AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Vandetanib
Study Code	D4200C00102
Edition Number	1
Date	15 October 2012

A Phase I, Open-label, Single-center Study to Assess the Pharmacokinetics of Metformin, an OCT2 Substrate, in Healthy Subjects When Administered Alone and in Combination with a Single Oral Dose of Vandetanib (CAPRELSA™) 800 mg

Study dates: First subject enrolled: 28 March 2012
Last subject last visit: 18 June 2012

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	Assess metformin C_{max} and AUC in healthy subjects (wild type for OCT2) for metformin administered alone and in combination with vandetanib 800 mg	C_{max} and AUC of metformin
Secondary	Safety	Examine the safety and tolerability of vandetanib in combination with metformin	Adverse events, vital signs, electrocardiograms, clinical laboratory measurements, and bedside glucose monitoring
	Pharmacokinetic	Assess metformin $AUC_{(0-t)}$, $t_{1/2}$, t_{max}, CL/F, and V_z/F in healthy subjects (wild type for OCT2) for metformin administered alone and in combination with vandetanib 800 mg	t_{max}, $AUC_{(0-t)}$, $AUC_{(0-48)}$, λ_z, $t_{1/2,\lambda z}$, CL/F, and V_z/F for metformin
	Pharmacokinetic	Assess in vandetanib $AUC_{(0-t)}$, C_{max}, and t_{max} in healthy subjects (wild type for OCT2) for vandetanib in combination with metformin	C_{max}, t_{max}, and $AUC_{(0-t)}$ for vandetanib
	Pharmacokinetic	Assess the pharmacokinetics of metformin in urine when administered alone and in combination with vandetanib	$A_{e(0-48)}$, $F_{e(0-48)}$,and CL_R for metformin
Exploratory	Pharmacokinetic	Store selected plasma for further potential metabolism and pharmacokinetic investigations	These data do not form part of the main report for this study.
	Pharmacogenetic	Collect and store deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability, and efficacy) to vandetanib and/or agents used in combination	These data do not form part of the main report for this study.
	Biomarker	Collect an optional blood sample for safety biomarker testing that will allow future assessment of safety biomarkers	These data do not form part of the main report for this study.

$A_{e(0-48)}$ amount of drug excreted in urine from zero (predose) to 48 hours; AUC area under the plasma concentration versus time curve from zero (predose) extrapolated to infinity; $AUC_{(0-t)}$ area under the plasma concentration versus time curve from zero (predose) to time of last quantifiable concentration; $AUC_{(0-48)}$ area under the plasma concentration versus time curve from time zero (predose) to 48 hours; CL/F apparent oral clearance from plasma; CL_R renal clearance; C_{max} maximum plasma concentration; $F_{e(0-48)}$ fraction of drug excreted in urine from zero (predose) to 48 hours postdose; λ_z apparent terminal rate constant; NA not applicable; $t_{1/2,\lambda z}$ apparent terminal half-life; t_{max} time of maximum concentration; V_z/F apparent volume of distribution.

Study design

This was a single-center, open-label, nonrandomized, 2 sequential period study to evaluate the plasma metformin concentration-time profiles and the resulting pharmacokinetic parameters in 14 healthy adult male and female volunteers (wild type for OCT2).

On Day 1 in Period 1 volunteers received a single oral dose of metformin 1000 mg alone followed by an at least 7-day washout period. On Day 1 in Period 2, all volunteers received a single oral dose of vandetanib 800 mg alone. Three hours after the dose of vandetanib, all volunteers received a single oral dose of metformin 1000 mg.

On Day 1 in Period 1, volunteers received a light breakfast 4 hours prior to metformin dose and continued to abstain from food until 4 hours postdose. Water was withheld for 1 hour predose until 2 hours postdose. On Day 1 in Period 2, volunteers received a light breakfast 1 hour prior to vandetanib dose and continued to abstain from food until 4 hours after the metformin dose. Water was withheld for 1 hour prior to the vandetanib dose until 2 hours after the vandetanib dose and 1 hour before the metformin dose.

Serial blood samples for pharmacokinetic analysis of metformin were collected following the metformin dose in Period 1 for 96 hours. In Period 2, blood samples for pharmacokinetic analysis of vandetanib and metformin were collected for 672 hours and 96 hours following the vandetanib and metformin dose, respectively. Urine was collected for metformin pharmacokinetics in Period 1 and 2 on Day 1 (continuing through Day 2) from 0 to 24 and 24 to 48 hours following the metformin dose.

Target subject population and sample size

Healthy male and nonchildbearing female volunteers aged 18 to 50 years (inclusive) with a minimum weight of 50 kg and a body mass index between 18 to 30 kg/m^2 (inclusive) (wild type for OCT2) were eligible for study participation.

Fourteen volunteers were enrolled to assure a minimum of 12 volunteers completed the study.

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

All study medications were administered with 240 mL water. In Period 1, volunteers received a single, oral dose of 1000 mg metformin on Day 1. In Period 2, volunteers received a single, oral dose of 800 mg vandetanib and a single, oral dose of 1000 mg metformin 3 hours following the vandetanib dose on Day 1.

Vandetanib 100 mg, batch number TX28132; Vandetanib 300 mg, batch number TX28131; Metformin batch number 1C75334A.

Duration of treatment

This study consisted of a screening period of up to 28 days before the first administration of study medication on Day 1 in Period 1. All volunteers were to undergo 2 study periods, which

were separated by a washout period of at least 7 days after the metformin dose on Day 1 in Period 1 until the dose of vandetanib on Day 1 in Period 2. The duration of Period 1 was 6 days including a 5-day and 4-night residential period and a 1-day nonresidential period. The duration of Period 2 was 44 days including a 5-day and 4-night residential period and a 38-day nonresidential period. A follow-up visit occurred 7 to 14 days after completion of the last pharmacokinetic draw of Period 2 and included routine safety assessments.

Statistical methods

Safety, tolerability, pharmacokinetics, and other outcome variables were analyzed by descriptive statistics, including listings, summary statistics, and graphs, as appropriate.

The influence of vandetanib on the pharmacokinetics of metformin was assessed statistically using mixed-effects models on the log-transformed pharmacokinetic parameters (AUC and C_{max}). The ratios of the geometric least-squares means (metformin in the presence of vandetanib and in the absence of vandetanib) with the corresponding 90% confidence interval were presented. If the confidence interval for both AUC and C_{max} was entirely contained within 0.67 and 1.50 (or equivalently, the ratio in percent is entirely within 67% and 150%), it was concluded that the pharmacokinetics of metformin was not influenced by vandetanib; otherwise, it was concluded that the pharmacokinetics of metformin was influenced by vandetanib.

Subject population

The 14 male volunteers in this study had a mean age of 31 years (range 20 to 47 years), a mean weight of 79.9 kg (range 59.5 to 106.0 kg), and a mean body mass index of 25.83 kg/m^2 (range 20.30 to 29.93 kg/m^2). All volunteers were considered healthy at study entry and no previous medications were continued during the study.

Of the 14 volunteers enrolled and dosed, 13 volunteers received all planned doses of investigational product; 12 volunteers completed all study procedures and 1 volunteer was lost to follow-up. One volunteer was withdrawn after receiving only the metformin dose in Period 1. All 14 volunteers were included in the safety analysis set; 14 evaluable volunteers and 13 evaluable volunteers were included in the pharmacokinetic analysis sets for Periods 1 and 2, respectively. There were no important protocol deviations.

Summary of pharmacokinetic results

When a single dose of metformin was coadministered with a single dose of vandetanib 800 mg in healthy volunteers wild type for OCT2, the metformin AUC and C_{max} geometric least-squares mean ratios (90% confidence interval) were 174.45% (158.12, 192.46) and 149.60% (149.60, 167.10), respectively, when compared to metformin given alone. The corresponding 90% confidence interval lies above and crosses the predefined (67%, 150%) no-influence window for AUC and C_{max}, respectively. Coadministration with vandetanib appeared to cause a 52% decrease in CL_R. This increase in metformin exposure and corresponding decrease in metformin CL_R is likely due to vandetanib's inhibition of OCT2 in the kidneys.

Coadministration with vandetanib appeared to also cause an increase in metformin $AUC_{(0-t)}$ and a decrease in CL/F, CL_R, and V_z/F while metformin t_{max} and $t_{1/2,\lambda z}$ did not appear to change.

Vandetanib plasma concentrations and resulting PK parameters following a single 800 mg dose were consistent with those observed in previous studies.

Summary of safety results

There were no deaths, serious adverse events, discontinuations due to adverse events, or adverse events of severe intensity during study conduct. Overall, 9 (64.3%) volunteers experienced at least 1 adverse event during the study; 1 (7.1%) volunteer had adverse events following the single dose of metformin alone and 8 (61.5%) volunteers had adverse events during the vandetanib + metformin combination treatment period. Although the numbers of volunteers with AEs was higher during the combination treatment than during the metformin alone treatment, there were no clinically relevant differences between the treatments for any individual preferred term. The most frequently occurring adverse events included diarrhea in 3 (21.4%) volunteers, Chlamydial urethritis in 2 (14.3%) volunteers, and skin irritation (from electrocardiogram patches) in 2 (14.3%) volunteers. Moderate adverse events included pyrexia (acute febrile illness) and syncope of a few seconds duration, both in 1 volunteer. Otherwise all reported adverse events were of mild intensity.

There was a slight increase in mean serum creatinine during the combination treatment period from 91 µmol/L on Day -1 of Period 2 to 117 and 111µmol/L on Days 3 and 8, respectively. Mean serum creatinine returned to near baseline by Day 15 (96 µmol/L). Mean serum creatinine values during Period 1 (metformin alone) remained stable at 93 µmol/L on Day -1 and 99 µmol/L on Day 3. Bedside glucose monitoring was unremarkable with only mild, transient abnormalities noted that were not felt to be clinically relevant. There were no adverse events reported for laboratory findings.

There were no trends or clinically meaningful changes noted in mean or median vital signs throughout the study and individual vital signs remained generally stable during study conduct.

Increases in mean QTcF beginning at 8 hours postdose on Day 1 of Period 2 following the vandetanib + metformin combination treatment and continuing through Day 8 were noted. There was a mean increase of 19 ms at 8 hours postdose with a maximum increase of 23 ms noted on Day 2. Similar increases were noted in mean QT and QTcB with comparable decreases in mean ventricular heart rate. No adverse events were reported for abnormal electrocardiogram findings.