK) of Microgynon® 30 in healthy female volunteers.

Each healthy volunteer received the 2 treatments (Treatment A and Treatment B) in a fixed order.

Treatment A in Period 1: monophasic oral contraceptive (Microgynon) every day at approximately the same time in the morning (preferably at breakfast) and 2 placebo to fostamatinib tablets twice daily (approximately 12 hours apart) for 21 days, except on Day 21 when placebo was administered only once in the morning.

Treatment B in Period 2: monophasic oral contraceptive (Microgynon) every day at approximately the same time in the morning (preferably at breakfast) and 100 mg (2 x 50 mg tablets) of fostamatinib administered twice daily (approximately 12 hours apart) for 21 days, except on Day 21 when fostamatinib was administered only once in the morning.

Target subject population and sample size

Healthy female volunteers aged 18 to 45 years (inclusive) who were not pregnant, not planning pregnancy within the study period, not breastfeeding, premenopausal, and who had been taking Microgynon (or an A/B rated generic equivalent) for at least 3 months with a body weight of at least 50 kg and a body mass index between 18 and 30 kg/m^2 (inclusive).

The intra-subject geometric coefficient of variation (GCV%) of ethinyl estradiol was assumed at 25%. The intra-subject GCV% for levenorgestrel was assumed to be equal to or less than 25%. Under this assumption, a sample size of 28 subjects would provide 90% power that a 2-sided 90% confidence interval (CI) for the ratios of interest (maximum plasma concentration at steady state [$C_{max,ss}$] and the area under the plasma concentration-time curve from zero to tau at steady state [AUC_{ss}] for each analyte) of Microgynon administered with fostamatinib to that of Microgynon alone would be completely contained within the prespecified equivalence range of 0.80 to 1.25, if there is truly no drug-drug interaction between Microgynon and fostamatinib. These calculations were based on a two 1-sided testing procedure at a level of significance of 0.05, assuming a true ratio of 1.00.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 Details of the investigational products

Investigational product	Route of administration, strength, and dosage form	Manufacturer	Batch number
Fostamatinib	Oral 50 mg tablet	Patheon	DKWF CKZP
Placebo to fostamatinib	Oral tablet	AstraZeneca	CKZS
Microgynon	Oral 30 µg ethinyl estradiol + 150 µg levonorgestrel tablet	Bayer	WEE7HA WEE8HR WEE7XK WEE8HT WEE8XA

Before the morning dose on Day 21, healthy volunteers were required to fast overnight (except for tap water) from 2200 on Day 20, until at least 4 hours postdose. The healthy volunteers were not to drink water from 2 hours before the investigational product administration and until 1 hour postdose, except for the 240 mL water allowed for administration.

Duration of treatment

The study consisted of a screening period of up to 35 days, followed by 2 treatment periods (28 days each). Healthy volunteers participated in a follow-up visit 7 to 10 days following the last inpatient visit (Day 22).

Healthy volunteers already taking Microgynon were to continue taking Microgynon in the morning for at least 21 days from screening to Day -1 of Period 1. Administration in this run-in period could be extended beyond 21 days, up to a maximum of 49 days, for the purpose of synchronising the cycles of healthy volunteers, so that they could participate in the study in groups.

Healthy volunteers not already taking Microgynon were to start taking Microgynon after screening and were to continue this for 3 stabilisation cycles of at least 21 days. The last stabilisation cycle could be extended beyond 21 days, up to a maximum of 49 days, for the purpose of synchronising the cycles of healthy volunteers so that they could participate in the study in groups.

Statistical methods

The PK parameters AUC_{ss} and $C_{max,ss}$ for ethinyl estradiol and levonorgestrel for oral contraceptive administered in combination with fostamatinib (test) were compared with the PK parameters for oral contraceptive administered alone (reference). Natural log transformed AUC_{ss} and $C_{max,ss}$ were formally analysed using a linear fixed effects model. The results were back-transformed and presented as geometric least-squares (LS) means, the ratio of these geometric LS means, and its associated 90% confidence interval (CI).

The pharmacodynamic (PD) parameters AUC_{ss} and C_{max} were analysed using a similar methodology as described above for the comparison of the PK parameters between the test and reference treatments.

For ethinyl estradiol and levonorgestrel, if the CIs for AUC_{ss} and C_{max} were entirely contained within the interval (80%, 125%), then a lack of drug-drug interaction was concluded.

Subject population

Enrolled: 33 healthy volunteers

Completed: 27 healthy volunteers

Thirty-three healthy female volunteers enrolled into the study, of which 27 completed and 6 were prematurely withdrawn. All healthy volunteers met the study entry criteria, except

2 healthy volunteers who had a weight <50 kg; however this was not considered an important protocol deviation. Three healthy volunteers were excluded from the PK and PD analysis sets due to important protocol deviations. There was no cause for concern with respect to concomitant medications used.

Summary of pharmacokinetic results

Table S3 Statistical comparison of primary pharmacokinetic endpoints

Analyte	Parameter (units)	Treatment	N	Geometric LS mean	Microgynon + fostamatinib/ Microgynon alone Ratio (%)	90% CI
Ethinyl Estradiol	AUC_{ss}	Microgynon alone	27	828.1		
	(pg·h/mL)	Microgynon + fostamatinib	27	1062	128.20	(121.06, 135.77)
	$C_{max,ss}$	Microgynon alone	27	86.20		
	(pg/mL)	Microgynon + fostamatinib	27	115.7	134.27	(126.07, 143.00)
Levonorgestrel	AUC_{ss}	Microgynon alone	27	75970		
	(pg·h/mL)	Microgynon + fostamatinib	27	79830	105.08	(97.53, 113.21)
	$C_{max,ss}$	Microgynon alone	27	6652		
	(pg/mL)	Microgynon + fostamatinib	27	6439	96.81	(90.43, 103.63)

LS least-squares; CI: confidence interval. Results were analysed by employing a linear fixed effects model with treatment and subject as fixed effects.
Source: Table 11.2.7.

While levonorgestrel exposure was similar across treatments, ethinyl estradiol AUC_{ss} and $C_{max,ss}$ increased by 28% and 34%, respectively, when Microgynon was coadministered with fostamatinib. For both analytes, $t_{max,ss}$ was similar across treatments.

The R406 steady-state plasma geometric mean $C_{max,ss}$ and AUC_{ss} were 812 ng/mL and 5020 ng*h/mL, respectively. R406 mean concentrations and pharmacokinetic parameters were within a similar range to those previously observed after fostamatinib 100 mg twice-daily dosing.

Summary of pharmacodynamic results

Table S4 Statistical comparison of key pharmacodynamic endpoints

Analyte	Parameter (units)	Treatment	N	Geometric LS mean	Microgynon + fostamatinib/ Microgynon alone	
					Ratio (%)	90% CI (%)
Progesterone	AUC_{ss} (nmol·h/L)	Microgynon alone	27	66.53		
		Microgynon + fostamatinib	27	69.39	104.31	(96.39, 112.88)
	$C_{max,ss}$ (nmol/L)	Microgynon alone	27	4.916		
		Microgynon + fostamatinib	27	4.904	99.75	(90.41, 110.05)
Sex Hormone Binding Globulin	AUC_{ss} (nmol·h/L)	Microgynon alone	27	2020		
		Microgynon + fostamatinib	27	2023	100.12	(94.86, 105.67)
	$C_{max,ss}$ (nmol/L)	Microgynon alone	27	92.57		
		Microgynon + fostamatinib	27	92.92	100.38	(94.27, 106.89)
Follicle Stimulating Hormone	AUC_{ss} (IU·h/L)	Microgynon alone	27	5.639		
		Microgynon + fostamatinib	27	4.265	75.63	(62.08, 92.13)
	$C_{max,ss}$ (IU/L)	Microgynon alone	27	0.2941		
		Microgynon + fostamatinib	27	0.2235	75.99	(56.24, 102.68)
Luteinising Hormone	AUC_{ss} (IU·h/L)	Microgynon alone	27	4.432		
		Microgynon + fostamatinib	27	3.687	83.20	(65.52, 105.65)
	$C_{max,ss}$ (IU/L)	Microgynon alone	27	0.3230		
		Microgynon + fostamatinib	27	0.2443	75.64	(51.26, 111.61)

LS least-squares, CI confidence interval. Results were analysed by employing a linear fixed effects model with treatment and subject as fixed effects.
Source: Table 11.2.17.

When Microgynon was coadministered with fostamatinib, follicle-stimulating hormone AUC_{ss} and $C_{max,ss}$ appeared to decrease by 24%. Similarly, luteinising hormone AUC_{ss} and $C_{max,ss}$ appeared to decrease during the combination treatment by 17% and 24%, respectively. However, progesterone and sex hormone binding globulin AUC_{ss} and $C_{max,ss}$ appeared to be similar across treatments.

Summary of safety results

Of the 33 healthy volunteers enrolled, 27 healthy volunteers received all the planned investigational product administrations. Six healthy volunteers were prematurely withdrawn and did not receive all the planned investigational product administrations.

No deaths or serious adverse events (SAEs) were reported. Two healthy volunteers were prematurely withdrawn from the study due to adverse events (AEs): gastroenteritis and upper respiratory tract infection.

At least 1 AE was reported for 18 healthy volunteers (54.5%): 16 healthy volunteers (48.5%) on Microgynon/placebo and 8 healthy volunteers (26.7%) on Microgynon/fostamatinib. The most frequently reported AE was headache, 8 healthy volunteers (24.2%), all on Microgynon/placebo. All AEs reported on Microgynon/fostamatinib were only reported for 1 healthy volunteer each.

No clinically relevant mean or median changes from baseline were reported in laboratory measurements or vital signs and no clinically relevant changes were reported in electrocardiogram (ECG) or physical examination findings.