AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | Vandetanib |
| Study Code | D4200C00101 |
| Edition Number | 1 |
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# A Phase I, Randomized, Open-label, Single-center Study to Assess the Pharmacokinetics of Vandetanib (CAPRELSA™) in Healthy Subjects when a Single Oral Dose of Vandetanib 300 mg is Administered Alone and in Combination with Omeprazole or Ranitidine

**Study dates:** First subject enrolled: 28 February 2012
Last subject last visit: 20 September 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 vandetanib $C_{max}$ and $AUC_{(0-t)}$ for a single dose of vandetanib 300 mg in healthy volunteers administered alone and in combination with omeprazole (proton pump inhibitor) | Vandetanib $C_{max}$, $AUC_{(0-t)}$ |
| | Pharmacokinetic | To assess vandetanib $C_{max}$ and $AUC_{(0-t)}$ for a single dose of vandetanib 300 mg in healthy volunteers administered alone and in combination with ranitidine (histamine antagonist) | Vandetanib $C_{max}$, $AUC_{(0-t)}$ |
| Secondary | Safety | To examine the safety and tolerability of vandetanib in combination with omeprazole | Adverse events, vital signs, electrocardiograms, and clinical laboratory measurements (hematology, clinical chemistry, and urinalysis) |
| | Pharmacokinetic | To assess vandetanib AUC, $AUC_{(0-672)}$, $\lambda_z$, $t_{1/2,\lambda z}$, $t_{max}$, CL/F, and $V_z$/F for vandetanib alone and in combination with omeprazole | Vandetanib AUC, $AUC_{(0-672)}$, $\lambda_z$, $t_{1/2,\lambda z}$, $t_{max}$, CL/F, $V_z$/F |
| | Safety | To examine the safety and tolerability of vandetanib in combination with ranitidine | Adverse events, vital signs, electrocardiograms, and clinical laboratory measurements (hematology, clinical chemistry, and urinalysis) |
| | Pharmacokinetic | To assess vandetanib AUC, $AUC_{(0-672)}$, $\lambda_z$, $t_{1/2,\lambda z}$, $t_{max}$, CL/F, and $V_z$/F of vandetanib alone and in combination with ranitidine | Vandetanib AUC, $AUC_{(0-672)}$, $\lambda_z$, $t_{1/2,\lambda z}$, $t_{max}$, CL/F, $V_z$/F |
| Exploratory | Pharmacokinetic | To store selected plasma for further potential metabolism and pharmacokinetic investigations | See CSP Section 6.6. |

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| | 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 | See CSP Section 6.6. |
| | Biomarker | To collect optional blood samples for safety biomarker testing that will allow future assessment of safety biomarkers | See CSP Section 6.6. |

Results from exploratory analyses, if performed, were reported separately from the Clinical Study Report.

## Study design

This was a single-center, open-label, randomized, 2-group, 2-period crossover study to evaluate the interaction of vandetanib with omeprazole and with ranitidine in 32 healthy adult male and female volunteers.

Interaction with omeprazole and interaction with ranitidine was evaluated in 2 separate groups (Group 1 and Group 2) of 16 volunteers each using a 2-group, 2-period crossover design for each group. Enrollment into Group 1 was completed prior to the start of enrollment into Group 2. Within Group 1, volunteers were randomly assigned into 1 of 2 treatment sequences AB and BA (AB: vandetanib 300 mg [Clinical Trial formulation] alone in Period 1 then crossover to omeprazole in combination with vandetanib 300 mg in Period 2; BA: omeprazole followed in combination with vandetanib 300 mg in Period 1 then crossover to vandetanib 300 mg alone in Period 2). Within Group 2, volunteers were randomly assigned into 1 of 2 treatment sequences AC and CA (AC: vandetanib 300 mg alone in Period 1 then crossover to ranitidine in combination with vandetanib 300 mg in Period 2; CA: ranitidine in combination with vandetanib 300 mg in Period 1 then crossover to vandetanib 300 mg alone in Period 2).

Serial blood samples for pharmacokinetic analysis of vandetanib were collected following vandetanib dosing in Periods 1 and 2 in both groups.

## Target subject population and sample size

Healthy male and female (nonpregnant, nonlactating) 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).

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

All study medications were administered with 240 mL water. Treatments were as follows:

**Group 1:**

Treatment A: a single oral dose of vandetanib 300 mg on the morning of Day 1

Treatment B: a morning daily oral dose of omeprazole 40 mg (Days 1 to 4), and a single oral dose of omeprazole 40 mg and vandetanib 300 mg on the morning on Day 5

**Group 2:**

Treatment A: a single oral dose of vandetanib 300 mg on the morning of Day 1

Treatment C: single oral dose of ranitidine 150 mg (evening of Day 1), followed by a single oral dose of ranitidine 150 mg and vandetanib 300 mg on the morning of Day 2

Vandetanib 300 mg batch number TX28131

Ranitidine (Zantac) 150 mg lot number 1ZP9344

Omeprazole (Prilosec) 40 mg lot number G000106

There was no comparator.

**Duration of treatment**

The study consisted of a screening period of up to 28 days before the first administration of drug on Day 1 in Period 1.

All volunteers underwent 2 study periods. The 2 study periods were separated by a washout of at least 3 months (90 days) from the first dose in Period 1 until the first dose of Period 2. The duration of each period was 29 to 33 days in Group 1 and 29 to 30 days in Group 2. A follow-up visit occurred 7 to 14 days after completion of the last pharmacokinetic blood 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.

Influence of omeprazole and ranitidine on the pharmacokinetics of vandetanib was assessed statistically using mixed effects models on the log-transformed pharmacokinetic parameters [$AUC_{(0-t)}$ and $C_{max}$]. The least-squares means of each treatment and their 95% confidence intervals were calculated from the model. The ratios of the geometric least-squares means (vandetanib in the presence of omeprazole/vandetanib in the absence of omeprazole and vandetanib in the presence of ranitidine/vandetanib in the absence of ranitidine) with the corresponding 90% confidence interval were presented.

## Subject population

A total of 34 male volunteers were enrolled in the study and received at least 1 dose of investigational product. There were 29 (85.3%) volunteers that completed the study. There were 2 (12.5%) volunteers in Group 1 and 3 (16.7%) volunteers in Group 2 who did not complete the study. All 34 volunteers enrolled in the study were included in the pharmacokinetics and safety analysis sets.

## Summary of pharmacokinetic results

When vandetanib was coadministered with omeprazole in Group 1, the vandetanib $AUC_{(0-t)}$ geometric least squares mean ratio was 93.87% compared to vandetanib given alone. The corresponding 90% confidence interval (88.63%, 99.42%) was completely contained within the (80%, 125%) no influence window. However, $C_{max}$ geometric least-squares mean ratio was 84.52% compared to vandetanib given alone. The corresponding 90% confidence interval (74.51%, 95.88%) crossed the lower limit of the (80%, 125%) no influence window.

When vandetanib was coadministered with ranitidine in Group 2, the vandetanib $AUC_{(0-t)}$ and $C_{max}$ geometric least-squares mean ratios were 101.43% and 108.05%, respectively, compared to vandetanib given alone. The corresponding 90% confidence intervals (96.13, 107.03) for $AUC_{(0-t)}$ and (95.80, 121.86) for $C_{max}$ were completely contained within the (80%, 125%) no influence window.

## Summary of safety results

There were no deaths, discontinuations due to adverse events, or adverse events of severe intensity. There was 1 volunteer with a serious adverse event of abnormal electrocardiogram changes on Day 15 of Period 1, Treatment A. The event was assessed as not related to study drug and was resolved on Day 21 of the same period.

Overall, 19 (55.9%) volunteers experienced at least 1 adverse event following dosing. The most frequently occurring adverse events were nausea, headache, and contact dermatitis. There was 1 adverse event of moderate intensity and the remaining adverse events were of mild intensity.

There was an increase noted in mean serum creatinine in all treatments between Day 3 through Day 12 and values returned to baseline at follow-up. Otherwise, there were no important findings observed in laboratory values, electrocardiograms, vital signs, or physical examinations.