AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Vandetanib
Study Code	D4200C00100
Edition Number	1
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A Phase I, Open-label, Single-center Study to Assess the Pharmacokinetics of Digoxin in Healthy Subjects When Administered Alone and in Combination with a Single Dose of Vandetanib (CAPRELSA ™) 300 mg

Study dates:	First subject enrolled: 03 April 2012
	Last subject last visit: 20 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 digoxin C_{max} and AUC in healthy volunteers for digoxin administered alone and in combination with vandetanib 300 mg	C_{max}, AUC
Secondary	Safety	To examine the safety and tolerability of vandetanib in combination with digoxin	Adverse events, clinical laboratory assessments, vital signs, physical examinations, and 12-lead electrocardiograms
	Pharmacokinetic	To assess digoxin $AUC_{(0-t)}$, $AUC_{(0-48)}$, λ_z, $t_{1/2,\lambda z}$, t_{max}, CL/F, and V_z/F in healthy volunteers for digoxin administered alone and in combination with vandetanib 300 mg	Digoxin plasma $AUC_{(0-t)}$, $AUC_{(0-48)}$, λ_z, $t_{1/2,\lambda z}$, t_{max}, CL/F, and V_z/F Digoxin urine $A_{e(0-48)}$, $F_{e(0-48)}$, and CL_R
	Pharmacokinetic	To assess vandetanib $AUC_{(0-t)}$, C_{max}, and t_{max} in healthy volunteers for vandetanib in combination with digoxin	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.

$A_{e(0-48)}$ amount of digoxin excreted in the urine from predose to 48 hours postdose; 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 zero (predose) to 48 hours postdose; CL/F apparent oral clearance from plasma; CL_R renal clearance; C_{max} maximum plasma concentration; $F_{e(0-48)}$ fraction of digoxin dose excreted in urine from 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 an open-label, nonrandomized, 2 sequential period study conducted at a single study center to investigate the effects of coadministration of vandetanib on the plasma digoxin-time profiles and resulting pharmacokinetic parameters. This study consisted of 2 treatment periods (Periods 1 and 2).

There was a screening period of 28 or less days. On Day 1 in Period 1, a single oral dose of digoxin 0.25 mg was administered. On Day 1 in Period 2, a single oral dose of vandetanib 300 mg and digoxin 0.25 mg was administered.

Serial blood samples for the determination of digoxin concentrations were collected for 168 hours postdose on Day 1 of each treatment period and samples for the determination of vandetanib concentrations were collected for 96 hours postdose on Day 1 of Period 2. Volunteers in Period 1 were admitted to the study center on Day -1 and remained resident until the completion of Day 3 procedures. Volunteers returned to the study center on Days 4, 5, 6, 7, and 8 for nonresidential visits. Volunteers began Period 2 of the study following a minimum 14-day washout period between the digoxin dose on Day 1 of Period 1 and the vandetanib plus digoxin dose on Day 1 of Period 2. Period 2 consisted of 1 residential period (Days -1 to 4). Volunteers returned to the study center on Days 5, 6, 7, 8, 15, 22, and 29 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 45 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.

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. On the morning of Day 1 in Period 1, a single oral dose of digoxin 0.25 mg (lot no. A81318) was administered. On the morning of Day 1 in Period 2, a single oral dose of vandetanib 300 mg (batch no. TX28131) plus digoxin 0.25 mg was administered.

Duration of treatment

The duration of this study for each volunteer was approximately 88 days, including a screening period of 28 days or less (relative to the first dose of digoxin 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), 5 nonresidential visits (on Days 4, 5, 6, 7, and 8), a washout period of at least 14 days between the digoxin dose on Day 1 in Period 1 and the vandetanib plus digoxin dose on Day 1 in Period 2, Period 2 residential treatment period of 5 days (Day -1 to Day 4), 7 nonresidential

visits (on Days 5, 6, 7, 8, 15, 22, and 29), 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. All data were listed.

The influence of vandetanib on the pharmacokinetics of digoxin was assessed statistically using mixed-effects models on the log-transformed pharmacokinetic parameters (AUC, $AUC_{(0-t)}$, and C_{max}). The ratios of the geometric least-squares means (digoxin 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, $AUC_{(0-t)}$, and C_{max} was entirely contained within 0.67 and 1.50, it was concluded that the pharmacokinetics of digoxin was not influenced by vandetanib; otherwise, it was concluded that the pharmacokinetics of digoxin were influenced by vandetanib.

Subject population

The 14 male volunteers in this study had a mean age of 30 years (range 18 to 44 years), a mean weight of 80.5 kg (range 56.6 to 101.5 kg), and a mean body mass index of 25.81 kg/m^2 (range 18.63 to 30.00 kg/m^2). All volunteers were considered healthy at study entry and no previous medications were continued during the study.

All 14 volunteers received all planned doses of investigational product and completed all study procedures; therefore, all 14 volunteers were included in the safety and pharmacokinetic analysis sets. There were no important protocol deviations.

Summary of pharmacokinetic results

The majority of the subjects did not have any AUC estimated reported as the AUC% extrapolated were greater than 20% and made the estimates too uncertain. Therefore, $AUC_{(0-t)}$ was included in the statistical analysis.

When a single dose of digoxin was coadministered with a single dose of vandetanib, the digoxin AUC, $AUC_{(0-t)}$, and C_{max} geometric least-squares mean ratios (90% confidence interval) were 119.01% (102.13, 138.68), 122.61% (112.14, 134.05), and 129.46% (109.93, 152.46), respectively, compared to digoxin given alone.

The 90% confidence intervals surrounding digoxin AUC and $AUC_{(0-t)}$ geometric mean ratios was entirely within the predefined (0.67, 1.50) no-influence limits, however the 90% confidence interval surrounding digoxin C_{max} was not fully contained within the predefined no-influence window (ie, exceeded the upper limit).

Geometric mean digoxin AUC appeared to be increased when coadministration of a single dose of digoxin with a single dose of vandetanib compared to digoxin alone. However, only 4

(combination treatment) and 5 (digoxin alone) subjects out of 14 had an AUC estimate. The AUC values were not reported due to an AUC% extrapolated greater than 20%.

Coadministration with vandetanib appeared to cause a slight increase in digoxin F_e and a slight decrease in digoxin CL_R.

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, 6 (42.9%) volunteers experienced at least 1 adverse event during the study; 3 (21.4%) volunteer had adverse events following the single dose of digoxin alone and 5 (35.7%) volunteers had adverse events during the vandetanib plus digoxin combination treatment period. All adverse events during the study were of mild intensity.

There was an increase in mean serum creatinine from 90 µmol/L prior to dosing to 114 and 105 µmol/L on Days 3 and 8, respectively, during the combination treatment period (Period 2). During the digoxin-alone treatment (Period 1), mean serum creatinine remained stable from Day -1 (90 µmol/L) to Day 3 (98 µmol/L). Otherwise, no clinically relevant changes in mean or median laboratory values were noted following dosing in either treatment period.

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. There were no adverse events reported for abnormal vital sign findings.

There were no clinically important changes in mean QTcB or QTcF during the study.