AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Vandetanib
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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

[redacted]

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PROTOCOL SYNOPSIS

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

Investigator

[redacted]

Study center and number of subjects planned

This study will be conducted at 1 study center. Up to 32 volunteers will be enrolled.

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	Phase I
Estimated date of last subject completed	[redacted]	

Objectives

Primary objectives

The primary objectives for this study are:

- 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)
- 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)

Secondary objectives

The secondary objectives for this study are:

- To examine the safety and tolerability of vandetanib in combination with omeprazole

- To assess vandetanib AUC, $AUC_{(0\text{-}672h)}$, λ_z, $t_{1/2,\lambda z}$, t_{max}, CL/F, and V_z/F for vandetanib alone and in combination with omeprazole

- To examine the safety and tolerability of vandetanib in combination with ranitidine

- To assess vandetanib AUC, $AUC_{(0\text{-}672h)}$, λ_z, $t_{1/2,\lambda z}$, t_{max}, CL/F, and V_z/F of vandetanib alone and in combination with ranitidine

Exploratory objectives

The exploratory objectives for this study are:

- To store selected plasma for further potential metabolism and pharmacokinetic investigations

- 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

- To collect optional blood samples for safety biomarker testing that will allow future assessment of safety biomarkers

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

Study design

This is 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.

Group 1 will consist of Treatment A (a single oral dose of vandetanib 300 mg on the morning of Day 1) and 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 will consist of Treatment A and 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).

Interaction with omeprazole and interaction with ranitidine will be 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 will be completed prior to enrollment into Group 2. Within Group 1, volunteers will be 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 followed by vandetanib 300 mg in Period 2; BA: omeprazole followed by vandetanib 300 mg in Period 1 then crossover to vandetanib 300 mg alone in Period 2). Within Group 2, volunteers will be randomly assigned into 1 of 2 treatment sequences AC and CA (AC: vandetanib 300 mg alone in Period 1 then crossover to ranitidine

followed by vandetanib 300 mg in Period 2; CA: ranitidine followed by vandetanib 300 mg in Period 1 then crossover to vandetanib 300 mg alone in Period 2).

Volunteers should abstain from food beginning 10 hours prior to vandetanib dosing in each period and continuing until 4 hours after dosing. On the vandetanib dosing days in each period, water (other than that administered with the dose) will be restricted from 1 hour predose until 2 hours postdose.

Serial blood samples for pharmacokinetic analysis of vandetanib will be collected following vandetanib dosing in Periods 1 and 2 in both groups. Within each group, study periods will be separated by a washout of at least 3 months (90 days) from the first dose in Period 1 until the first dose in Period 2.

Target subject population

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, dosage, and mode of administration

All study medications will be administered with 240 mL water. Treatments are 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.

Comparator, dosage, and mode of administration

Not applicable.

Duration of treatment

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

All volunteers will undergo 2 study periods. The 2 study periods will be 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 is 29 to 33 days in Group 1 and 29 to 30 days in

Group 2. A follow-up visit will occur 7 to 14 days after completion of the last pharmacokinetic draw of Period 2 and will include routine safety assessments.

Outcome variable(s):

- Pharmacokinetic

  The following pharmacokinetic parameters will be calculated (if estimable) from vandetanib plasma concentrations during each treatment: observed maximum concentration (C_{max}), time of maximum concentration (t_{max}), area under the plasma concentration-time curve from zero to infinity (AUC), area under the concentration-time curve in plasma from zero to the last quantifiable concentration [$AUC_{(0-t)}$], area under the plasma concentration-time profile from zero to 672 hours postdose [$AUC_{(0-672h)}$], apparent terminal rate constant (λ_z), apparent terminal half-life ($t_{1/2,\lambda z}$), apparent systemic clearance following extravascular dosing (CL/F), and apparent volume of distribution in the terminal phase (V_z/F).

- Safety

  Safety and tolerability will be assessed by the incidence and severity of adverse events, abnormalities in vital signs, electrocardiograms, and clinical laboratory measurements (hematology, clinical chemistry, and urinalysis).

Statistical methods

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

Influence of omeprazole and ranitidine on the pharmacokinetics of vandetanib will be 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 will be 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 will be presented.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve in plasma from zero to infinity
$AUC_{(0-t)}$	Area under the concentration-time curve in plasma from zero to the last quantifiable concentration
$AUC_{(0-672h)}$	Area under the concentration-time curve in plasma from zero to 672 hours postdose
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation
BCRP	Breast cancer resistance protein
BLQ	Below the LLOQ
BMI	Body mass index
CL/F	Total plasma clearance
CI	Confidence interval
C_{max}	Maximum concentration in the plasma
CPA	Clinical Pharmacology Alliance
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV%	Coefficient of variation
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EGF	Epidermal growth factor
EGFR	Endothelial growth factor receptor
FMO	Flavine monooxygenase
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation or special term	Explanation
hERG	Human-ether-a-go-go gene
HIV	Human immunodeficiency virus
HR	Hazard ratio
HUVEC	Human umbilical vein endothelial cell
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IP	Investigational Product
λ_z	Apparent terminal rate constant
LH	Lutenizing hormone
LLOQ	Lower Limit of Quantification
MDR1	Multi drug resistance 1
MedDRA	Medical Dictionary for Regulatory Activities
MRP1	Multidrug-resistance-associated protein-1
MRP2	Multidrug-resistance-associated protein-2
MTC	Medullar thyroid carcinoma
NA	Not applicable
ND	Not determined
NSCLC	Non-small cell lung cancer
OAE	Other Significant Adverse Event (see definition in Section 11.1.2)
OATP	Organic anion transporting polypeptide
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitors
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
RET	Rearranged during transfection

Abbreviation or special term	Explanation
Rsq	Goodness-of-fit statistic for calculation of λ_z
SAE	Serious adverse event (see definition in Section 6.3.2).
SD	Standard deviation
SOP	Standard Operating Procedures
t_{max}	Time to C_{max}
$t_{1/2}$	Terminal half-life
ULN	Upper limits of normal
VEGF	Vascular endothelial growth factor
VEGFR-2	Vascular endothelial growth factor receptor-2
V_z/F	Apparent volume of distribution in the terminal phase calculated as $CL/F/\lambda_z$

1. INTRODUCTION

Vandetanib is an inhibitor of the tyrosine kinase activity of vascular endothelial growth factor receptor-2 (VEGFR-2), an endothelial cell receptor for vascular endothelial growth factor (VEGF) and the tyrosine kinase activity of the endothelial growth factor receptor (EGFR) and the rearranged during transfection (RET) tyrosine kinase.

1.1 Background

1.1.1 Nonclinical pharmacology

Vandetanib is a potent inhibitor of VEGFR-2 tyrosine kinase activity (the molar concentration required to produce 50% inhibition of a biological effect [IC_{50}]=40 nM). In isolated enzyme assays, vandetanib was also found to be a sub-micromolar inhibitor of Feline McDonough Sarcoma-like tyrosine kinase 4 (Flt 4) (the VEGF C and D receptor: IC_{50}=110 nM) and EGFR tyrosine kinase (IC_{50}=500 nM). Additional vandetanib activity has been demonstrated against oncogenic RET kinase (IC_{50}=100 nM), which is activated in certain thyroid carcinomas.

Vandetanib inhibited VEGF-stimulated human umbilical vein endothelial cell (HUVEC) proliferation potently (IC_{50}=60 nM), but did not affect basal endothelial cell growth at a 50-fold greater concentration. Vandetanib can also inhibit EGFR signaling in endothelial cells at an approximately 3-fold greater concentration than is required to inhibit a VEGF-induced response (vandetanib IC_{50}=170 nM versus epidermal growth factor receptor [EGF]-stimulated HUVEC proliferation).

Vandetanib was shown to be a potent inhibitor of EGFR-dependent (IC_{50}=90 nM) and RET-dependent (IC_{50}=100 nM) in vitro tumor cell growth in non-small cell lung cancer (NSCLC) and thyroid cancer cells, respectively. Therefore, in addition to inhibition of VEGFR-2 tyrosine kinase, inhibition of EGFR and RET tyrosine kinases may provide additional antitumor effects for vandetanib in the treatment of tumors dependent on these signaling pathways for continued growth and survival. Vandetanib significantly inhibited the proliferation of medullar thyroid carcinoma (MTC) cell lines TT and MZ-CRC-1. In addition to inhibiting RET phosphorylation, vandetanib reduced levels of phosphorylated EGFR and phosphorylated VEGFR-2 in MTC cells.

The inhibitory activity of the N-desmethyl and N-oxide metabolites of vandetanib, originally identified in the plasma of rats and dogs, and later confirmed as being present in human plasma, was also examined in a growth factor-stimulated HUVEC-proliferation assay. N-desmethyl vandetanib was found to retain similar potency (versus VEGF) and selectivity (versus EGF and basic fibroblast growth factor) to vandetanib itself, while the N-oxide of vandetanib had relatively weak activity in cells (IC_{50} greater than 3 μM) versus each growth factor stimulus examined.

Vandetanib was orally active with once-daily dosing in a range of in vivo test systems. Vandetanib inhibited a hypotensive change induced by a bolus dose of VEGF in anaesthetized

rats, and because VEGF-induced hypotension is thought to depend upon VEGFR signaling, the data supported VEGFR tyrosine kinase inhibition by vandetanib in vivo. Vandetanib also produced a dose-dependent increase in the femorotibial epiphyseal zone of hypertrophy in growing rats when dosed daily for 14 days (an observation consistent with an ability to inhibit VEGF signaling and also angiogenesis in vivo). Furthermore, vandetanib inhibited tumor-induced angiogenesis significantly in a model involving intradermal implantation of A549 human lung tumor cells into athymic mice and assessment of vascular recruitment over a period of 5 days.

Vandetanib had broad spectrum antitumor activity in vivo, which extended to a range of models (subcutaneously or orthotopically implanted human tumor xenografts or syngeneic murine tumors) and histological types (breast, colon, lung, ovarian, prostate, vulval, anaplastic, and medullary thyroid tumors). Reduced CD31 (endothelial cell) staining and increased tumor cell necrosis has been observed in human tumor xenografts from mice treated chronically with vandetanib (once daily, orally, for 24 days), observations that are consistent with inhibition of angiogenesis and tumor vascular permeability.

At clinically relevant plasma concentrations in a xenograft model, vandetanib significantly reduced levels of phosphorylated EGFR and phosphorylated VEGFR-2 in tumor tissue.

In vitro studies using the human-ether-a-go-go gene (hERG) assay and canine Purkinje fibers indicated that vandetanib may prolong cardiac action potential. N-desmethyl and the N-oxide metabolites were shown to have IC_{50} values similar to vandetanib in the hERG assay.

Vandetanib elevated systolic and diastolic blood pressure in rats and dogs.

In a mouse model, vandetanib delayed but did not prevent wound healing.

1.1.2 Pharmacokinetics and metabolism in animals

The key findings of the oral and intravenous, pharmacokinetics (PK) and metabolism studies performed in support of the safety evaluation of vandetanib in the rat and dog were as follows:

The bioavailability after oral dosing was high (75% to 92%) in the rat and less than 33% in the dog. The absorption was not rapid, with peak concentrations occurring 3 to 8 hours postdose. At higher doses in rats and dogs, profiles were flat, indicating prolonged absorption.

In rats and dogs, the PK of vandetanib exhibited high clearance and high volume of distribution. There was a sex difference in PK in rats, with females showing higher exposure.

Toxicokinetic monitoring in rats showed dose-proportional increases between 1 and 10 mg/kg, but a less-than-proportional increase in exposure between 25 and 75 mg/kg. Dosing to rats for 6 months at 5 mg/kg resulted in a 3-fold increase in exposure. There was evidence of a small degree of accumulation in the dog (13%) in the 1-month toxicity study that was confirmed in the 9-month toxicology study. Exposure was approximately dose linear in the dog at lower doses, but with a less-than-proportional increase between 5 and 15 mg/kg.

Radioactivity was rapidly and extensively distributed in the rat, with the highest concentrations in the gastrointestinal tract, liver, spleen, adrenal glands and other glandular tissues. There was evidence of slow clearance of radioactivity from some tissues (adrenal glands, kidney, and testes) and high concentrations in pigmented tissue, indicating an association of vandetanib-related material with melanin. Drug-related material penetrated the central nervous system. Vandetanib was shown not to be a substrate for P-glycoprotein (Pgp), multidrug-resistance-1 (MDR1), breast cancer resistance protein (BCRP), multidrug-resistance-associated protein 1 (MRP1), multidrug-resistance-associated protein-2 (MRP2), organic cation transporter 1 (OCT1), organic anion transporting polypeptide (OATP) 1B1, or OATP1B3. N-desmethyl vandetanib was not a substrate of OATP1B1 or OATP1B3. Vandetanib did not inhibit MRP1 or MRP2 but did show some inhibition of BCRP and Pgp. Vandetanib was not a substrate but was an inhibitor of organic cation transporter 2 (OCT2), a transporter involved in the renal excretion of creatinine.

Plasma protein binding ranged from 83% (in rats) to 90% (in humans). Vandetanib was shown to bind to both human serum albumin and human α-1-acid glycoprotein.

Two metabolites have been identified in samples from rats and dogs: the N-oxide of vandetanib and N-desmethyl vandetanib. These metabolites and a vandetanib glucuronide have been identified in humans. N-desmethyl vandetanib is primarily produced by *CYP3A4*, and vandetanib N-oxide by flavine containing monooxygenase enzymes flavine monooxygenase (FMO) 1 and FMO3.

Vandetanib had no inhibitory effect on the activity of human P450 isozymes *CYP1A2*, *2A6*, *2B6*, *2C9*, *2C19*, *2E1*, or *3A4*, but did inhibit *2D6* activity (inhibition constant of 13 μg/mL) and *2C8* (57% reduction at vandetanib 100 μg/mL). Vandetanib induced *CYP1A2*, *2C9*, and *3A4* in human hepatocytes. Maximal induction was seen at vandetanib 2 μM, and was 3-fold and 28% of the positive control for *1A2*, 2.3-fold and 38% for *2C9*, and 17.2-fold and 33% for *3A4*.

Urinary recoveries in mouse, rat, and dog ranged from 4% to 12% of the dose, and the majority of the radioactivity was recovered in the feces. In rat, 5% to 8% of the dose remained in the carcass after 7 days. Studies in rat demonstrated biliary excretion and enterohepatic recirculation of vandetanib-related material and excretion into milk.

1.1.3 Toxicology

The majority of findings from the completed nonclinical safety evaluation studies were consistent with the pharmacological activity of vandetanib:

Gastrointestinal tract toxicity (emesis and loose feces) was the dose-limiting finding in dogs; however, there were no associated histopathological findings.

Acute folliculitis and epidermal microabscess formation were seen in the skin of the muzzle region of rats in the 1- and 6-month studies.

Renal papillary necrosis was observed at the higher doses in the 1-month rat study but was not seen in the 6-month rat study or in any dog study.

Elevated plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), and glutamate dehydrogenase activities, hepatocellular necrosis, and acute cholangitis were seen at the highest doses used in the rat 1- and 6-month studies. Such changes were not seen in the 1 or 9-month dog studies.

Changes in the growth plate of long bones were observed in young rats and dogs but not in mature animals.

Dysplasia of the incisor teeth was seen at high doses in rats but not dogs.

Vandetanib had effects on female reproduction in rats. Effects included reduced numbers of corpora lutea, oestrus cycle irregularity, embryofoetal loss, delayed fetal development, and heart vessel abnormalities. Vandetanib had no effect on male fertility in rats.

Vandetanib shows evidence of phototoxicity potential.

Vandetanib has shown no mutagenic or clastogenic potential.

1.1.4 Human pharmacokinetics

A summary of the current findings of the PK and metabolism of vandetanib in man are presented below.

Absorption was relatively slow, with median time to maximum plasma concentration (t_{max}) of 4 to 10 hours. The slow clearance, total plasma clearance after an oral dose (CL/F) 11 L/h, and large volume of distribution, 3000 L combined to give a long terminal half-life ($t_{1/2}$) of about 10 to 19 days.

The PK of vandetanib in both healthy volunteers and patients appeared to be linear and predictable with respect to both increasing dose and, in patients, duration of dosing.

On once-daily dosing, steady-state exposure to vandetanib was achieved from about Day 28 onwards. At steady state there is a marked accumulation in the exposure to vandetanib of about 10-fold (3- to 30-fold range) to that determined after a single dose.

Both biliary and urinary clearances are important in the elimination of vandetanib.

The exposure to vandetanib increased by about 1.5-fold in patients with mild and moderate renal impairment, and by 2-fold in patients with severe renal impairment. Exposure to vandetanib in mild, moderate, and severe hepatically-impaired patients was no higher than in healthy volunteers. However in previous healthy volunteer studies where single doses of vandetanib of 300 mg have been administered, increases in mean QTcF values have been less than 5 ms.

The disposition of the N-oxide and N-desmethyl metabolites of vandetanib in the systemic circulation of healthy volunteers is similar to that for vandetanib. The exposure to the N-desmethyl metabolite is about 10% and to the N-oxide metabolite about 1% to that of vandetanib. The formation of the N-desmethyl metabolite is *CYP3A4* mediated, and that of the N-oxide by flavine-containing monooxygenase.

There is no effect of food on the exposure to vandetanib.

There is no effect on the exposure to vandetanib of the *CYP3A4* inhibitor, itraconazole. The exposure to vandetanib was significantly reduced by about 40% when given with the *CYP3A4* inducer, rifampicin.

There is no clinically relevant PK interaction between vandetanib and docetaxel; pemetrexed; FOLFIRI (chemotherapy regimen consisting of irinotecan, leucovorin, and 5 fluorouracil [5 FU]); FOLFOX (chemotherapy regimen consisting of 5 FU, leucovorin, and oxaliplatin); gemcitabine; and vinorelbine. The exposure to cisplatin was increased by about 30% which may be due to a PK interaction with vandetanib. The combination of paclitaxel and carboplatin has been shown not to affect the exposure to vandetanib. There is no clinically relevant PK interaction between vandetanib and the 5-hyroxytriptamine 3 antagonist ondansetron.

Both the PK and pharmacodynamics of vandetanib appear to be similar in Western, Japanese, and Chinese patients.

The mean corrected electrocardiogram (ECG) QT interval (Bazett's correction if not otherwise specified) (QTc) prolongation at steady state is about 10 to 20 ms for 100 mg and about 20 to 30 ms for 300 mg.

1.1.5 Clinical safety and efficacy

The key clinical safety and efficacy findings to date, in healthy volunteers and patients, can be summarized as follows:

Vandetanib is tolerable at up to, and including, a daily dose of 300 mg.

The most common adverse events (AEs) have been related to skin (eg, rash, acne, or pruritus), gastrointestinal tract (eg, nausea or diarrhea), and fatigue.

The single, oral, 800-mg dose of vandetanib was well tolerated in healthy volunteers with normal renal function and patients with mild, moderate, and severe renal impairment.

In the Phase III studies, QTc prolongation was seen in less than 2% of patients treated with vandetanib 100 mg in combination with chemotherapy, and in approximately 5% to 10% of patients treated with vandetanib 300 mg, depending on the study.

In Phase III NSCLC studies, there was a statistically significant advantage in progression-free survival (PFS) for the addition of vandetanib to docetaxel compared with docetaxel alone

(D4200C00032). There was a trend for PFS in favor of vandetanib in combination with pemetrexed compared with pemetrexed alone, although this did not reach statistical significance (D4200C00036). Neither study showed a significant advantage in overall survival (OS) as a consequence of adding vandetanib to standard chemotherapy. In a comparison with erlotinib, PFS and OS were similar for vandetanib (D4200C00057). There was a statistically significant improvement for vandetanib over placebo (both in combination with best supportive care) for PFS; however, OS was similar for vandetanib and placebo (D4200C00044).

In a Phase III study in patients with MTC (D4200C00058), there was a statistically significant improvement in PFS for vandetanib compared with placebo (hazard ratio [HR] 0.46; 95% confidence interval [CI]: 0.31, 0.69; p=0.0001) and a statistically significant improvement for vandetanib over placebo for objective response rate (ORR) odds ratio ([OR] 5.48; 95% CI: 2.99, 10.79; p less than 0.0001) and disease control rate (OR 2.64; 95% CI: 1.48, 4.69; p=0.0010). A total of 45% and 13% of patients had objective tumor response in the vandetanib and placebo arms, respectively. The responses in 12 of the 13 responders began after they were receiving open-label vandetanib treatment. There was also a statistically significant improvement in both calcitonin (OR 72.86; 95% CI: 26.22, 303.2; p less than 0.0001) and carcinoembryonic antigen (OR 52.03; 95% CI: 15.95, 320.3; p less than 0.0001) biochemical response for the vandetanib arm compared with placebo arm. There was no statistically significant difference between vandetanib and placebo in the analysis of OS (HR 0.89; 99.98% CI: 0.28, 2.85; p=0.7115). Median OS could not be calculated because too few deaths had occurred at the time of data cut off. The assessment of OS was confounded by the use of subsequent therapy, as patients in the 2 treatment groups who had progression and subsequently discontinued randomized treatment were unblinded and given the option to take open-label vandetanib.

In the D4200C00058 Phase III study, 94 (92.2%) of patients had at least 1 AE; 51 (50.0%) patients had AEs of common terminology criteria for AEs Grade 3 or higher; 28 (27.5%) patients had serious AEs (SAEs), including 1 patient who died due to an SAE. The 5 most frequently reported AEs during open-label vandetanib treatment were diarrhea (34 [33.3%] patients), rash (26 [25.5%] patients), decreased appetite (19 [18.6%] patients), photosensitivity reaction (9 [8.8%] patients), and acne (19 [18.6%] patients). A total of 8 (7.8%) patients had an AE of QT prolongation. One death (1.0%) was reported during open-label treatment. Patient (E2902001) died due to an SAE of aspiration pneumonia.

1.2 Research hypothesis

Omeprazole and ranitidine may cause a decrease in plasma concentrations of vandetanib.

1.3 Rationale for conducting this study

Vandetanib exhibits pH-dependent solubility. It is possible that coadministration of vandetanib with proton pump inhibitors (PPIs) and H2-antagonists could affect exposure to vandetanib.

The study is a regulatory commitment and is being run at the request of the European Medicines Agency. The data will be used to derive label text to advise patients about taking vandetanib and antacids concomitantly in normal clinical practice. As PPIs and H2-antagonist antacids are widely used and have different mechanisms of action it is considered necessary to study both types of antacids.

1.4 Benefit/risk and ethical assessment

There is no benefit for the volunteers participating in this study. Vandetanib given as a single dose of 300 mg has been well tolerated in previous healthy volunteer studies. Vandetanib 300 mg is the highest single daily dose approved for medullary thyroid cancer. As any interaction with an antacid is likely to occur in the gastrointestinal tract it is considered appropriate to use a 300-mg dose. Inclusion and exclusion criteria as well as study restrictions are chosen to ensure that the selected volunteers are exposed to minimal risk in this study.

1.4.1 Cardiovascular events

If volunteers meet either of the following criteria post medication, volunteers will remain under medical observation at the study center until resolution:

- QTc prolongation as defined by an increase from baseline in QTcF interval of greater than or equal to 60 ms and/or a QTcF interval of greater than 480 ms on 2 separate occasions (volunteers will remain under medical observation in the center until resolution ie, QTcF less than 460 ms)

- An increase from baseline in systolic blood pressure greater than 30 mmHg on more than 2 consecutive occasions which are more than 4 hours apart on the same study day (volunteers will remain under medical observation in the center at the Investigator's discretion)

1.4.2 Cutaneous events

It is strongly recommended that all volunteers follow a program of sun protective measures during the study. The aim is to reduce the risk of development of skin rash, or minimize the severity of skin rash.

If a volunteer develops a skin rash that requires treatment, a mild to moderate strength steroid cream or topical or systemic antihistamine can be used.

1.4.3 Gastrointestinal events

If a volunteer develops nausea, vomiting, or diarrhea, supportive care should be given as appropriate until symptoms subside.

2. STUDY OBJECTIVES

2.1 Primary objectives

The primary objectives for this study are:

- 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 (PPI)
- 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)

2.2 Secondary objectives

The secondary objectives for this study are:

- To examine the safety and tolerability of vandetanib in combination with omeprazole
- To assess vandetanib AUC, $AUC_{(0-672h)}$, λ_z, $t_{1/2,\lambda z}$, t_{max}, CL/F, and V_z/F for vandetanib alone and in combination with omeprazole
- To examine the safety and tolerability of vandetanib in combination with ranitidine
- To assess vandetanib AUC, $AUC_{(0-672h)}$, λ_z, $t_{1/2,\lambda z}$, t_{max}, CL/F, and V_z/F of vandetanib alone and in combination with ranitidine

2.3 Exploratory objectives

The exploratory objectives for this study are:

- To store selected plasma for further potential metabolism and PK investigations
- To collect and store deoxyribonucleic acid (DNA) 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
- To collect optional blood samples for safety biomarker testing that will allow future assessment of safety biomarkers

Results from exploratory analyses, if performed, may be reported separately from the Clinical Study Report (CSR).

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol (CSP) has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This is 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.

Treatments within each of the 2 groups are as follows:

Group 1:

Treatment A: a single oral dose of vandetanib 300 mg (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 of Day 5

Group 2:

Treatment A: a single oral dose of vandetanib 300 mg (morning of Day 1)

Treatment C: a 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

Interaction with omeprazole and interaction with ranitidine will be evaluated in 2 separate groups (Group 1 and Group 2) of 16 volunteers each. Enrollment into Group 1 will be completed prior to enrollment into Group 2. Within each group, volunteers will be randomized into 1 of 2 treatment sequences (ie, sequence AB or BA in Group 1 and sequence AC or CA in Group 2). All volunteers will receive a single dose of vandetanib 300 mg (Clinical Trial formulation) alone and with either omeprazole (Group 1) or ranitidine (Group 2) during treatment Periods 1 and 2.

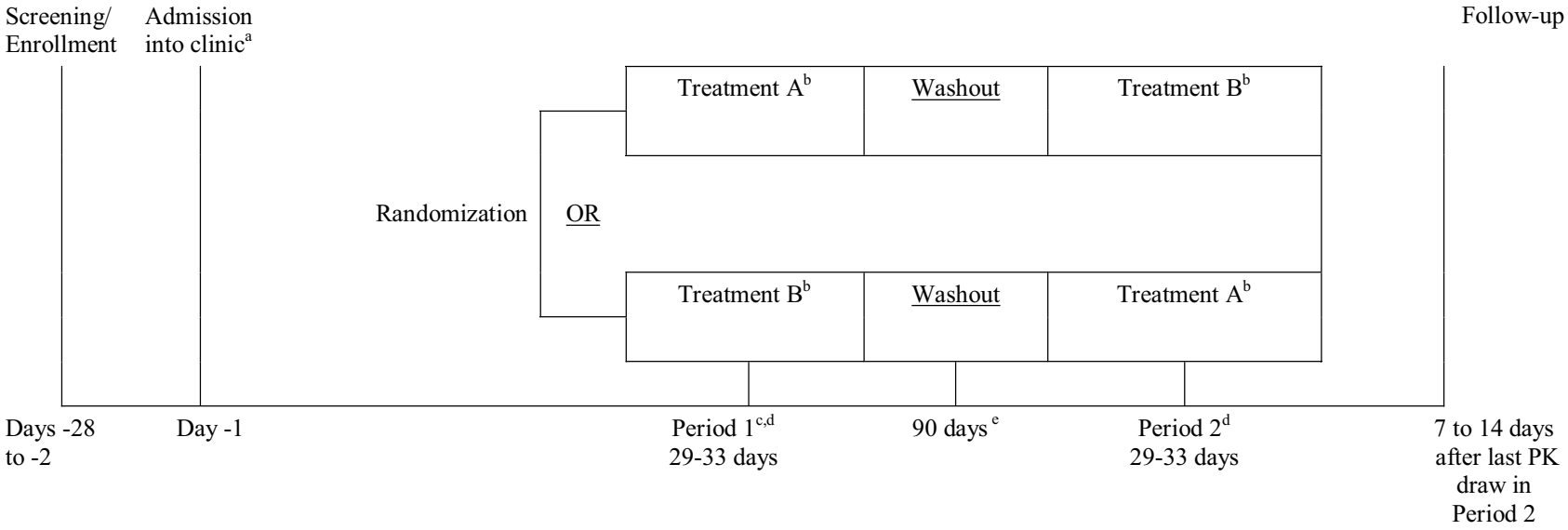
Volunteers should abstain from food beginning 10 hours prior to vandetanib dosing in each period and continuing until 4 hours after dosing. On the vandetanib dosing days in each period, water (other than that administered with the dose) will be restricted from 1 hour predose until 2 hours postdose.

Serial blood samples for PK analysis of vandetanib will be collected following vandetanib dosing in Periods 1 and 2 in both groups. Within each group, study periods will be separated by a washout of at least 3 months (90 days) from the first dose in Period 1 until the first dose of vandetanib in Period 2.

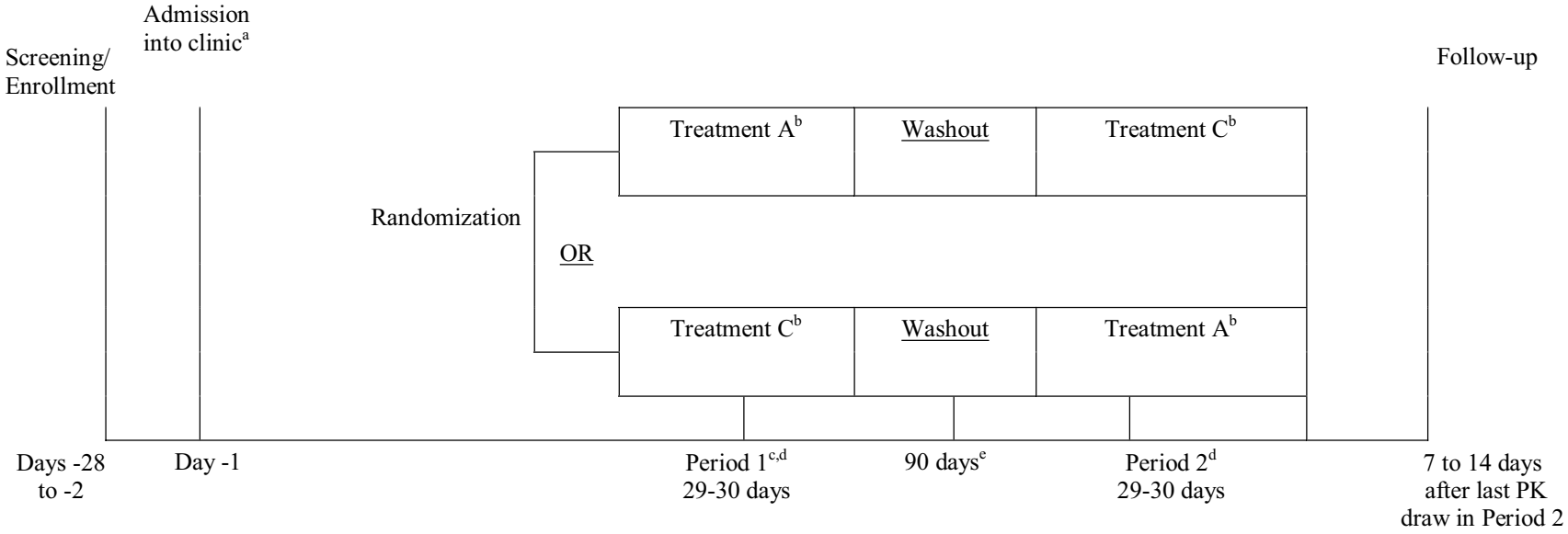
During the study, risk mitigation strategies will be utilized to deal with potential cardiovascular, cutaneous, or gastrointestinal events in study volunteers.

Figure 1 Study flow chart for Group 1 and Group 2

Group 1



Group 2



[a] In each period, subjects will be admitted into the clinic on Day -1.
[b] See Section 3.1 for description of treatments to be administered.
[c] Enrollment into Group 1 will be completed prior to enrollment into Group 2. Within each group, on Day 1 of Period 1, subjects will be randomly assigned to a treatment sequence.
[d] The length of the periods will vary between 29-33 days in Group 1 and 29-30 days in Group 2, depending upon the treatment being administered.
[e] The 2 study periods will be separated by a washout of at least 3 months (90 days) from the first dose in Period 1 until the first dose of vandetanib in Period 2.

Table 1 Study plan, Group 1 Sequence AB (vandetanib alone followed by vandetanib and omeprazole)

Assessment	Screening	Period 1 Day -1	Period 1 Day 1-29		3 month washout	Period 2 Day -1	Period 2 Day 1-33		Follow up visit 7-14 Days
Day	**-28 to -2**	**-1**	**1-4**	**5-29**		**-1**	**1-8**	**9-33**	
Informed consent	X								
Demography	X								
Inclusion/exclusion criteria	X	X							
Medical history	X								
Clinical laboratory tests[a]	X	X	X	X		X	X	X	X
Pregnancy test	X	X				X			
Serology	X								
Body temperature	X	X				X			
Height and BMI	X								
Weight	X	X				X			
Optional pharmacogenetics sample[b]			X						
Optional biomarker sample[c]		X							
Drugs of abuse and alcohol screen[d]	X	X				X			
Physical examination[e]	X	X	X			X	X		X
Vital signs (supine blood pressure and pulse)[f]	X	X	X	X		X	X	X	X
12-lead ECG[g]	X	X	X	X		X	X	X	X
Vandetanib administration[h]			X				X		
Omeprazole administration[i]							X		
Vandetanib PK blood sampling[j]			X	X			X	X	
Concomitant medications	X	X	X	X		X	X	X	X
Adverse event recording[k]		X	X	X		X	X	X	X
Residential period[l]		X	X			X	X		
Nonresidential visits[m]				X				X	X

BMI body mass index.

[a] Clinical laboratory tests Period 1: Days -1, 3, 8, 15, 22 and 29 Period 2: Days -1, 5, 7, 12, 19, 26, and 33.

[redacted]

[b] Optional pharmacogenetic sampling will occur if the subject has signed the optional pharmacogenetic informed consent. If the sample is not taken Day 1 predose, it may be taken any time until the follow-up visit.

[c] Optional biomarker sampling will occur if the subject has signed the optional biomarker informed consent. This sample must be taken predose.

[d] The Investigator may perform random drugs of abuse and/or alcohol screens at any time during the study at his discretion.

[e] Physical examination: Period 1: Day -1 and 4 brief examination. Period 2: Day -1 and Day 8 brief examination.

[f] Vital signs Period 1: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 8) and Days 15, 22, and 29; Period 2: Day 5 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day12), Days 19, 26, and 33.

[g] 12-lead ECG Period 1: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 8) and Days 15, 22, and 29; Period 2: Day 5 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day12), Days 19, 26, and 33.

[h] Vandetanib administration Period 1: Day 1 (0 hour) Period 2: Day 5 in the morning at the same time as the omeprazole.

[i] Omeprazole administration Period 2: Days 1 to 5 (40 mg each day in the morning).

[j] Vandetanib PK blood sampling Period 1: Day 1: predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose; Period 2: Day 5: predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose.

[k] Adverse event recording will begin at the subject's check-in to the study center in Period 1.

[l] Residential period: Period 1: Check-in Day -1/Check-out Day 4; Period 2: Check-in Day -1/Check-out Day 8.

[m] Nonresidential visits Period 1: Days 4 (72 hours), 5, 6, 7, 8, 9, 10, 11, 15, 22, and 29; Period 2: Days 9, 10, 11, 12, 13, 14, 15, 19, 26, and 33.

Table 2 Study plan, Group 1 Sequence BA (vandetanib and omeprazole followed by vandetanib alone)

Assessment	Screening	Period 1 Day -1	Period 1 Day 1-33		3 month washout	Period 2 Day -1	Period 2 Day 1-29		Follow up visit 7-14 Days
Day	**-28 to -2**	**-1**	**1-8**	**9-33**		**-1**	**1-4**	**5-29**	
Informed consent	X								
Demography	X								
Inclusion/exclusion criteria	X	X							
Medical history	X								
Clinical laboratory tests[a]	X	X	X	X		X	X	X	X
Pregnancy test	X	X				X			
Serology	X								
Body temperature	X	X				X			
Height and BMI	X								
Weight	X	X				X			
Optional pharmacogenetics sample[b]			X						
Optional biomarker sample[c]		X							
Drugs of abuse and alcohol screen[d]	X	X				X			
Physical examination[e]	X	X	X			X	X		X
Vital signs (supine blood pressure and pulse)[f]	X	X	X	X		X	X	X	X
12-lead ECG[g]	X	X	X	X		X	X	X	X
Vandetanib administration[h]			X				X		
Omeprazole administration[i]			X						
Vandetanib PK blood sampling[j]			X	X			X	X	
Concomitant medications	X	X	X	X		X	X	X	X
Adverse event recording[k]		X	X	X		X	X	X	X
Residential period[l]		X	X			X	X		
Nonresidential visit[m]				X				X	X

BMI body mass index.

[a] Clinical laboratory tests Period 1: Days -1, 5, 7, 12, 19, 26, and 33; Period 2: Days -1, 3, 8, 15, 22, and 29.

[redacted]

[b] Optional pharmacogenetic sampling will occur if the subject has signed the optional pharmacogenetic informed consent. If the sample is not taken Day 1 predose, it may be taken any time until the follow-up visit.

[c] Optional biomarker sampling will occur if the subject has signed the optional biomarker informed consent. This sample must be taken predose.

[d] The Investigator may perform random drugs of abuse and/or alcohol screens at any time during the study at his discretion.

[e] Physical examination Period 1: Day -1 and 8 brief examination; Period 2: Day -1 and Day 4 brief examination.

[f] Vital signs Period 1: Day 5 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 12), Days 19, 26, and 33; Period 2: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 8) and Days 15, 22, and 29.

[g] 12-lead ECG Period 1: Day 5 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 12), Days 19, 26, and 33; Period 2: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day8) and Days 15, 22, and 29.

[h] Vandetanib administration Period 1: Day 5 in the morning at the same time as the omeprazole; Period 2: Day 1 (0 hour).

[I] Omeprazole administration Period 1: Days 1-5 (40 mg each day in the morning).

[j] Vandetanib PK blood sampling Period 1: Day 5: predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose; Period 2: Day 1: predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose.

[k] Adverse event recording will begin at the subject's check-in to the study center in Period 1.

[l] Residential period: Period 1: Check-in Day -1/Check-out Day 8; Period 2: Check-in Day -1/Check-out Day 4.

[m] Nonresidential visits Period 1: Days 9, 10, 11, 12, 13, 14, 15, 16, 19, 26, and 33; Period 2: Days 4 (72 hours), 5, 6, 7, 8, 9, 10, 11, 15, 22, and 29.

Table 3 Study plan, Group 2 Sequence AC (vandetanib alone followed by vandetanib and ranitidine)

Assessment	Screening	Period 1 Day -1	Period 1 Day 1-29		3 Month wash out	Period 2 Day -1	Period 2 Day 1-30		Follow up Visit 7-14 Days
Day	**-28 to -2**	**-1**	**1-4**	**5-29**		**-1**	**1-5**	**6-30**	
Informed consent	X								
Demography	X								
Inclusion/exclusion criteria	X	X							
Medical history	X								
Clinical laboratory tests[a]	X	X		X		X	X	X	X
Pregnancy test	X	X				X			
Serology	X								
Body temperature	X	X				X			
Height and BMI	X								
Weight	X	X				X			
Optional pharmacogenetics sample[b]			X						
Optional biomarker sample[c]		X							
Drugs of abuse and alcohol screen[d]	X	X				X			
Physical examination[e]	X	X	X			X	X		X
Vital signs (supine blood pressure and pulse)[f]	X	X	X	X		X	X	X	X
12-lead ECG[g]	X	X	X	X		X	X	X	X
Vandetanib administration[h]			X				X		
Ranitidine administration[i]							X		
Vandetanib PK blood sampling[j]			X	X			X	X	
Concomitant medications	X	X	X	X		X	X	X	X
Adverse event recording[k]		X	X	X		X	X	X	X
Residential period[l]		X	X			X	X		
Nonresidential visits[m]				X				X	X

BMI body mass index.

[a] Clinical laboratory tests Period 1: Days -1, 3, 8, 15, 22, and 29; Period 2: Days -1, 4, 9, 16, 23, and 30.

[redacted]

[b] Optional pharmacogenetic sampling will occur if the subject has signed the optional pharmacogenetic informed consent. If the sample is not taken Day 1 predose, it may be taken any time until the follow-up visit.

[c] Optional biomarker sampling will occur if the subject has signed the optional biomarker informed consent. This sample must be taken predose.

[d] The Investigator may perform random drugs of abuse and/or alcohol screens at any time during the study at his discretion.

[e] Physical examination Period 1 Day -1 and 4 brief examination; Period 2: Day -1 and Day 5 brief examination.

[f] Vital signs Period 1: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 8) and Days 15, 22, and 29; Period 2: Day 2 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 9), Days 16, 23, and 30.

[g] 12-lead ECG Period 1: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 8) and Days 15, 22, and 29; Period 2: Day 2 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 9), Days 16, 23, and 30.

[h] Vandetanib administration Period 1: Day 1 (0 hour); Period 2: Day 2 in the morning at the same time as the ranitidine.

[i] Ranitidine administration Period 2: Day 1 150 mg single dose in the evening, Day 2 150 mg single dose in the morning with vandetanib.

[j] Vandetanib PK blood sampling Period 1: Day 1: predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose; Period 2: Day 2 predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose.

[k] Adverse event recording will begin at the subject's check-in to the study center in Period 1.

[l] Residential period: Period 1: Check-in Day -1/Check-out Day 4 Period 2: Check-in Day -1/Check-out Day 5.

[m] Nonresidential visits Period 1: Days 4 (72 hours), 5, 6, 7, 8, 9, 10, 11, 15, 22, and 29; Period 2: Days 6, 7, 8, 9, 10, 11, 12, 16, 23, and 30.

Table 4 Study plan, Group 2 Sequence CA (vandetanib and ranitidine followed by vandetanib alone)

Assessment	Screening	Period 1 Day -1	Period 1 Day 1-30		3 Month wash out	Period 2 Day -1	Period 2 Day 1-29		Follow up Visit 7-14 Days
Day	**-28 to -2**	**-1**	**1-5**	**6-30**		**-1**	**1-4**	**5-29**	
Informed consent	X								
Demography	X								
Inclusion/exclusion criteria	X	X							
Medical history	X								
Clinical laboratory tests[a]	X	X	X	X		X	X	X	X
Pregnancy test	X	X				X			
Serology	X								
Body temperature	X	X				X			
Height and BMI	X								
Weight	X	X				X			
Pharmacogenetics sample[b]			X						
Optional biomarker sample[c]		X							
Drugs of abuse and alcohol screen[e]	X	X				X			
Physical examination[e]	X	X	X			X	X		X
Vital signs (supine blood pressure and pulse)[f]	X	X	X	X		X	X	X	X
12-lead ECG[g]	X	X	X	X		X	X	X	X
Vandetanib administration[h]			X				X		
Ranitidine administration[i]			X						
Vandetanib PK blood sampling[j]			X	X			X	X	
Concomitant medications	X	X	X	X		X	X	X	X
Adverse event recording[k]		X	X	X		X	X	X	X
Residential period[l]		X	X			X	X		
Nonresidential visits[m]				X				X	X

BMI body mass index.

[a] Clinical laboratory tests Period 1: Days -1, 4, 9, 16, 23, and 30; Period 2: Days -1, 3, 8, 15, 22, and 29.

[redacted]

[b] Optional pharmacogenetic sampling will occur if the subject has signed the optional pharmacogenetic informed consent. If the sample is not taken Day 1 predose, it may be taken any time until the follow-up visit.

[c] Optional biomarker sampling will occur if the subject has signed the optional biomarker informed consent. This sample must be taken predose.

[d] The Investigator may perform random drugs of abuse and/or alcohol screens at any time during the study at his discretion.

[e] Physical examination Period 1: Day -1 and 5 brief examination; Period 2: Day -1 and Day 4 brief examination.

[f] Vital signs Period 1: Day 2 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 9), Days 16, 23, and 30; Period 2: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day8) and Days 15, 22, and 29.

[g] 12-lead ECG Period 1: Day 2 predose, 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 9), Days 16, 23, and 30; Period 2: Day 1 (predose), 4, 8, 12, 24, 48, 72, and 168 hours postdose (Day 8) and Days 15, 22, and 29.

[h] Vandetanib administration Period 1: Day 2 in the morning at the same time as the ranitidine; Period 2: Day 1 (0 hour).

[i] Ranitidine administration Period 1: Day 1 150 mg single dose in the evening, Day 2 150 mg single dose in the morning with vandetanib.

[j] Vandetanib PK blood sampling Period 1: Day 2 predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose; Period 2: Day 1: predose, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 336, 504, and 672 hours postdose.

[k] Adverse event recording will begin at the subject's check-in to the study center in Period 1.

[l] Residential period, Period 1: Check-in Day -1/Check-out Day 5; Period 2: Check-in Day -1/Check-out Day 4.

[m] Nonresidential visits Period 1: Days 6, 7, 8, 9, 10, 11, 12, 16, 23, and 30; Period 2: Days 4 (72 hours), 5, 6, 7, 8, 9, 10, 11, 15, 22, and 29.

3.2 Rationale for study design, doses, and control groups

This study utilizes a standard crossover design used for assessment of drug-drug interactions. An open-label design is appropriate since the main outcome variables are PK parameters that are not likely to be influenced by the volunteer's knowledge of the treatment.

This study will be conducted in healthy male and female volunteers in order to avoid interference with the study results from disease processes and other drugs. The selection criteria are defined such that volunteers selected for participation in the study are known to be free from any significant illness.

Based on clinical data, the terminal half-life of vandetanib has been estimated to be 10 to 19 days, so a long washout period of 3 months is being allowed between periods to ensure complete washout.

Vandetanib 300 mg is the highest single dose approved for medullary thyroid cancer.

Omeprazole 40 mg is a relatively high dose to elicit a significant effect on stomach pH. Four days of dosing will be given to allow steady state to establish and maximum change in gastric pH.

Ranitidine 150 mg is a mid-range dose to elicit significant effect on stomach pH in this healthy volunteer population. Maximum effect is established with short duration of dosing so ranitidine will be administered the evening before vandetanib administration and coincident with vandetanib administration the next morning.

4. SUBJECT SELECTION CRITERIA

The Investigator should keep a record, the volunteer screening log, of volunteers who enter prestudy screening.

Each volunteer should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study volunteers should fulfill the following criteria:

1. Provision of signed and dated, written informed consent prior to any study-specific procedures

2. Volunteers must be males or females aged 18 to 50 years and with a weight of at least 50 kg and body mass index (BMI) between 18 and 30 kg/m^2, inclusive

3. Females must have a negative pregnancy test at screening and on admission to the study center, must not be lactating and must be of nonchildbearing potential, confirmed at screening by fulfilling 1 of the following criteria:

   - Postmenopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments and with follicle-stimulating hormone (FSH) and lutenizing hormone (LH) levels in the laboratory defined postmenopausal range

   - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation

For inclusion in the optional genetic component and/or the safety biomarker sample collection of the study, volunteers must fulfill the following additional criterion:

4. Provision of signed and dated informed consent for genetic research and the safety biomarker collection. If a volunteer declines to participate in the genetic component or safety biomarker component of the study, there will be no penalty or loss of benefit to the volunteer.

4.2 Exclusion criteria

Volunteers should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study

2. History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs

3. Volunteers who smoke more than 5 cigarettes per day or are unable to refrain from smoking while resident in the study center

4. Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the first administration of investigational product (IP)

5. Any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results as judged by the Investigator (Note, serum potassium must be greater than 4 mEq/L and serum magnesium and calcium must be within normal reference range.)

6. Screening blood pressure of greater than 140/90 mmHg and/or a resting heart rate of less than 45 beats per minute (repeat test allowed at the Investigator's discretion)

7. Clinically significant abnormal 12-lead ECG as assessed by the Investigator, QTcF interval greater than 450 ms

8. Personal or family history of long QT syndrome or sudden unexplained death in a first degree relative age less than 40 years

9. Clinically significant current active skin disease as judged by the Investigator eg, moderate to severe acne, psoriasis, or eczema

10. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV)

11. Known or suspected history of drug abuse as judged by the Investigator

12. Has received another new chemical entity (defined as a compound which has not been approved for marketing) or has participated in any other clinical study that included drug treatment within 3 months of the first administration of IP in this study. The period of exclusion begins at the time of the poststudy medical examination of the prior study. Note, volunteers consented and screened but not dosed in previous Phase I studies are not excluded.

13. Plasma donation within 30 days of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening

14. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to vandetanib, omeprazole, or ranitidine

15. Positive screen for drugs of abuse at screening or on admission to the study center or positive screen for alcohol on admission to the study center prior to the first administration of IP

16. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IP

17. Use of any prescribed or nonprescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, vitamins, and minerals during the 2 weeks prior to the first administration of IP or longer if the medication has a long half-life. Occasional use of paracetamol/ acetaminophen is allowed for minor pains and headache.

18. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of IP

19. Past (within 1 year of enrollment) or present alcohol or substance abuse per the Investigator's discretion

20. Previous randomization to treatment in the present study

21. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

22. Judgment by the Investigator that the volunteer should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements

In addition, the following are considered criteria for exclusion from the genetic research:

23. Nonleukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection

24. Previous allogenic bone marrow transplant

For procedures for withdrawal of incorrectly enrolled volunteers see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

Volunteers will be required to:

1. Fast from 10 hours prior to vandetanib dosing in each period until 4 hours postdose (note, fasting is not required for the omeprazole or rantidine dosing)

2. On the vandetanib dosing days of each period, water intake will be restricted from 1 hour predose until 2 hours postdose, excluding the water required to take the doses

3. Abstain from drinking alcohol from 72 hours prior to the start of each study period until after the final PK sample. Otherwise no more than 2 units of alcohol should be consumed per day up until the follow-up visit.

4. Caffeine-containing drinks during the residential period apart from any provided as part of a standardized meal. Excessive intake of caffeine (ie, more than 5 cups of coffee or equivalent per day) should be avoided between discharge from the study center and the follow-up visit.

5. Energy drinks containing taurine or glucuronolactone eg, Red Bull from 72 hours before admission

6. Abstain from consuming grapefruit, grapefruit juice, Seville oranges (as found in orange marmalade), or licorice from 7 days prior to the start of each treatment period until after the last PK sample is taken

7. Abstain from consuming foods containing poppy seeds from 7 days before dosing until 7 days after dosing with each IP

8. Abstain from smoking while resident in the study center

9. Abstain from taking any medication (including over-the-counter or over-the-internet remedies) from 2 weeks prior to first administration of IP or longer if the medication has a long half-life until the poststudy medical examination, unless the Investigator has given prior consent. This excludes paracetamol/acetaminophen of which 1 g may be taken for minor symptoms such as a headache. However, a maximum daily dose of 4 g should not be exceeded in any 24-hour period.

10. At the end of each residential period, any volunteers with prolonged QTcF will be required to remain in the center at the Investigator's discretion.

11. Abstain from strenuous exercise (eg, playing squash, football, and weightlifting) from 7 days prior to admission to the study center

12. Abstain from donating blood during the study and for 3 months following the poststudy medical examination

13. Due to the experimental nature of vandetanib, males, if sexually active, should practice reliable methods of birth control (vasectomy or condoms in addition to their partner's choice of contraception) and abstain from donating sperm from receiving the first dose of vandetanib until 3 months after the follow-up visit

14. Abstain from sunbathing or using sunbeds, and must use high sun protection factor (SPF 45 or greater) sunscreens if directly exposed to strong sunlight, from the first dose of vandetanib until the poststudy medical

5.2 Subject enrollment, randomization, and initiation of investigational product

The Investigator or designee will:

1. Obtain signed informed consent from the potential volunteer before any study-specific procedures are performed

2. Assign potential volunteer a unique enrollment number, beginning with 'E#'

3. Determine volunteer eligibility. See Sections 4.1 and 4.2.

4. Assign eligible volunteers unique randomization code (volunteer number). A separate number sequence of unique random codes will be used for each of 2 standard, 2-period, 2-treatment crossover designs; 1001 to 1016 for Group 1 (vandetanib/omeprazole) and 2001 to 2016 for Group 2 (vandetanib/ranitidine).

5. If a volunteer withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

5.2.1 Procedures for randomization

Randomization schemes will be produced by Quintiles Overland Park, Kansas, United States using the global randomization system (GRand). A separate randomization schedule will be generated for each of 2 standard, 2-period, 2-treatment crossover designs: 1 for vandetanib/omeprazole study (Group 1), and 1 for vandetanib/ranitidine study (Group 2). The randomization will be done using consecutive randomization codes. Randomization codes will be assigned strictly sequentially as volunteers become eligible for randomization.

5.3 Procedures for handling subjects incorrectly enrolled, randomized, or initiated on investigational product

Volunteers who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

5.4 Blinding and procedures for unblinding the study

This is an open-label study.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Vandetanib	300-mg tablet	AstraZeneca
Omeprazole	40-mg capsule	Source locally
Ranitidine	150-mg tablet	Source locally

The vandetanib tablets will be supplied as a bulk supply and repackaged into individual doses. Omeprazole and rantidine will be supplied locally.

5.5.2 Doses and treatment regimens

All study medications will be administered with 240 mL water. Treatments are 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 single oral doses of omeprazole 40 mg and vandetanib 300 mg on the morning of Day 5

Group 2:

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

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

All morning doses will be administered at approximately the same time each morning. Evening doses will be administered approximately 12 hours prior to the next morning dose.

Volunteers should abstain from food beginning 10 hours prior to vandetanib dosing in each period and continuing until 4 hours after dosing. On the vandetanib dosing days in each period, water (other than that administered with the dose) will be restricted from 1 hour predose until 2 hours postdose.

Standardized meals will be served at all other times when volunteers are resident at the study center.

5.5.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

5.5.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage. The study medication should be stored in the packs provided according to the instructions.

5.6 Concomitant and poststudy treatment(s)

Apart from acetaminophen/paracetamol, no concomitant medication or therapy will be allowed from 2 weeks prior to the first administration of IP until after the final medical examination at the follow-up visit has been completed.

Other medication, which is considered necessary for the volunteer's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form (CRF).

5.7 Treatment compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the CRF.

5.7.1 Accountability

The IP provided for this study will be used only as directed in the CSP.

Study site personnel will account for all IP received at the site, unused IP, and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation of investigational product

Volunteers may be discontinued from IP in the following situations:

- Volunteer decision. The volunteer is at any time free to discontinue treatment, without prejudice to further treatment.
- AE
- Severe noncompliance to CSP
- At the discretion of the Investigator and/or AstraZeneca

5.8.1 Procedures for discontinuation of a subject from investigational product

A volunteer who decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (see Sections 6.3.3 and 6.3.4).

If a volunteer is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Volunteers are at any time free to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such volunteers will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by the Investigator. Adverse events will be followed up (see Sections 6.3.3 and 6.3.4).

The number of volunteers withdrawn for nondrug-related reasons will be monitored. Volunteers may be replaced in order to reach the desired number of completed volunteers. A discussion will occur between the Investigator and AstraZeneca prior to additional volunteers being enrolled.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections below. The Study Plans and timing of these assessments are detailed in Table 1 to Table 4.

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1. 12-lead ECG
2. Vital signs (blood pressure and pulse rate)
3. Physical examinations
4. Pharmacokinetic blood sample (Note: PK sampling must be performed at the precise CSP scheduled time.)
5. Laboratory assessments (chemistry, hematology, and urinalysis)

Predose assessments may be performed 60 minutes prior to administration of the IP.

6.1 Recording of data

The Investigator will ensure that data are recorded on the CRFs as specified in the CSP and in accordance with the instructions provided. Optional informed consents will be available for pharmacogenetic and biomarker blood sampling.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed electronic CRFs. A copy of the completed electronic CRFs will be archived at the study site.

6.2 Data collection at enrollment and follow-up

6.2.1 Enrollment procedures

At screening (Visit 1), each potential volunteer will provide informed consent prior to starting any study-specific procedures.

Demographic data and other characteristics will be recorded and will include: date of birth, gender, race, alcohol consumption, smoking, and drug abuse history.

Each volunteer will undergo screening during the 28 days prior to admission to confirm eligibility. This will consist of:

1. Inclusion and exclusion criteria
2. Medical history
3. Clinical laboratory tests (including pregnancy test)
4. Height, weight, and calculation of BMI
5. Serology
6. Physical examination
7. Vital signs (supine blood pressure and pulse)
8. 12-lead ECG
9. Concomitant medication recording
10. Drugs of abuse and alcohol screen

6.2.2 Follow-up procedures

A poststudy medical examination will be performed approximately 7 to 14 days after discharge from Period 2 of the study. This will include clinical laboratory tests, a physical examination, vital signs (supine blood pressure and pulse rate), 12-lead ECG, and concomitant medication and AE recording.

6.3 Safety

The Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea or chest pain), signs (eg, tachycardia or enlarged liver), or the abnormal results of an investigation (eg, laboratory findings or ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and nonserious AEs.

6.3.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, or follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the volunteer or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix B to the CSP.

6.3.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from Day -1 throughout the treatment period and including the follow-up period.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the volunteer's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any volunteer with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused volunteer's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to additional IP
- Description of AE

The following intensity ratings will be used:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the IP’?

For SAEs causal relationship will also be assessed for other medication, study procedures, and additional IP. Note, for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

Adverse events and SAEs will be considered associated with the last dose of IP given prior to onset, as judged by the Investigator.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the volunteer or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from CSP-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs, or ECGs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

At the Investigator's discretion, if deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Cases where a volunteer shows an AST **or** ALT greater than or equal to 3 times the upper limits of normal (ULN) **or** total bilirubin greater than or equal to 2 times the ULN may need to be reported as SAEs, please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.3.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then the Investigator or other site personnel must inform appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plans (see Table 1 to Table 4).

Laboratory variables to be measured are shown in Table 5.

Table 5 Laboratory variables

Clinical chemistry	Hematology	Urinalysis[a]
Serum (S) -Albumin	Blood (B)-Hemoglobin	U-Glucose
S-ALT	B-Red blood cell count	U-Creatinine
S-AST	B-Leukocyte (White Blood Cell count)	U-Hemoglobin
S-Alkaline phosphatase	B-Absolute leukocyte differential count (Neutrophils, Basophils, Lymphocytes, Monocytes & Eosinophils expressed as concentration)	U-Total protein
S-Bilirubin, total and unconjugated	B-Platelet count	U-Cotinine
S-Creatinine	B-MCH	U- Methadone
S-Glucose (Fasting)	B-MCV	U-Cannabis
S-Sodium		U-Cocaine
S-hs-CRP		U-Benzodiazepines
S-Total protein		U-Amphetamine
S-Uric acid		U-Methamphetamines
S-Urea		U-Opiates
S-FSH[b, c]		U-Barbiturates
S-LH[b, c]		U-Ethanol
S-Pregnancy test[b]		
S-Calcium, total		
S-Potassium		
S-Magnesium		

B blood; hs-CRP high sensitivity C-reactive protein, MCH mean corpuscular hemoglobin; MCV mean corpuscular volume; S serum; U urine.
[a] A microscopic examination will be performed if any results are positive on the dipstick.
[b] Women only.
[c] At screening only.

Blood will be tested for hepatitis B surface antigen, antibodies to hepatitis C, and antibodies to HIV at the screening visit.

Urine will be tested at the times specified in Table 1 to Table 4 for the following drugs of abuse: methadone, cannabis, cocaine, benzodiazepines, amphetamine, methamphetamines (including ecstasy), opiates, ethanol, and barbiturates. The test will be performed at the study

center. If a volunteer tests positive for drugs of abuse, a retest may be performed and they may be excluded from entering the study, as judged by the Investigator. Serum pregnancy tests will be performed on female volunteers at the times specified in Table 1 to Table 4.

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Volunteers in whom suspected clinical significance is confirmed will either not be included or if already enrolled will be followed until normalization or for as long as the Investigator considers necessary. Additional laboratory variables may be performed for safety reasons if judged appropriate by the Investigator. Further details are provided in the Laboratory Manual.

The safety laboratory samples will be analyzed using routine methods at the site's accredited clinical laboratory (Physician's Reference Laboratory, Overland Park, Kansas, United States).

In case a volunteer shows an AST **or** ALT greater than or equal to 3 times the ULN **or** total bilirubin greater than or equal to 2 times the ULN please refer to Appendix E 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

For blood volume see Section 7.1.

6.3.6 Physical examination

A complete physical examination will be performed at the times specified in Table 1 to Table 4 and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities), and neurological systems.

A brief physical examination, which will include assessment of respiratory and cardiovascular systems and general inspection will be performed at the times specified in Table 1 to Table 4.

Height (in centimeters) and weight (in kilograms) will be measured at the times specified in Table 1 to Table 4. Measurements should be taken in scrubs without shoes and a calibrated scale will be used for all measurements. Body mass index will be calculated from the height and weight measurements.

The outcome of the physical examination is to be recorded as normal/abnormal in the CRF, with any abnormalities specified. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

For AEs based on examinations and tests, see Section 6.3.3.

6.3.7 Resting 12-lead ECG

A 12-lead ECG will be obtained after the volunteer has been resting in the supine position for at least 10 minutes.

The Investigator will judge the overall interpretation as normal or abnormal, and record this in the CRF. Any abnormalities (including QTc values) should be reviewed by a cardiologist or an appropriately qualified person. Abnormalities will be deemed as either clinically significant or not clinically significant, and the reason for the abnormality will also be recorded. All ECG readings will be stored as source documents as a paper printout.

If indicated, additional ECG assessments can be made at the discretion of the Investigator. These assessments should be entered as an unscheduled assessment.

6.3.8 Vital signs and body temperature

6.3.8.1 Pulse and blood pressure

Supine blood pressure and pulse rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. The volunteers will be required to rest in a supine position for at least 10 minutes prior to blood pressure and pulse rate measurements.

For timings of assessments refer to the Study Plans (see Table 1 to Table 4).

6.3.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times specified in the Study Plans (see Table 1 to Table 4).

6.4 Pharmacokinetics

6.4.1 Collection of samples

Blood samples (3 mL) for determination of vandetanib concentrations in plasma will be taken at the times presented in the study plan schedules (Table 1 to Table 4).

Samples will be collected, labeled, stored, and shipped as detailed in Laboratory Manual.

For blood volume see Section 7.1.

6.4.2 Determination of drug concentration

Vandetanib concentration in plasma will be analyzed by York Bioanalytical Solutions, United Kingdom, on behalf of AstraZeneca, using liquid chromatography with mass-spectrometric detection after solid phase extraction. The lower limit of quantification (LLOQ) of vandetanib in plasma is 5 ng/mL. Details of the method will be given in the CSR or in a separate document.

6.5 Pharmacodynamics (Not applicable)

6.6 Pharmacogenetics

All volunteers enrolled in the study will have the option to provide a blood sample for pharmacogenetic analysis and safety biomarker assessment. Volunteers will not be excluded from participating in the study if they decline participation in the genetic analysis or the safety biomarker assessment. Blood samples for these analyses will be taken only after the volunteer has signed a separate genetic informed consent and separate consent for safety biomarker sample collection. The analyses and results from these optional studies will be handled and reported separately from the main study.

Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from the volunteers on Day 1. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding volunteers who may withdraw due to an AE, such volunteers would be important to include in any genetic analysis. If for any reason the sample is not drawn Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per volunteer for genetics during the study. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

6.7 Safety biomarker

See Appendix D for details on the safety biomarkers.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each volunteer in this study is as follows:

Table 6 Volume of blood to be drawn from each subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	8	15	120
	Hematology	4	15	60
	Serology	8	1	8
Pharmacokinetic		3	52	156
Optional biomarkers		10	1	10
Optional pharmacogenetics		10	1	10
Total				364

7.2 Handling, storage, and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use, as described here.

Biological samples for future research will be retained at AstraZeneca Research and Development on behalf of AstraZeneca for a maximum of 25 years following the last volunteer's last visit in the study. The results from future analysis will not be reported in the CSR.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Samples will be disposed of after the CSR has been finalized, unless retained for future analyses.

Key samples for biological research can be retained at Clinical Pharmacology & DMPK, AstraZeneca Research and Development, for a maximum of 1 year following the finalization of the CSR. The results from this investigation will not be reported in the CSR.

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain volunteer confidentiality. Samples will be stored for a maximum of 25 years, from the date of the last volunteer's last visit, after which they will be destroyed. Deoxyribonucleic acid is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information

on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the volunteer enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and to trace samples for destruction in the case of withdrawal of consent when the volunteer has requested disposal/destruction of collected samples not yet analyzed.

7.3 Labeling and shipment of biohazard samples

The Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the volunteer unless agreed with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The Investigator keeps full traceability of collected biological samples from the volunteers while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of the study center, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a volunteer withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Note, the pharmacogenetics and safety biomarker blood samples are optional parts of the study and are not required by the volunteer in order to participate in or remain in the study.

The Investigator:

- Ensures volunteers' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that volunteer, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented, and the signed document returned to the study site
- Ensures that the volunteer and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study center.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Subject data protection

The informed consent form(s) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to volunteers, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the volunteer. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a volunteer. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a volunteer's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the volunteer's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An ethics committee should approve the final CSP, including the final versions of the informed consent form(s) and any other written information and/or materials to be provided to the volunteers. The Investigator will ensure the distribution of these documents to the applicable ethics committee and to the study center staff.

The opinion of the ethics committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any volunteer into the study.

The ethics committee should approve all advertising used to recruit volunteers for the study.

AstraZeneca should approve any modifications to the informed consent form(s) that are needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the ethics committee annually.

Before enrollment of any volunteer into the study, the final CSP, including the final versions of the informed consent form(s), is/are approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, ethics committees, and Investigator with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

The Investigator is responsible for providing the ethics committees/Institutional Review Board with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Investigator at the study center will:

- Ensure each volunteer is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each volunteer is notified that they are free to discontinue from the study at any time
- Ensure that each volunteer is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each volunteer provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed informed consent form(s) is/are given to the volunteer
- Ensure that any incentives for volunteers who participate in the study as well as any provisions for volunteers harmed as a consequence of study participation are described in the informed consent form(s) that are approved by an ethics committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Investigator and AstraZeneca.

If there are any substantial changes to the CSP, these changes will be documented in a CSP amendment and, where required, in a new version of the CSP (Revised CSP).

The amendment is to be approved by the relevant ethics committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for Revised CSP.

AstraZeneca will distribute any subsequent amendments and new versions of the CSP to the Investigator. For distribution to ethics committee see Section 8.3.

If a CSP Amendment requires a change to the center's informed consent form(s), AstraZeneca and the center's ethics committee are to approve the revised informed consent form(s) before the revised form is used.

If local regulations require, any administrative change will be communicated to ,or approved by, each ethics committee.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an ethics committee may perform audits or inspections at the study center, including source data verification. The

purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the CSP, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT BY ASTRAZENECA

Quintiles will manage the study on behalf of AstraZeneca.

9.1 Prestudy activities

Before the first volunteer is entered into the study, it is necessary for a representative of AstraZeneca or designee to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate volunteers for the study
- Discuss with the Investigator (and other personnel involved with the study) their responsibilities with regard to CSP adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the Investigator.

9.2 Training of study site personnel

Before the first volunteer is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator
- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the CSP, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs with the volunteer's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating volunteers. This will require direct access to all original records for each volunteer (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the volunteer's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the volunteer.

The AstraZeneca representative will be available between visits if the Investigator or other staff at the study center needs information and advice about the study conduct.

Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The Investigator at the study center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of volunteers and in all other respects, not relating to study conduct or treatment of volunteers, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Investigator should be in place before any study-related procedures can take place, or volunteers are enrolled.

Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last volunteer undergoing the study'.

[redacted]

The study may be terminated at the center if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with vandetanib.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by Quintiles, Inc. A 21 Code of Federal Regulations Part 11-compliant electronic data capture system will be used for this study. Case Report Forms will be produced by Quintiles for each volunteer.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by Quintiles.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, a clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of safety variable(s)

11.1.1 Calculation of change from baseline

Change-from-baseline variables will be calculated for the safety variables listed below, as the posttreatment value minus the value at baseline. The baseline values will be as follows:

- Clinical laboratory tests: Day -1
- Vital signs: Day 1 predose
- ECG: Period 1, Day 1 predose

If a volunteer is missing the baseline collection, the previous nonmissing evaluation will become the baseline value. If no baseline or previous-to-baseline evaluations exist, then the baseline value will be treated as missing and no change-from-baseline value will be calculated.

11.1.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to AEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

11.2 Calculation or derivation of pharmacokinetic variables

The PK analyses of the plasma concentration data for vandetanib will be performed at Quintiles, Inc, Overland Park, Kansas, United States by standard noncompartmental methods using WinNonlin Professional, version 5.2 or higher (Pharsight Corp., Mountain View, California, United States) or SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, United States).

Quintiles' Standard Operating Procedures (SOPs) and Work Instructions will be used as the default methodology if not otherwise specified. The actual sampling times will be used in the PK parameter calculations.

Volunteers who withdraw from the study following dosing, but prior to study completion, will be included in the PK analysis provided they have evaluable concentrations over the planned collection period. Volunteers with partial data will be evaluated on a case-by-case basis to determine if sufficient data are available for meaningful analysis.

The following PK parameters will be determined for vandetanib for each treatment:

C_{max}	Maximum concentration in the plasma, obtained directly from the observed concentration versus time data
t_{max}	Time of maximum plasma concentration, obtained directly from the observed concentration versus time data
$AUC_{(0-t)}$	Area under the concentration-time curve in plasma from zero to the last quantifiable concentration calculated by linear up/log down trapezoidal summation
AUC	Area under the concentration-time curve in plasma from zero to infinity, calculated by linear up/log down trapezoidal summation
$AUC_{(0-672h)}$	Area under the concentration-time curve in plasma from zero to 672 hours postdose
λ_z	Apparent terminal rate constant

$t_{1/2,\lambda z}$	Apparent terminal half-life, determined as $\ln 2/\lambda_z$
CL/F	Apparent oral clearance, calculated as dose/AUC
V_z/F	Apparent volume of distribution in the terminal phase calculated as $CL/F/\lambda_z$

The following PK diagnostic parameters will be calculated for vandetanib, as appropriate, and will be listed but not summarized:

- The time interval ($t_{½}$, interval or λ lower/upper) of the log-linear regression to determine λ_z
- Number of data points ($t_{½}$, N) included in the log-linear regression analysis used to determine λ_z (a minimum of 3 points will be used)
- Rsq, a goodness-of-fit statistic for calculation of λ_z. If Rsq is less than 0.800, then λ_z and related parameters ($t_{1/2,\lambda z}$, AUC, CL/F, and V_z/F) will not be reported.
- Percentage of AUC obtained by extrapolation ($\%AUC_{ex}$). If the extrapolated area is greater than 20% of AUC, then AUC and parameters like CL/F and V_z/F will not be reported.

Other PK parameters may be estimated if deemed appropriate.

11.3 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 General principles

The analysis of data will be based on different subsets according to the purpose of analysis ie, for safety and PK, respectively.

The decision regarding validity of data for each of the analysis sets will be based on a blind review of data. The as-treated principle will be applied to all evaluations ie, volunteers who receive another treatment than the 1 assigned in the randomization list will be analyzed as belonging to the actual treatment group and not that assigned by randomization.

12.1.2 Safety analysis set

All volunteers who receive at least 1 dose of the IP and for whom any postdose data are available will be included in the safety population.

12.1.3 Pharmacokinetic analysis set

The PK analysis set will include all volunteers who receive at least 1 dose of the IP and have at least 1 postdose PK measurement without important protocol deviations or violations thought to significantly affect the PK of the drug (eg, volunteer vomited at or before 2 times median t_{max}; wrong dose administered; prohibited concomitant medications).

12.2 Methods of statistical analyses

12.2.1 General principles

Missing data will result in a reduced sample size for that parameter. Since the statistical analyses will be predominantly presentations in tables and individual data listings, no action will be taken to handle missing data.

A volunteer who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

12.2.2 Subject characteristics

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) and categorical variables will be summarized in frequency tables (frequency and proportion) for all volunteers overall.

12.2.3 Safety and tolerability

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables (hematology, clinical chemistry, and vital signs) will be summarized using descriptive statistics (n, mean, SD, minimum, median, and maximum) by scheduled time point. Where applicable, data will be summarized for the absolute value at each scheduled assessment, and for the corresponding change from baseline. Adverse events will be summarized in frequency tables (frequency and proportion) for each treatment. Graphical presentations may be used, as appropriate.

All AEs will be collected for each volunteer from Day -1 until the follow-up visit. On-treatment AEs (ie, those beginning after the first dose of IP) will be summarized by preferred term and system organ class using MedDRA vocabulary. Furthermore, listings of deaths (if any), SAEs, and AEs that lead to study discontinuation will be made. The number of volunteers who have any AEs, SAEs, AEs that lead to withdrawal, AEs of different intensity, and AEs judged causally related to IP by the Investigator will be summarized.

For clinical laboratory tests, listings of values for each volunteer will be presented with abnormal or out-of-range values flagged. Clinical laboratory data will be reported in Système International units in the CSR.

Results from the ECGs and physical examinations will be presented in listings only.

Safety variables (ie, clinical laboratory values and vital signs) will be reported to the same precision as the source data. Derived variables will be reported using similar precision to those from which they were derived (eg, QTc derived from QT interval).

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in data listings. All AEs and clinical laboratory outliers that occur following the first dose of IP will be included in the tabulations of AEs and outlier events, including episodes that occur at unscheduled evaluations or during the washout period between treatments.

12.2.4 Pharmacokinetics

Plasma concentrations will be summarized by nominal time points using descriptive statistics including: the population size (N for sample size and n for available data), geometric mean, geometric coefficient of variation (CV%), arithmetic mean, SD, median, minimum, and maximum.

The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The CV% is calculated as $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale. Pharmacokinetic concentrations will be reported to the same precision as the source data.

Plasma concentrations that are below the LLOQ (BLQ) will be handled as follows:

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated
- At a time point where more than half of the values are BLQ, the mean, SD, geometric mean, and CV% will be set to Not Determined (ND). The maximum value will be reported from the individual data, and the min and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for SD and CV% and BLQ will be written in fields for mean, geometric mean, minimum, median, and maximum.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

In general, individual data, descriptive statistics of concentrations, and PK parameters will be rounded for reporting purposes per Quintiles' SOPs.

The $AUC_{(0-t)}$ and C_{max} of vandetanib will be the primary PK outcome variables onto which the conclusion on the effect of omeprazole or ranitidine on vandetanib PK will be made. All other vandetanib parameters are secondary PK parameters.

To assess the effect of omeprazole or ranitidine on the PK of vandetanib, the primary PK parameters, $AUC_{(0-t)}$ and C_{max} of vandetanib, will be statistically analyzed separately for each group (Group 1 and Group 2) using a mixed-effects model on the log-transformed PK parameters with fixed effects for sequence, period, and treatment and random effect for volunteers nested within sequence. The least-squares means of each treatment and their 95% CIs will be calculated from the model. The geometric least-squares means, 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% CI will be presented.

Within each group, if the CIs for both $AUC_{(0-t)}$ and C_{max} are between 0.80 and 1.25 it will be concluded that the PK of vandetanib is not influenced by omeprazole and/or ranitidine.

12.3 Determination of sample size

The number of volunteers was based on a desire to gain adequate information on the primary endpoints while exposing as few volunteers as possible to study procedures. Based on the estimate of the within-volunteer SD from Study D4200C00012 of 0.077 for C_{max} (inflated to 0.120, the upper 80% confidence limit, to adjust for small volunteer numbers), 10 evaluable volunteers would give 90% power of showing that the 90% CI for the ratio of vandetanib in the presence and absence of omeprazole lies between 0.8 and 1.25 for C_{max}. However, regulatory guidelines suggest a minimum of 12 evaluable volunteers for adequate assessment of model assumptions. Consequently, a total of 16 volunteers will be randomized to Group 1 to allow for some nonevaluable volunteers.

Similarly, 16 volunteers will be randomized to Group 2 to give a 90% power of showing that the 90% CI for the ratio of vandetanib in the presence and absence of ranitidine lies between 0.8 and 1.20 for C_{max}, allowing for some nonevaluable volunteers. Thus a total of 32 volunteers will be randomized into the study.

Note that the estimates have been based on C_{max} because the AUC data were not available. However, C_{max} is generally more variable than AUC; therefore, basing the calculations on C_{max} would give adequate power for AUC as well.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.3.4.**

In the case of a medical emergency the Investigator may contact the Clinical Pharmacolopgy Alliance (CPA) Physician. If the CPA Physician is not available, the CPA Program Director should be contacted.

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

13.2 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel must inform appropriate AstraZeneca representatives **within 1 day** ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.3.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the volunteer was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel must inform appropriate AstraZeneca representatives **within 1 day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure

Male volunteers should refrain from fathering a child or donating sperm from the first administration of IP until 3 months after last administration of IP. Volunteers must ensure that their partners of childbearing potential use a reliable method of contraception, as well as using a barrier method (ie, condom) themselves.

Pregnancy of the volunteer's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should if possible be followed up and documented.

14. LIST OF REFERENCES (NOT APPLICABLE)

Clinical Study Protocol Appendix B

Drug Substance	Vandetanib
Study Code	D4200C00101
Edition Number	1.0
Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the volunteer was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the volunteer's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm and laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the volunteer was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the volunteer or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, Neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time course. Exposure to suspect drug. Has the volunteer actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where 1 or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	Vandetanib
Study Code	D4200C00101
Edition Number	1.0
Date	[redacted]

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Vandetanib
Study Code	D4200C00101
Edition Number	1
Date	[redacted]

Appendix D
Optional Biomarker Research Samples

OPTIONAL BIOMARKER RESEARCH SYNOPSIS

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®)

The research activities described in this appendix (including the collection and storage of body fluid samples), are optional for study centers as well as for individual subjects. These research activities will hereafter be referred to as "this research." The Clinical Study Protocol to which this document is appended will be referred to as "the main study." The term "sample" means:

Plasma, Serum, or Urine

This research will be performed only after the appropriate Institutional Review Board has approved it. Informed consent for this research will be obtained using a separate Informed Consent Form from that used for the main study. All sections of the Clinical Study Protocol for the main study also apply to this research.

Study center and number of subjects who may be enrolled in this biomarker research

It is the intent of AstraZeneca to collect serum, plasma or urine samples from all Clinical Pharmacology studies conducted by the Clinical Pharmacology Alliance to further the goal of improving biochemical markers that can be used to monitor or predict investigational product induced organ damage. The goal will be to collect approximately 3000 such samples.

Objectives

Objective	Outcome variables
To analyze biological samples (eg, human plasma) for circulating biomarkers from consenting subjects prior to administration of the investigational product.	

Study design

It is proposed to collect a single serum, plasma or urine sample from each subject enrolled in the study as optional samples for biomarker analysis. The type of sample to be collected will be determined at the outset of the study. Provision of these samples for analysis will be optional for all subjects entering the study, and acceptance of this procedure will not be a requirement for participation in the main study.

The samples and data for optional biomarker analysis in this research will be coded. Each sample will be labeled with the study number and subject enrollment number (E-code). Only the Principal Investigator will be able to link the sample to the individual subject. The samples and data will not be labeled with personal details.

Target population

All consenting subjects in the study center participating in the main study.

Statistical methods

The number of subjects who will agree to participate in this research is unknown. It is therefore not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ALT	Alanine aminotransferase
eCRF	electronic Case Record Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
mL	Milliliter

1. BACKGROUND

As part of collaborative efforts with other pharmaceutical companies, diagnostic companies, and academic institutions, AstraZeneca is collecting samples to perform general research for variations in "safety" biomarker profiles. These biomarkers may be derived from proteins and/or metabolites. By using this information, the aim is to better understand the investigational product effect on major organs in the human body and how circulating biomarkers can be used to better monitor organ function and thus improve the safety of the investigational products.

To achieve this goal, a systematic collection of biological samples (urine, serum and/or blood plasma) will be undertaken as specified where appropriate.

1.1 Rationale for research

AstraZeneca may perform optional sampling determination for biomarker research in some of the studies for the clinical programs of new chemical entities under development. The objective of this research is to explore normal variations in biomarkers (protein or small molecule based) that occur in subjects enrolled in this study **prior to investigational product treatment**. In particular, developing better biochemical markers to help assess potential deleterious drug effects is the primary goal of this research. A key aspect to understanding how to use these new markers is to assess the normal variation in these markers in healthy subjects so we will appropriately interpret how changes in these new biochemical markers are affected by investigational product treatment. Understanding this normal variation is part of a process known as qualification which attempts to establish sufficient evidence of changes in these biomarkers in relationship to organ damage that they are suitable for monitoring safety for clinical studies. Other recent studies have suggested that using proteomic and metabolomic platforms may help identify other new predictive biomarkers that help explain alanine aminotransferase (ALT) elevation (Andersson et al 2009).

The ability to acquire appropriate informed consent to collect biological samples to establish an archive and allow future meta-analysis of data derived from a number of studies is of the utmost importance. This research forms part of this strategy.

The benefits of being able to explore associations between biomarker variations and clinical outcomes are potentially many, including the possibility to identify subjects early who may be at risk of adverse drug reactions, or to explain potential adverse reactions related to investigational product exposure.

2. RESEARCH OBJECTIVES

Biomarker technologies enable the measurement of many different molecules, including proteins and metabolites, within a sample. The objective of this research is to determine if correlations exist between traditional biomarkers used to monitor organ function (such as

ALT and bilirubin for liver) and new biomarkers that may be more sensitive and/or specific indicators of drug induced organ damage.

2.1 Research plan

The subject will be asked to participate in this optional biomarker research during their enrollment or at Visit 1 (screening). If the subject agrees to participate the following samples will be requested:

- A single 10 mL plasma or serum sample or a single urine sample of up to 15 mL

2.2 Selection of optional biomarker research population

2.2.1 Study selection record

All subjects who take part in this study will be asked to participate in this optional biomarker research. Participation is voluntary, and if a subject declines to participate in this optional biomarker research they will not be excluded from any aspect of the main study.

2.2.2 Withdrawal of subjects from this optional biomarker research

2.2.2.1 Criteria for withdrawal

Specific reasons for withdrawing a subject from this optional biomarker research are:

- Withdrawal of consent for optional biomarker research. Subjects may withdraw from this optional biomarker research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment

2.2.2.2 Procedures for withdrawal

Subjects who withdraw from the main study should always be asked specifically whether they are withdrawing or continuing their informed consent for this optional biomarker research. It must be established whether the subject:

- Agrees to the optional biomarker samples and any preparations derived from the sample being kept for research in the future

- Withdraws consent for the samples to be kept for optional biomarker research in the future and wishes the samples to be destroyed. Destruction of the samples (or the preparations derived from the samples) will only be possible so long as the particular samples are traceable. In the event that optional biomarker research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons, but these will not be used in any subsequent analyses.

The Principal Investigator is responsible for providing written notification to AstraZeneca of any subject who has withdrawn consent for the use of the sample taken for optional biomarker

research. AstraZeneca will provide written confirmation to the Principal Investigator of the actions taken with the sample, which must be filed in the Investigator Study File.

3. MEASUREMENTS AND CO-VARIABLES

3.1 Summary of objectives and analysis

The purpose of this research is to generate data that will help interpret results from future clinical studies. The results of this research will not form part of the Clinical Study Report (CSR) for the main study. The results may be pooled with data from other studies generate hypotheses to be tested in future studies.

3.2 Collection of samples for optional biomarker research

AstraZeneca or its designee will act as the central laboratory for sample logistics. Details of sample collection, processing, shipping and storage will be described in the laboratory manual.

The samples and data for analysis in this research will be coded and will not be labeled with any personal details. Each sample will be identified with the study number and subject enrollment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled. However, only the Principal Investigator will be able to link the biomarker sample to the individual subject.

The coded samples may be made available to groups or organizations working with AstraZeneca on this research or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give samples, sample derivatives or data derived from the samples to any other parties, except as required by law.

3.2.1 Biomarker analysis

The precise details of the biomarker analysis will be established by AstraZeneca scientists. However, in some cases, samples may be sent to commercial or academic partners for specialized analyses.

In addition to studies to identify new candidate biomarkers, samples may also be used to measure existing candidate biomarkers by methods that will depend on the specific biomarker.

4. MANAGEMENT OF RESEARCH DATA

Some of the dataset from the main study may be duplicated within AstraZeneca for exploratory analyses in combination with the optional biomarker data. Neither the subject's name nor any other personal identifiers will be part of this dataset. Optional biomarker data will not be reported in the CSR. Only the date the subject gave consent for participation in the

research and the date and time the biological sample(s) (if applicable) was taken from the subject will be recorded in the electronic Case Report Form (eCRF) and database.

AstraZeneca will not provide optional biomarker research results to subjects, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The subject's samples will not be used for any purpose other than optional biomarker research.

Individual subjects will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the subject's name nor any other personal identifiers will appear in any publication or report.

5. STATISTICAL METHODS

One of the primary goals of these exploratory studies is to establish a large sample cohort that will help us understand the variability of new biomarkers in a general population. The samples that compose this cohort will come from multiple different studies and a statistical analysis plan will be prepared for analyses of each new biomarker. This analysis will help us determine how many subjects will be needed for future studies. However, neither the results of this biomarker work nor the statistical analysis will be included in the CSR for the studies from which these samples have been collected.

5.1 Monitoring

During the study, monitors will have regular contact with the study center. One of the purposes of these visits will be to perform source verification of the informed consent of participating subjects and to ensure that the investigational team is adhering to the specific requirements of this optional biomarker research.

5.2 Training of staff

Before the first subject is entered into the study the study center staff will have an opportunity to discuss the procedures associated with the collection of samples and optional biomarker research with a representative of AstraZeneca. The requirements for the collections of the subjects' sample will also be made clear.

5.3 Changes to the Clinical Study Protocol

Any changes to the optional biomarker research will comply with the principles described in Section 8.5 of the main body of the Clinical Study Protocol (CSP).

5.4 Study agreements

The Principal Investigator at each study center must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this research. In the event of any inconsistency between this CSP and the Clinical Study Agreement, the CSP shall prevail.

Specific reference to requirements relating to this optional biomarker research will be included in the study agreement(s).

6. ETHICS

6.1 Ethics review

In addition to documenting Institutional Review Board (IRB) approval of the main study, approval must be obtained for this optional biomarker research and the associated informed consent from the relevant IRB. It must be clearly stated in the approval that this optional biomarker research is approved. The Principal Investigator must submit written approval to AstraZeneca before any subject participates in this optional biomarker research.

6.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization(ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics.

6.3 Informed consent

The biomarker component of this research is optional and the subject may participate in other components of the study without participating in the optional biomarker component. To participate in the optional biomarker component of the study, the subject must sign and date both the Informed Consent Form for the main study and the Informed Consent Form for the optional biomarker component of the study. Copies of both signed and dated Informed Consent Forms must be given to the subject and the originals filed at the study center in the Investigator's Study File. The Principal Investigator is responsible for ensuring that written informed consent is given freely and that the subject understands that they may freely discontinue from the optional biomarker aspect of the study at any time.

6.4 Subject data protection

All data protection and confidentiality principles, described in the main study CSP, are applicable to this optional biomarker research.

Due to the exploratory nature of this optional biomarker research, there will be no routine communication of results to subjects. AstraZeneca will not provide individual results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

7. REFERENCES

Ozer et al 2008
Ozer J, Ratner M, Shaw M, Bailey W, Schomaker S. The current state of serum biomarkers of hepatotoxicity . Toxicology. 2008 Mar 20;245(3):194-205.

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Clinical Study Protocol Appendix E

Drug Substance	Vandetanib
Study Code	D4200C00101
Edition Number	1.0
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Appendix E

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a volunteer meets potential Hy's law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) decisive factors are fulfilled, indicating a Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP). Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than the IMP.

The Investigator fulfils requirements for the recording of data pertaining to PHL/HL cases and adverse event (AE)/serious AE (SAE) reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

For the purpose of this process definitions are as follows

Potential Hy's Law
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 3 times the upper limit of normal (ULN) **and** total bilirubin (TBL) greater than or equal to 2 times the ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law
Aspartate aminotransferase or ALT greater than or equal to 3 times ULN **and** TBL greater than or equal to 2 times the ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, or another drug.' The elevations do not have to occur at the same time or within a specified time frame.

3. ACTIONS REQUIRED IN CASES OF ALT ≥ 3X ULN, AST ≥ 3X ULN OR TBL ≥ 2X ULN

3.1 Identification and determination

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any volunteer who meets any of the following criteria in isolation or in combination:

- ALT greater than or equal to 3 times the ULN
- AST greater than or equal to 3 times the ULN
- TBL greater than or equal to 2 times the ULN

When a volunteer meets the criteria above, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

When this alert is received please follow the instructions below without delay:

- Review laboratory reports from all previous visits
- Review any available local laboratory reports and if a subject has ALT greater than or equal to 3 times the ULN, AST greater than or equal to 3 times the ULN **or** TBL greater than or equal to 2 times the ULN at any time
    - Repeat test with the central laboratory
    - Complete the appropriate laboratory case report form (CRF) modules with the original local laboratory test result
- Determine whether the volunteer meets PHL criteria (see Section 2 of this Appendix)
  Note: Applicable for both central laboratory and additional local laboratory reports

3.2 Follow-up

3.2.1 Potential Hy's Law Criteria not met

If the volunteer does not meet PHL criteria (see section 2 of this Appendix):

- Inform the AstraZeneca representative that the volunteer has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol

3.2.2 Potential Hy's Law Criteria met

If the volunteer meets PHL criteria (see section 2 of this Appendix):

- Notify the AstraZeneca representative who will then inform the central study team

The study physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study volunteer's follow-up and the continuous review of data.

The Investigator:

- Follows the volunteer until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigates the etiology of the event and perform diagnostic investigations as discussed with the study physician

- Completes the 3 liver CRF modules as information becomes available

- If at any time (in consultation with the study physician) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

3.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the study physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other volunteer matter experts as appropriate. According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the ALT or AST **and** TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation **is** an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST **and** TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes

- The 'Medically Important' serious criterion should be used if no other serious criteria apply

- As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If there is an unavoidable delay of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

4. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm