AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fostamatinib
Study Code	D4300C00014
Edition Number	1
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An Open-Label, Single Center Study to Assess the Pharmacokinetics of Pioglitazone in Healthy Subjects when Administered Alone and in Combination with Fostamatinib 100 mg Twice Daily

Study dates: First subject enrolled: 23 March 2011
Last subject last visit: 16 May 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(s)

This study was conducted at 1 study center,

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives[a]	Outcome variables	Type
Primary	**Primary**	
To assess the pharmacokinetics of pioglitazone in healthy subjects when administered alone and in combination with fostamatinib	Primary parameters: C_{max} and t_{max}, Secondary parameters: λ_z, $t_{1/2\lambda z}$, AUC, $AUC_{(0-t)}$, CL/F and V_z/F	Pharmacokinetic
Secondary	**Secondary**	
To assess the pharmacokinetics of pioglitazone's active hydroxylated metabolite M-IV (hydroxyl-pioglitazone), when pioglitazone is administered alone and in combination with fostamatinib	C_{max}, t_{max}, λ_z, $t_{1/2\lambda z}$, AUC, and $AUC_{(0-t)}$	Pharmacokinetic
To examine the safety and tolerability of fostamatinib in combination with pioglitazone	Adverse events, clinical laboratory results, vital signs, electrocardiograms, and physical examinations	Safety

[a] Two exploratory objectives were specified in the clinical study protocol, but results relating to these objectives are not included in this clinical study report.

Study design

This was an open-label, nonrandomized, 2-period (Periods 1 and 2) study conducted at a single study center to assess the pharmacokinetics of pioglitazone and its active metabolite, hydroxyl-pioglitazone, when pioglitazone was coadministered with fostamatinib in healthy males and females. Fostamatinib 100 mg was administered twice daily for 8 days (Period 2, Days 1 to 8). Pioglitazone was administered as a 30-mg dose on 2 occasions (Period 1, Day 1 and Period 2, Day 7).

Following an up to 28-day screening period, volunteers underwent 2 fixed-sequence treatment periods with a washout period between treatments of at least 5 days. In Period 1, volunteers remained in the clinic from check-in on Day -1 until Day 3. Volunteers returned to the clinic on Day -1 of Period 2 and remained confined until Day 9. A follow-up visit occurred 3 to 7 days following Period 2 discharge.

During each treatment period, serial blood samples for the determination of pioglitazone and hydroxyl-pioglitazone (M-IV) concentrations were collected prior to and for 48 hours following pioglitazone administration (Day 1 of Period 1 and Day 7 of Period 2). On Day 7 of

Period 2, samples for the determination of R406 concentrations were collected prior to dosing and serially postdose up to 12 hours. Trough R406 samples were collected prior to dosing on Days 4, 5, and 6.

Target subject population and sample size

The target population was healthy males and females aged 18 to 55 years (inclusive) with a minimum weight of 50 kg and a body mass index of 18 to 35 kg/m^2 (inclusive).

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

Each volunteer received single, oral doses of 30 mg pioglitazone on 2 separate occasions (batch number: C16930) and 16 doses of 100 mg fostamatinib administered twice daily (as two 50-mg tablets) over 8 days (batch number: CKZP). Study drug was administered with 240 mL water.

Duration of treatment

The duration of volunteer participation was approximately 54 days. This included a 28-day screening period, a 4-day treatment period, a minimum 5-day washout, a 10-day treatment period (Period 2), and a follow-up visit up to 7 days after Period 2 discharge. The duration of the study was approximately 2 months from screening until the last follow-up evaluation.

Statistical methods

To assess the effect of R406 on pioglitazone and hydroxyl-pioglitazone (M-IV) pharmacokinetics, the pharmacokinetic parameters of pioglitazone and hydroxyl-pioglitazone (M-IV) were analyzed using an analysis of variance model on the log transformed pioglitazone and hydroxyl-pioglitazone (M-IV) C_{max} and AUC [or $AUC_{(0-t)}$] with fixed effects for treatment and subject. Ratios of geometric means (test/reference) and the associated 90% confidence intervals were presented. Data was to be available for each volunteer in both periods in order to be included in any formal statistical analysis.

An assessment of fostamatinib steady-state was made using the R406 trough (predose) plasma concentrations collected in Period 2 on Days 4 through 7 via graphical presentations. Plasma concentrations of all analytes and their derived pharmacokinetic parameters were summarized by treatment using descriptive statistics.

Subject population

There were 15 study participants overall, 13 volunteers completed the study and 2 volunteers withdrew at their discretion due to family emergencies. All volunteers were male and 8 (53.3%) were white, 5 (33.3%) were black, and 2 (13.3%) were American Indian. Four (26.7%) volunteers reported their ethnicity as Hispanic. The mean (±standard deviation) age was 33.0 (±9.7) years and ranged from 20 to 54 years. All volunteers were considered healthy at study entry and there were no concomitant medications reported. All 15 volunteers were included in the safety analysis and summary statistics, as appropriate. The 13 volunteers

completing both treatment periods were included in the inferential analysis for pioglitazone and hydroxyl-pioglitazone (M-IV).

Summary of pharmacokinetic results

This study was conducted to determine if the in vitro potential of R406 as an inducer of *CYP2C8*-mediated metabolism was demonstrated in vivo. Pioglitazone was chosen as a probe due to the *CYP2C8*-mediated metabolism of pioglitazone to its primary active metabolite hydroxyl-pioglitazone (M-IV).

The results of the primary statistical comparison of pioglitazone and hydroxyl-pioglitazone pharmacokinetic parameters following administration of a single dose of pioglitazone concomitantly with multiple-dose fostamatinib dosed to steady state, compared to a single dose of pioglitazone administered alone are presented in Table S2.

Table S2 Statistical comparison of key pioglitazone and hydroxyl-pioglitazone pharmacokinetic parameters

					Pioglitazone + Fostmatinib/ Pioglitazone alone	
Analyte	**Parameter (units)**	**Treatment[a]**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
Pioglitazone	AUC	Pioglitazone Alone	11	10490		
	(ng·h/mL)	Pioglitazone + Fostamatinib	11	12350	117.82	(108.41, 128.04)
	C_{max}	Pioglitazone Alone	13	908.0		
	(ng/mL)	Pioglitazone + Fostamatinib	13	751.9	82.81	(64.20, 106.81)
Hydroxyl-pioglitazone	$AUC_{(0-t)}$	Pioglitazone Alone	13	14210		
	(ng·h/mL)	Pioglitazone + Fostamatinib	13	12740	89.65	(78.87, 101.90)
	C_{max}	Pioglitazone Alone	13	379.5		
	(ng/mL)	Pioglitazone + Fostamatinib	13	345.0	90.91	(78.64, 105.09)

LS least squares, CI confidence interval.
Results based on linear model with fixed effects for treatment and subject.
[a] Piolglitazone alone: Period 1, Day 1 pioglitazone 30 mg single dose; Pioglitazone + Fostamatinib: Period 2, Days 1 to 8 fostamatinib 100 mg twice daily; Period 2, Day 7 pioglitazone 30 mg single dose.

The results showed a trend of lower geometric mean maximum plasma concentrations for both pioglitazone and hydroxyl-pioglitazone when pioglitazone was coadministered with fostamatinib.

No differences in t_{max} were noted for either analyte between treatments with a median of approximately 2 and 24 hours for pioglitazone and hydroxyl-pioglitazone, respectively.

An approximately 18% mean increase in pioglitazone AUC was observed when pioglitazone was coadministered with fostamatinib, but no increase was noted for hydroxyl-pioglitazone $AUC_{(0\text{-}t)}$.

Taken together, these results are not indicative of in vivo induction of pioglitazone, which would be expected to produce a clinically significant decrease in parent exposure accompanied by an increase in metabolite exposure.

Pioglitazone $t_{1/2\lambda z}$ was 9.41 hours administered alone and 12.8 hours with fostamatinib coadministration. Hydroxyl-pioglitazone AUC and $t_{1/2\lambda z}$ could not be adequately characterized for either treatment.

Summary of safety results

All 15 volunteers received a single, oral dose of 30 mg pioglitazone during Period 1; 13 volunteers received 12 doses of 100 mg fostamatinib (administered twice daily from Days 1 to 6) and 1 volunteer received 9 doses of 100 mg fostamatinib (twice daily from Day 1 to the morning of Day 5); and 13 volunteers received the combination therapy (100 mg fostamatinib twice daily on Days 7 and 8 with 30 mg pioglitazone on Day 7 only).

There were no deaths, withdrawals due to adverse events, or adverse events of severe intensity reported during study conduct.

There was 1 serious adverse event of moderate upper gastrointestinal hemorrhage that began 8 days after the last dose of investigational product (Day 16 of Period 2), for which the volunteer was hospitalized. Endoscopic evaluation indicated a single 1-cm antral ulcer and *H. pylori* testing was positive. The treatment plan included oral antibiotics for 2 weeks and a proton pump inhibitor for 3 months with repeat endoscopy at the end of that time. Follow-up approximately 1 month after study conclusion indicated hemoglobin had improved and the volunteer was without symptoms. The repeat endoscopy performed approximately 4 months after study conclusion indicated the gastric ulcer had healed. Although the ulcer was felt to be directly related to *H. pylori*, a contributing role from the investigational product could not be ruled out completely.

There were 4 nonserious adverse events in 4 volunteers, all of which were assessed by the Investigator as mild in intensity and not related to investigational product. Nonserious adverse events included ecchymosis in 1 (6.7%) volunteer during the pioglitazone alone treatment and upper respiratory tract infection, contusion, and dizziness in 1 (7.7%) volunteer each during the combination treatment.

There were no trends or clinically meaningful changes noted in clinical laboratory, vital sign, or electrocardiogram findings throughout the study and no meaningful differences were noted between the treatments.