AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Vandetanib
Study Code	D4200C00103
Edition Number	1
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A Phase I, Open-label, Single-center Study to Assess the Pharmacokinetics of Midazolam, a CYP3A4 Substrate, in Healthy Subjects When Administered Alone and in Combination with a Single Dose of 800-mg Vandetanib (CAPRELSA™)

Study dates:	First subject enrolled: 11 April 2012
	Last subject last visit: 19 July 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	To assess midazolam C_{max} and AUC in healthy volunteers for midazolam administered alone and in combination with vandetanib 800 mg	Midazoloam C_{max} and AUC
Secondary	Safety	To examine the safety and tolerability of vandetanib in combination with midazolam	Adverse events, clinical laboratory assessments, vital signs, pulse oximetry, physical examinations, and 12-lead electrocardiograms
	Pharmacokinetic	To assess midazolam $AUC_{(0-t)}$, $t_{1/2,\lambda z}$, t_{max}, $\lambda_{z,}$ CL/F, and V_z/F in healthy volunteers for midazolam administered alone and in combination with vandetanib 800 mg	Midazolam $AUC_{(0-t)}$, $t_{1/2,\lambda z}$, t_{max}, $\lambda_{z,}$ CL/F, and V_z/F
	Pharmacokinetic	To assess vandetanib $AUC_{(0-t)}$, C_{max}, and t_{max} in healthy volunteers for vandetanib in combination with midazolam	Vandetanib $AUC_{(0-t)}$, C_{max}, and $t_{max.}$
Exploratory	Pharmacokinetic	To store selected plasma for further potential metabolism and pharmacokinetic investigations	These data do not form part of the main report for this study.
	Pharmacogenetic	To 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	To collect blood samples 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.

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; CL/F apparent oral clearance from plasma; C_{max} maximum plasma concentration; λ_z apparent terminal rate constant; $t_{1/2,\lambda z}$ apparent terminal half-life; t_{max} time of maximum concentration; V_z/F apparent volume of distribution.

Study design

This was an open-label, nonrandomized, 2 sequential period study conducted at a single study center to assess the pharmacokinetics of midazolam in healthy volunteers when administered alone and in combination with vandetanib 800 mg. This study consisted of 2 treatment periods (Periods 1 and 2).

On Day 1 in Period 1, a single oral dose of midazolam syrup 7.5 mg was administered. On Day 1 in Period 2, a single oral dose of vandetanib 800 mg was administered. On Day 8 in Period 2, a single oral dose of midazolam syrup 7.5 mg was administered.

Serial blood samples for the determination of midazolam were collected for 48 hours postdose and for the determination of vandetanib were collected for 216 hours postdose. Volunteers in Period 1 were admitted to the study center on Day -1 and remained resident until the completion of Day 3 procedures. Volunteers began Period 2 of the study following an at least 7-day washout period between the midazolam dose on Day 1 of Period 1 and the vandetanib dose on Day 1 of Period 2. Period 2 consisted of 2 residential periods (Days -1 to 4 and Days 7 to 10). Volunteers returned to the study center on Days 5, 6, 15, 22, 29, 36, and 43 for nonresidential visits. A follow-up visit occurred 7 to 14 days following the last nonresidential visit.

Target subject population and sample size

Healthy male and female volunteers of nonchildbearing potential between the ages of 18 and 50 years, inclusive, with a minimum weight of 50 kg, and a body mass index between 18 and 30 kg/m^2, inclusive, were eligible for study participation.

Sixteen volunteers were planned for enrollment to assure a minimum of 14 volunteers completed the study. Replacement volunteers were allowed.

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

All investigational products were administered with 240 mL water. On the morning of Day 1 in Period 1, a single oral dose of midazolam syrup 7.5 mg was administered. On the morning of Day 1 in Period 2, a single dose of vandetanib 800 mg (two 300-mg [Batch # TX28131] and two 100-mg tablets [Batch # TX28132]) was administered and on the morning of Day 8 in Period 2 a single oral dose of midazolam syrup 7.5 mg was administered (Lot # 162152A).

Duration of treatment

The duration of this study for each volunteer was approximately 92 days, including a screening period of 28 days or less (relative to the first dose of midazolam on Day 1 in Period 1), a Period 1 residential treatment period of 4 days (from check-in on Day -1 until discharge on Day 3), a washout period of at least 7 days between the midazolam dose on Day 1 in Period 1 and the vandetanib dose on Day 1 in Period 2, Period 2 residential treatment periods of 5 days (from check-in on Day -1 until check-out on Day 4) and 4 days (from Day 7

to 10), 7 nonresidential visits (Day 5, 6, 15, 22, 29, 36, and 43), and a follow-up visit 7 to 14 days after the last nonresidential visit.

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 midazolam 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 (midazolam in the presence of vandetanib and in the absence of vandetanib) with the corresponding 90% confidence intervals were presented. If the confidence intervals for both AUC and C_{max} were entirely contained within 0.67 and 1.50, it was concluded that the pharmacokinetics of midazolam were not influenced by vandetanib; otherwise, it was concluded that the pharmacokinetics of midazolam were influenced by vandetanib.

Subject population

The 17 volunteers in this study had a mean age of 31 years (range 18 to 49 years), a mean weight of 79.0 kg (range 65.4 to 105.9 kg), and a mean body mass index of 24.74 kg/m^2 (range 20.32 to 29.70 kg/m^2). There were 16 (94.1%) men and 1 (5.9 %) woman. All volunteers were considered healthy at study entry and no previous medications were continued during the study.

Of the 17 volunteers enrolled and dosed in this study, 16 volunteers received all planned doses of investigational product and completed all study procedures. One volunteer withdrew consent after receiving only the midazolam dose in Period 1. All 17 volunteers were included in the safety analysis; 17 and 16 volunteers were included in the pharmacokinetic analyses for Periods 1 and 2, respectively. There were no important protocol deviations that led to exclusion of data from the analyses.

Summary of pharmacokinetic results

When midazolam was administered after vandetanib, midazolam AUC and C_{max} geometric least-squares mean ratios (90% confidence intervals) were 97.87 (92.02, 104.10) and 97.35 (87.72, 108.04). The corresponding 90% confidence intervals lie entirely within the predefined no influence limits of 0.67 and 1.5. In fact the 90% confidence intervals fell within the more stringent bioequivalence bounds of 0.8 to 1.25.

The geometric means of midazolam AUC, C_{max}, t_{max} (median), $t_{1/2,\lambda z}$, CL/F, and V_z/F were similar when midazolam was administered alone and when midazolam was administered following vandetanib.

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

Summary of safety results

There were no deaths, discontinuations due to adverse events, or adverse events of severe intensity during study conduct. One volunteer experienced a serious adverse event of electrocardiogram changes for which he was hospitalized. The event began approximately 8 hours after receiving vandetanib alone (Day 1 of Period 2) when electrocardiogram findings included ST and T wave abnormality and possible lateral and inferior ischemia. The volunteer was asymptomatic; a 2-dimensional echocardiogram was normal and a stress echocardiogram revealed no myocardial ischemia. Treatment included acetylsalicylic acid (324 mg, once) and oxygen (2 L/min via nasal cannula). The event resolved approximately 40 hours after onset (Day 3) and the volunteer completed the study as planned. The event was assessed by the Investigator as mild in intensity and potentially related to vandetanib.

Overall, 17 (100.0%) volunteers experienced at least 1 adverse event during the study; 14 (82.4%) volunteers had adverse events during the midazolam alone treatment period, 6 (37.5%) volunteers had adverse events during the vandetanib alone treatment period, and 16 (100.0%) volunteers had adverse events during the combination treatment period. There were 28 adverse events of sedation in 17 (100.0%) volunteers, all of which occurred following midazolam dosing in both periods and is an expected effect of this drug. Frequently reported adverse events included contact dermatitis in 4 (23.6%) volunteers (2 volunteers each during the midazolam alone and vandetanib alone treatments) and abdominal discomfort in 3 (17.6%) volunteers (2 volunteers during the vandetanib alone and combination treatment). All adverse events during the study were of mild or moderate intensity.

There was a slight increase in mean serum creatinine during the vandetanib alone treatment period from 86 µmol/L on Day -1 of Period 2 to 109 µmol/L on Day 3. Mean serum creatinine returned to near baseline by Day 8 (93 µmol/L). Mean serum creatinine values during Period 1 (midazolam alone) remained stable at 86 µmol/L on Day -1 and 89 µmol/L on Day 3.

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

There was an increase in mean QTcF beginning 4 hours following the vandetanib alone treatment on Day 1 of Period 2 continuing through Day 5 and resolving by Day 8. A mean increase of 15 ms was noted at 8 hours postdose on Day 1; the maximum increase of 33 ms was noted on Day 2. There were similar increases in mean QT and QTcB with slight decreases in mean ventricular heart rate on Days 2 and 3.