AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00026
Edition Number	1
Date	15 December 2011

An Open-Label, Non-Randomised, 2-Period, Single Centre Study to Assess the Pharmacokinetics of Digoxin in Healthy Subjects when Administered Alone and in Combination with Fostamatinib 100 mg Twice Daily

Study dates: First subject enrolled: 29 June 2011
Last subject last visit: 15 September 2011

Phase of development: Clinical pharmacology (I)

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

Study centre

One study centre in the United Kingdom

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate whether the plasma concentration-time profiles and resulting PK parameters of digoxin are altered during steady-state fostamatinib administration	Primary endpoints: digoxin (Day 8 and Day 15) AUC_{ss} and $C_{max,ss}$ Secondary endpoints: digoxin (Day 8 and Day 15) $t_{max,ss}$, CL_{ss}/F, and $V_{z,ss}/F$	Pharmacokinetic
Secondary	**Secondary**	
To examine the safety and tolerability of fostamatinib in combination with digoxin	Adverse events, vital signs, 12-lead electrocardiogram, laboratory safety variables, and physical examination	Safety
To examine the steady-state PK of R406 during co-administration of fostamatinib with digoxin at steady-state	Secondary endpoints: R406 (Day 15): AUC_{ss}, $t_{max,ss}$, and $C_{max,ss}$	Pharmacokinetic
To examine the urinary steady-state PK of digoxin in healthy subjects when administered alone and in combination with fostamatinib at steady-state	Secondary endpoints: digoxin (Day 8 and Day 15): $A_{e(0-t)}$, f_e, and CL_R	Pharmacokinetic

Exploratory objectives were defined in the Clinical Study Protocol, but any results will be reported separately from the Clinical Study Report.

$A_{e(0-t)}$: cumulative amount of unchanged drug excreted in the urine from zero to time t; AUC_{ss}: area under the plasma concentration-time curve during the dosing interval at steady-state; CL_R: renal clearance; CL_{ss}/F: apparent plasma systemic clearance at steady-state; $C_{max,ss}$: maximum plasma concentration at steady-state; DNA: deoxyribonucleic acid; f_e: fraction of the dose excreted in urine; NA: not applicable; PK: pharmacokinetic(s); R406: the analyte in plasma for the dephosphorylated drug; $t_{max,ss}$: time of maximum plasma concentration at steady-state; $V_{z,ss}/F$: apparent volume of distribution at steady-state.

Study design

This was an open-label, non-randomised, fixed sequence, 2-period study conducted at a single study centre to investigate the effects of the co-administration of fostamatinib on the plasma digoxin concentration-time profiles in healthy male and female subjects.

The study consisted of 2 treatment periods (Period 1 and Period 2). A digoxin loading dose of 0.25 mg twice daily (bid) was administered to subjects on Day 1 and once daily administrations of 0.25 mg digoxin on each of Days 2 to 8. Once daily digoxin

administrations continued throughout Period 2 with co-administration of 100 mg bid fostamatinib on each of Days 9 to 15. Subjects were resident in the study centre from Day -1 to Day 17 (48 hours after the last fostamatinib administration). Serial pharmacokinetic PK blood and urine samples were collected for measurement of digoxin concentrations on Day 8 (digoxin alone treatment) and on Day 15 (digoxin + fostamatinib treatment). Serial PK blood samples were collected for measurement of R406 concentrations on Day 15 (digoxin + fostamatinib treatment).

Target subject population and sample size

Twenty-one healthy male and female (of non-childbearing potential) subjects aged 18 to 45 years (inclusive) with a body mass index (BMI) of 18 to 30 kg/m^2 (inclusive) were to be enrolled in this study.

This study was not statistically powered in terms of claiming no effect of fostamatinib on exposure of digoxin (ie, if 90% confidence interval [CI] is within 0.8 to 1.25). Interpretation of the results is based on the size of the treatment ratio and associated 90% CI. To illustrate the size of effect that could be detected, it was estimated that 18 completed subjects would provide approximately 87% power to detect a 30% change in area under the plasma concentration-time curve during the dosing interval at steady-state (AUC_{ss}) and 68% power to detect a 30% change in maximum plasma concentration at steady-state ($C_{max,ss}$), significant at the 5% level. This was based on data from a previous digoxin study that suggested an approximate coefficient of variation of 35% for the area under the plasma concentration-time curve (AUC) and 45% for the maximum plasma concentration (C_{max}).

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

Table S2 Details of investigational products

Investigational product	Route of administration, strength, and dosage form	Manufacturer	Batch number
Digoxin	Oral 0.25 mg tablet	Generic	DG348
Fostamatinib	Oral 50 mg tablet	Patheon	10048.7/1

Duration of treatment

Period 1: a digoxin loading dose of 0.25 mg bid on Day 1 and once daily digoxin administrations on Days 2 to 8

Period 2: once daily digoxin administrations and 100 mg bid fostamatinib administrations on Days 9 to 15

Statistical methods

To assess the effect of fostamatinib on digoxin, the primary PK parameters ($C_{max,ss}$ and AUC_{ss}) of digoxin were analysed using an analysis of variance (ANOVA) model following a natural logarithmic transformation, with fixed effects for treatment and subject. Least-squares geometric means, 2-sided 95% CI, ratios of geometric means together with 2-sided 90% CI of test treatment (fostamatinib + digoxin) over reference treatment (digoxin alone) were estimated and presented. Data were to be available for each subject in both treatments in order to be included in any formal statistical analysis.

Subject population

Enrolled: 23 subjects

Completed: 20 subjects

All subjects enrolled were male and eligible to be included in this study.

Summary of pharmacokinetic results

The digoxin PK parameters in plasma, urine, and resulting statistical analysis are presented below in Tables S3, S4, and S5, respectively.

Table S3 Summary statistics of digoxin pharmacokinetic parameters

Parameter		Period 1 digoxin alone (N = 21)	Period 2 digoxin + fostamatinib (N = 20)
AUC_{ss} (ng*h/mL)	Geomean	13.4	18.3
	CV%	23.0	19.3
$C_{max,ss}$ (ng/mL)	Geomean	1.32	2.18
	CV%	27.2	27.3
$t_{max,ss}$ (h)	Median	1.48	1.00
	(Minimum, Maximum)	(0.50, 2.60)	(0.50, 3.00)
CL_{ss}/F (L/h)	Geomean	18.7	13.7
	CV%	23.0	19.3

Geomean: Geometric mean; N: number of subjects.

Table S4 Key digoxin urinary pharmacokinetic parameters

Parameter		Period 1 Digoxin Alone (N = 21)	Period 2 Digoxin + Fostamatinib (N[a] = 19)
$A_{e(0-24)}$ (ng)	Geomean	114000	153000
	CV%	23.2	17.8
f_e (%)	Geomean	45.5	61.4
	CV%	23.2	17.9
CL_R (L/h)	Geomean	8.51	8.48
	CV%	17.1	17.4

a The 0 to 6 hour collection urine volume was missing for Subject E0001035 during Period 2; therefore the digoxin amount excreted and related parameters could not be calculated

Table S5 Statistical comparison of primary digoxin pharmacokinetic endpoints

				Digoxin + fostamatinib/ Digoxin alone	
Parameter (units)	Treatment	N	Geometric LS mean	Ratio (%)	90% CI
AUC_{ss}	Digoxin alone	20	13.31		
(ng·h/mL)	Digoxin + fostamatinib	20	18.29	137.39	(129.61, 145.64)
$C_{max,ss}$	Digoxin alone	20	1.285		
(ng/mL)	Digoxin + fostamatinib	20	2.183	169.88	(145.76, 197.98)

LS; least-squares. Results based on an analysis of variance model following a natural logarithmic transformation with fixed effects for treatment and subject.

The results of the statistical analysis show that digoxin exposure parameters AUC_{ss} and $C_{max,ss}$ increased when digoxin was given concomitantly with fostamatinib when compared to digoxin alone.

Digoxin average cumulative amount of unchanged drug excreted in the urine from zero to 24 hours postdose ($A_{e(0-24)}$) also increased by 34% when digoxin was given with fostamatinib. Renal clearance (CL_R) did not change across treatments.

In light of this interaction, it is advisable to monitor digoxin levels around the start of coadministration and at any change in dosing of fostamatinib. Additionally, if fostamatinib is prescribed concomitantly with P-gp substrates, a potential interaction should be considered. R406 steady state plasma concentrations were reached within 3 days of the start of 100 mg bid fostamatinib dosing and resulted in a median $t_{max,ss}$ of 1.74 hours, geometric mean R406 $C_{max,ss}$ of 808 ng/mL, and AUC_{ss} of 5930 ng*h/mL.

Summary of safety results

No deaths, serious adverse events (SAEs), or other significant adverse events (OAEs) were reported. At least 1 adverse event (AE) was reported for 11 subjects (47.8%): 6 subjects

(26.1%) after digoxin; 4 subjects (20.0%) after digoxin + fostamatinib; and 1 subject (5.0%) during the follow-up period. One AE of interest, increased hepatic enzyme, were reported after the follow-up period.

No important safety concerns were reported and fostamatinib was well tolerated when co-administered with digoxin.