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Pharmacokinetic Drug Interactions with Vandetanib during Coadministration with Rifampicin or Itraconazole

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Abstract

Background: Vandetanib, an inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2), epidermal growth factor receptor (EGFR), and rearranged during transfection (RET), is a developmental oncology drug, that is in part metabolized by cytochrome P450 (CYP) 3A4. Clinical studies were performed to assess the potential for 3A4 inhibitors and inducers to affect exposure to vandetanib.

Objective: The aim of this study was to investigate the effects of a potent CYP3A4 inducer, rifampicin (Study A), and a potent CYP3A4 inhibitor, itraconazole (Study B), on the pharmacokinetics of a single 300 mg dose of vandetanib in healthy subjects.

Study Design and Setting: Two phase I, randomized, open-label, two-way crossover, single-center studies.

Participants and Intervention: Study A: 18 healthy male subjects aged 21–44 years were randomized to receive each of the following two regimens, separated by a ≥6-week washout period: (i) oral rifampicin 600 mg/day on days 1–31 with a single oral dose of vandetanib 300 mg on day 10; and (ii) a single oral dose of vandetanib 300 mg on day 1. Study B: 16 healthy male subjects aged 20–44 years were randomized to receive each of the following two regimens, separated by a 3-month washout period: (i) oral itraconazole 200 mg/day on days 1–24 with a single oral dose of vandetanib 300 mg on day 4; and (ii) a single oral dose of vandetanib 300 mg on day 1.

Main Outcome Measure: Blood samples for measurement of vandetanib (both studies) concentrations and its metabolites, N-desmethylvandetanib and vandetanib N-oxide (Study A only), were collected before and at various timepoints after vandetanib administration for up to 28 days (Study A) and 37 days (Study B). Pharmacokinetic parameters were determined using non-compartmental methods. The area under the plasma concentration-time curve from time 0 to 504 hours (AUC_{504}) and maximum plasma concentration (C_{max}) of vandetanib were compared in the presence and absence of rifampicin, and in the presence and absence of itraconazole.

Results: Study A: coadministration of vandetanib with rifampicin resulted in a statistically significant reduction in AUC_{504} (geometric least square [GLS]mean ratio [vandetanib + rifampicin/vandetanib alone] 0.60; 90% CI 0.58, 0.63). There was no significant difference in C_{max} of vandetanib (GLSmean ratio 1.03; 90% CI 0.95, 1.11). AUC_{504} and C_{max} of N-desmethylvandetanib increased by 266.0% and 414.3%, respectively, in the presence of rifampicin compared with vandetanib alone. Exposure to vandetanib N-oxide was very low compared with that of vandetanib, but was increased in the presence of rifampicin. Study B: coadministration of vandetanib with itraconazole resulted in a significant increase in AUC_{504} (GLSmean ratio [vandetanib + itraconazole/vandetanib alone] 1.09; 90% CI 1.01, 1.18) and no significant change in C_{max} (GLSmean ratio 0.96; 90% CI 0.83, 1.11). Vandetanib was well tolerated in both studies.

Conclusions: Exposure to vandetanib, as assessed by AUC_{504} in healthy subjects, was reduced by around 40% when a single dose was given in combination with the potent CYP3A4 inducer rifampicin. Because of this, it may be appropriate to avoid coadministration of potent CYP3A4 inducers with vandetanib. Vandetanib exposure was increased by about 9% when it was taken in combination with the CYP3A4 inhibitor itraconazole. It is unlikely that coadministration of vandetanib and potent CYP3A4 inhibitors will need to be contraindicated.

Background

Vandetanib (ZD6474) is a novel, orally available inhibitor of vascular endothelial growth factor receptor 2 (VEGFR-2), epidermal growth factor receptor (EGFR), and rearranged during transfection (RET) tyrosine kinase activity.[1-3] VEGFR-2, EGFR, and RET are involved in signaling pathways promoting angiogenesis and tumor growth.[4-6] Vandetanib is in development as an anti-tumor drug in several tumor types, including medullary thyroid cancer.[7] Data have recently been reported from three double-blind, randomized, phase III studies of vandetanib in patients with advanced, previously-treated non-small cell lung cancer (NSCLC).[8-10] In the ZODIAC (Zactima™ in cOmbination with Docetaxel In non-small cell lung Cancer) study, vandetanib in combination with docetaxel produced a significant improvement in progression-free survival compared with docetaxel alone ($p < 0.001$).[9] Results from the ZEAL (Zactima™ Efficacy with Alimta® in Lung cancer)[8] and ZEST (Zactima™ Efficacy when Studied versus Tarceva®)[10] studies demonstrated activity in NSCLC for the combination of vandetanib with pemetrexed,[8] and for monotherapy with vandetanib.[10]

In vitro studies have shown that cytochrome P450 (CYP) 3A4 is the main CYP enzyme involved in the metabolism of vandetanib.[11] Vandetanib is converted by CYP3A4 to N-desmethylvandetanib and by flavine-containing mono-oxygenases in the kidney (FMO1) and liver (FMO3) to vandetanib N-oxide. A recent study in healthy male subjects using radiolabelled vandetanib confirmed the presence of N-desmethylvandetanib and vandetanib N-oxide in plasma, urine, and feces.[12] Both N-desmethylvandetanib and vandetanib N-oxide have shown *in vitro* pharmacologic activity in cellular assays for vascular endothelial growth factor and epidermal growth factor.[13] N-desmethylvandetanib is of similar potency to vandetanib, while vandetanib N-oxide is >50-fold less active than vandetanib. Since vandetanib is metabolized by CYP3A4, it was considered important to determine whether induction or inhibition of this enzyme would influence exposure to vandetanib. Oncology patients are

likely to take a range of other drugs in addition to their therapy for cancer, possibly including agents that induce or inhibit metabolic enzymes. Significant pharmacokinetic drug-drug interactions could lead to alterations in plasma concentrations of vandetanib, potentially resulting in a reduction in efficacy or an increase in drug-related toxicity.

This article reports the results of two studies investigating potential pharmacokinetic drug-drug interactions between vandetanib and rifampicin, a potent CYP3A4 inducer (Study A; AstraZeneca study code D4200C00026), and vandetanib and itraconazole, a potent CYP3A4 inhibitor (Study B; D4200C00015). Further objectives included determining the effects of rifampicin on the pharmacokinetics of the vandetanib metabolites N-desmethylvandetanib and vandetanib N-oxide (Study A only), and confirming the safety and tolerability of vandetanib (both studies).

Methods

Study Subjects

Both studies recruited healthy male subjects aged 21–50 years (Study A) or 21–45 years (Study B) with no clinically significant medical history or clinically important abnormalities in vital signs, ECG, or clinical chemistry, hematology, or urinalysis results, and who had not received any recent treatment with CYP inhibitors or inducers.

The studies were performed in compliance with the ethical principles of the Declaration of Helsinki, which are consistent with the International Conference on Harmonisation and Good Clinical Practice. Ethics committee approval was obtained and all subjects were required to give written, informed consent before taking part.

Study Design

Both studies were phase I, randomized, open-label, two-way crossover studies of similar design (figure 1) and were conducted at a single center in France between December 2006 and May 2007 (Study A), or October 2003 and April 2004 (Study B).

In each study, subjects received two treatment regimens in random order. In Study A, subjects first received either (i) oral rifampicin 600 mg/day on days 1–31 with a single oral dose of vandetanib 300 mg on day 10; or (ii) a single oral dose of vandetanib 300 mg on day 1 (no rifampicin). After a washout period of at least 6 weeks following the vandetanib dose, the subjects received the alternative treatment. In Study B, subjects first received either (i) oral itraconazole 200 mg/day on days 1–24 with a single oral dose of vandetanib 300 mg on day 4; or (ii) a single oral dose of vandetanib 300 mg on day 1 (no itraconazole). After a 3-month washout period following the dose of vandetanib, subjects received the alternative treatment.

Concomitant medication was not allowed in either study, except for paracetamol (not to exceed 4 g in 24 hours) or where the investigator had given prior consent.

Subjects in Study B were required to fast for 8 hours before any dose of vandetanib or itraconazole, until 1 hour after dosing with itraconazole, or 2 hours after dosing with vandetanib with or without itraconazole.

Pharmacokinetic Assessments

Blood samples for determination of vandetanib concentrations in plasma were collected in tubes containing lithium heparin anticoagulant as follows: pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 18, 24, 36, and 48 hours post-dose. In Study A, samples were then collected at 24-hour intervals up to 10 days post-dose, at 48-hour intervals up to 18 days post-dose, and at 21 and 28 days after the dose. In Study B, samples were collected at 24-hour intervals up to 14 days post-dose, at 48-hour intervals up to 22 days post-dose, and at 25, 32, and 37 days after the dose.

In Study A, during the rifampicin treatment period, blood samples for the determination of rifampicin in plasma were collected at 2 hours after the dose of rifampicin on days 1, 5, 10, 20, and 31. In Study B, during the itraconazole treatment period, blood samples for the determination of itraconazole and hydroxy-itraconazole in plasma were collected before dosing with vandetanib and at 1, 2, 4, 6, 8, 12, 24, and 48 hours post-dose, at 48-hour intervals up to 22 days post-dose, and at

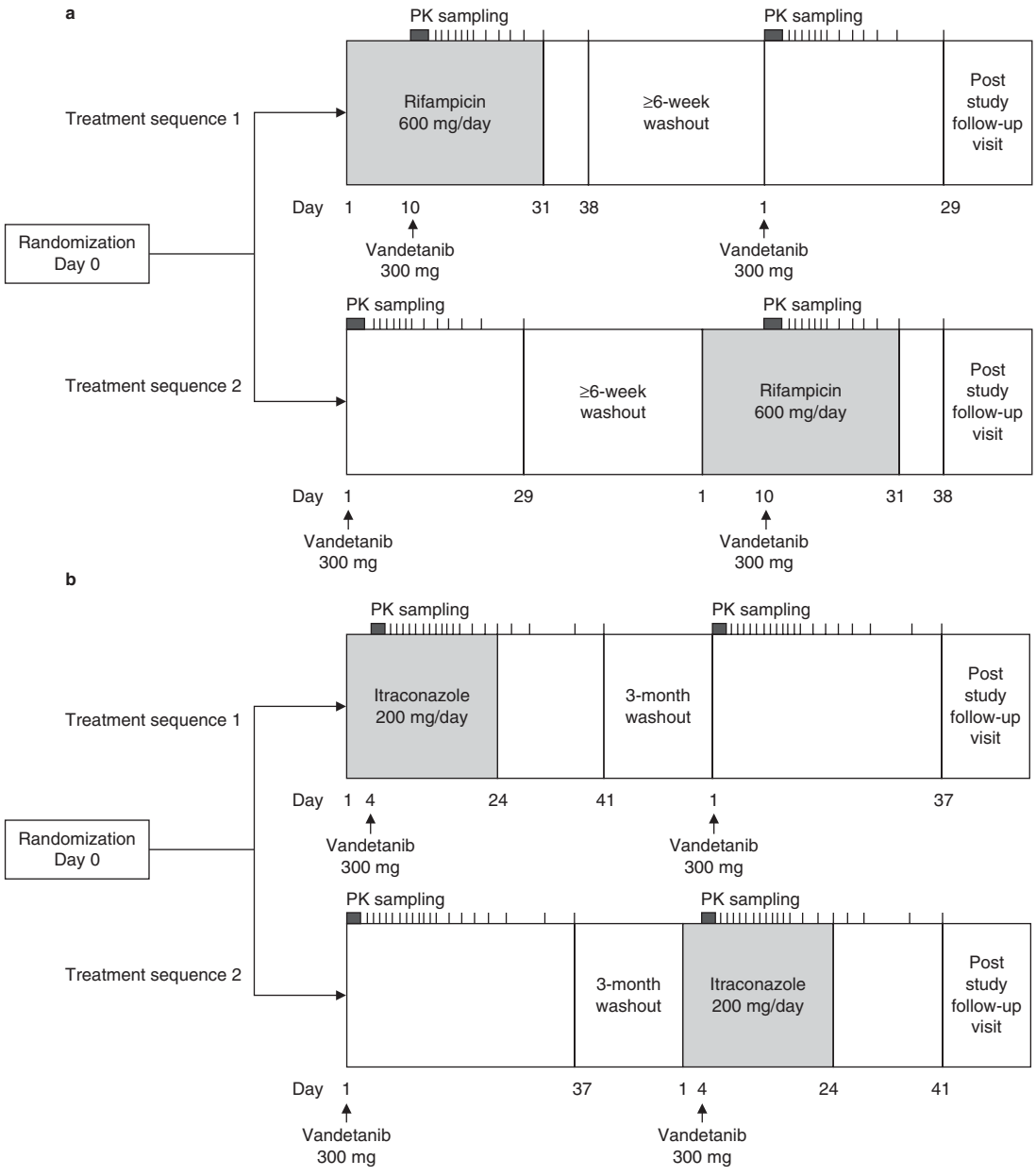

Fig. 1. Study design for (**a**) Study A and (**b**) Study B. **PK** = pharmacokinetic.

25 and 37 days after the dose. These samples were taken to confirm exposure to the CYP3A4 inducer or inhibitor.

All blood samples were centrifuged within 30 minutes of collection and the plasma stored at –20°C. In Study A, plasma samples were analyzed for vandetanib and its metabolites by Eurofins Medinet, the Netherlands, and for rifampicin by Pharma Bio-Research Group, the Netherlands. In Study B, plasma samples were analyzed for

vandetanib and itraconazole by BAS Analytics, UK, and for hydroxy-itraconazole by MDS Pharma Services, UK. The method used for analysis of vandetanib and its metabolites was protein precipitation extraction followed by reversed phase high-performance liquid chromatography (RP-HPLC) and tandem mass spectrometry (MS/MS). 'Solvent first' methodology, using Isolute® PPT+ protein precipitation plates (Biotage, Sweden), was used to remove proteins from the plasma sample. A total of 0.3 mL acetonitrile, internal standard, and 0.1 mL sample were applied sequentially onto the PPT+ plates. After homogenization, filtration was performed under a vacuum and the filtrate was transferred to a clean tube. After evaporation to dryness at 40°C under a stream of nitrogen, the dry residue was reconstituted in 100 μL of mobile phase (acetonitrile : water-ammonium acetate 8 : 2). Aliquots of 10 μL were injected onto an HPLC system comprising an Inertsil ODS-3 150 × 4.6 mm C18 column (GL Sciences Inc., USA), a 4 × 2 mm C18 guard column, and a flow rate of 1.0 mL/min. Detection was performed using a PE Sciex triple quadrupole mass spectrometer with heated nebulizer source. Vandetanib and vandetanib N-oxide were detected by positive ion multiple reaction monitoring (MRM) with mass settings of 475 → 112 and 491 → 128. The mass settings for the internal standard, ^{13}C-D_3-vandetanib, were 479 → 116. N-desmethylvandetanib was detected by MRM with mass settings of 461 → 98 and a mass setting for the internal standard (AZ10031527) of 418 → 98. The peak areas of vandetanib and its metabolites relative to the internal standard were calculated and the concentration was determined by reference to the relevant calibration curve. The lower limits of quantification were 5 ng/mL for vandetanib, and 1 ng/mL for N-desmethylvandetanib and vandetanib N-oxide. For vandetanib, mean accuracy was 105–110% and precision was 6.6–7.4%. For N-desmethylvandetanib, mean accuracy was 99.5–104% and precision was 6.3–12.3%. For vandetanib, mean accuracy was 100–105% and precision was 9.8–11.1%.

Pharmacokinetic parameters for vandetanib, N-desmethylvandetanib, and vandetanib N-oxide were determined from plasma concentration data using non-compartmental methods (WinNonlin Enterprise Version 4.1, Study A).

The primary pharmacokinetic parameters were the area under the plasma concentration-time curve (AUC) from time 0 to 504 hours post-dose (AUC_{504}) and the maximum plasma concentration (C_{max}) of vandetanib.

Secondary pharmacokinetic parameters were as follows: (i) for vandetanib (both studies) – AUC from time zero to infinity (AUC_∞), time to reach C_{max} (t_{max}), and elimination half-life ($t_{½}$); (ii) for metabolites (Study A only) – AUC_{504}, C_{max}, AUC_∞, t_{max}, $t_{½}$, and the ratio of metabolite exposure to vandetanib exposure (AUC_{504} ratio).

Pharmacokinetic parameters were calculated as follows: C_{max} and t_{max} were derived directly from the AUC data; AUC_{504} was calculated by the linear trapezoidal rule; the disposition rate constant (λ_z) was calculated by log-linear regression of the terminal portion of the AUC where there were sufficient data to define this for at least three half-lives and/or no more than 15% of the total AUC was extrapolated; $t_{½}$ was calculated as $0.693/\lambda_z$; the AUC up to the time of the last quantifiable plasma concentration (AUC_{last}) was calculated by the linear trapezoidal rule and extrapolated to infinity to using λ_z to obtain AUC_∞; and the ratio of metabolite exposure to vandetanib exposure was determined from the respective AUC_{504} values.

Safety and Tolerability Assessments

Safety and tolerability assessments included adverse events, ECGs, vital signs, blood chemistry, hematology, and urinalysis.

Statistical Analyses

The safety analysis included all subjects who had received at least one dose of any study medication. Subjects with valid pharmacokinetic data were included in the pharmacokinetic analysis.

For Study A only, plasma concentration data were not available for a number of samples due to analytical failure. Pharmacokinetic parameters were only derived for subjects with adequate plasma concentration data.

The statistical analysis compared the primary pharmacokinetic parameters (AUC_{504} and C_{max} of vandetanib) in the presence and absence of rifampicin or itraconazole. AUC_{504} and C_{max} were logarithmically transformed and analyzed using a mixed effects model with fixed effects for period and treatment, with subject fitted as a random effect (Study A) or an ANOVA model with factors fitted for the effect of sequence, subject within sequence, period, and treatment (Study B). Results were presented as adjusted geometric means (geometric least square means [GLSmeans]) for AUC_{504} and C_{max} of vandetanib in the presence and absence of rifampicin or itraconazole, and the ratio of these GLSmeans with the corresponding 90% confidence interval (CI). Coadministration with rifampicin or itraconazole would be considered to have no significant effect on the pharmacokinetics of vandetanib if the 90% CI for the ratio of exposure lay between 0.8 and 1.25.

Sample sizes were based on estimates of within-subject standard deviations (SD_W) of pharmacokinetic parameters in previous studies.[14] A sample size of 12 evaluable subjects for Study A would provide 89% and 99% power of showing that the 90% CI for the ratio of vandetanib in the presence and absence of rifampicin lay between 0.8 and 1.25 for C_{max} ($SD_W = 0.117$) and AUC_{504} ($SD_W = 0.158$), respectively. Ten evaluable subjects in Study B would give 90% power of showing that the 90% CI for the ratio of vandetanib in the presence and absence of itraconazole lay between 0.8 and 1.25 for C_{max} ($SD_W = 0.077$ inflated to 0.120, the upper 80% confidence limit, to adjust for small subject numbers). Since C_{max} is generally more variable than AUC, the study was also expected to have adequate power for AUC_{504}. Each study aimed to recruit 16 subjects to allow for potential withdrawals.

Results

Subjects

In Study A, 18 healthy male subjects received study medication. The majority of subjects were Caucasian (77.8%), mean age was 31.7 years (range 21–44 years), and mean body mass index (BMI) was 24.0 kg/m^2 (range 19.4–29.1 kg/m^2). Three subjects withdrew from the study during the first treatment period. Two of these subjects withdrew after the first dose of rifampicin (one due to an adverse event, one withdrew consent); these subjects did not provide any pharmacokinetic data. The third subject withdrew after receiving rifampicin for 19 days and a single dose of vandetanib on day 10 because of adverse events; data from this subject were included in the pharmacokinetic analysis. Thus, 18 and 16 subjects were included in the safety and pharmacokinetic analyses, respectively.

Sixteen healthy male subjects were enrolled in Study B. Most subjects were Caucasian (68.8%), mean age was 30.2 years (range 20–44 years), and mean BMI was 23.7 kg/m^2 (range 19.0–29.0 kg/m^2). Two subjects withdrew consent to participate in the study during the first treatment period. One of these subjects had received itraconazole for 11 days and a single dose of vandetanib on day 4; the other had received a single dose of vandetanib alone. All 16 subjects were included in the safety and pharmacokinetic analyses.

In Study A, five subjects took anilides (such as paracetamol) mostly for headache, one subject took benzodiazepine derivatives for stress, and one subject took phenothiazine derivatives for varicella zoster virus infection (chickenpox). In Study B, one subject took ibuprofen and metronidazole for a dental abscess, and one subject used Locabiotal® spray (fusafungine) for rhinopharyngitis.

Pharmacokinetics

Study A (Cytochrome P450 (CYP) 3A4 Induction)

Rifampicin

Plasma concentrations of rifampicin measured 2 hours after dosing were mostly within the range expected. Geometric mean [gmean] (coefficient of variation [CV%]) plasma concentrations of rifampicin on days 1, 5, 10, 20, and 31 were 12.2 (14.8), 10.7 (26.5), 6.5 (95.5), 8.9 (31.3), and 9.9 (22.3) μg/mL, respectively. One subject had a low value (0.70 μg/mL) on day 10 compared with concentrations in other subjects on day 10, and with other concentrations in the same subject on days 1, 5, 20, and 31.

Vandetanib

Vandetanib was not detected in any pre-dose plasma samples. Following a single oral dose of vandetanib 300 mg to healthy subjects, plasma concentrations of vandetanib reached maximum at a median time of 6 hours post-dose, and then declined slowly with an approximate biphasic disposition (figure 2). Plasma concentrations of vandetanib were still quantifiable in most subjects at 672 hours after dosing.

In the presence of rifampicin, plasma concentrations of vandetanib declined at a more rapid rate, with divergence of the AUC at 48 hours after dosing. The vandetanib gmean $t_{½}$ was reduced from 217.6 hours to 116.3 hours. More than half of the subjects had undetectable levels of vandetanib by 504 hours after dosing.

There was a statistically significant reduction of 40% in the AUC_{504} of vandetanib when a single dose of vandetanib 300 mg was given in combination with rifampicin compared with vandetanib alone (GLSmean ratio 0.60; 90% CI 0.58, 0.63; table I). However, there was no statistically significant difference in the C_{max} of vandetanib in the presence or absence of rifampicin (GLSmean ratio 1.03; 90% CI 0.95, 1.11; table I).

Coadministration with rifampicin did not affect the t_{max} of vandetanib (table II).

N-Desmethylvandetanib

Following a single dose of vandetanib 300 mg, plasma concentrations of N-desmethylvandetanib reached maximum at a median time of 5 hours post-dose, then declined slowly and were still measurable in most subjects at 504 hours (table II; figure 3). AUC_{∞} and $t_{½}$ were not calculable for 12 subjects because the terminal phase was poorly defined or more than 20% of the AUC was extrapolated. The ratio of exposure to N-desmethylvandetanib relative to vandetanib was low, indicating that plasma concentrations of this metabolite were low compared with those of the parent compound. The AUC_{504} of

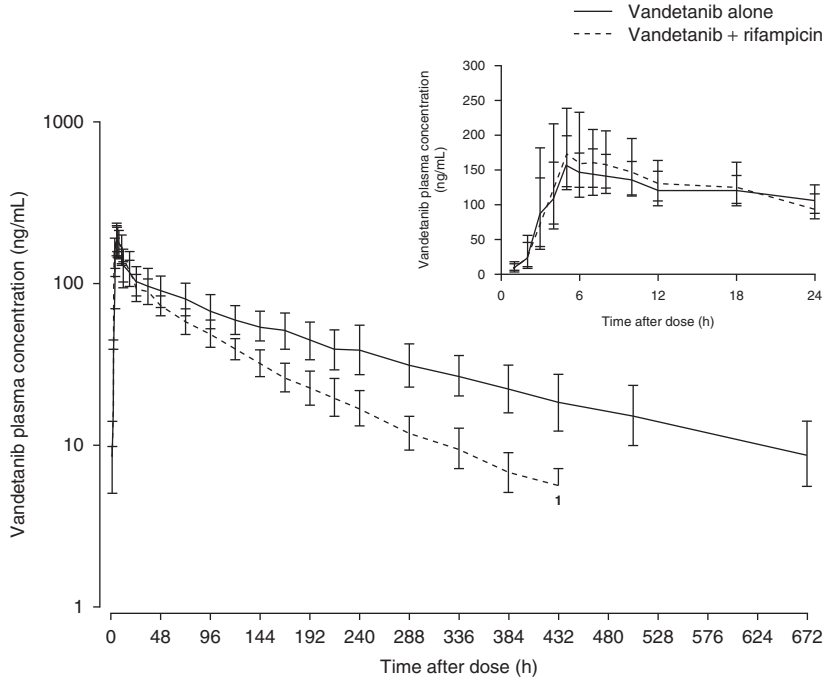

Fig. 2. Geometric mean (± SD) plasma concentrations of vandetanib following a single oral 300 mg dose alone or in combination with rifampicin. Insert shows more detailed plasma concentrations of vandetanib over the first 24 h. **1** = lower limit SD is not quantifiable <5 ng/mL.

Table I. Comparison of area under plasma concentration-time curve from time 0 to 504 hours (AUC_{504}) and maximum plasma concentration (C_{max}) of vandetanib following a single oral dose of vandetanib 300 mg alone or in combination with rifampicin

Parameter	GLSmean[a]		GLSmean ratio[b] (90% CI)[c]
	vandetanib	vandetanib + rifampicin	
AUC_{504} (ng • h/mL)	23 129 (n = 12)	13 895 (n = 12)	0.60 (0.58, 0.63)
C_{max} (ng/mL)	178.2 (n = 12)	183.1 (n = 13)	1.03 (0.95, 1.11)

a The number of subjects varies depending on availability of adequate plasma concentration data.

b Vandetanib in the presence of rifampicin : vandetanib in the absence of rifampicin.

c Coadministration with rifampicin is considered to have no statistically significant effect on the pharmacokinetics of vandetanib if the 90% CI for the ratio of exposure lay between 0.8 and 1.25.

GLS = geometric least squares.

N-desmethylvandetanib was ≈7% of the AUC_{504} of vandetanib.

In the presence of rifampicin, plasma concentrations of N-desmethylvandetanib were higher than those observed following administration of vandetanib alone (table II; figure 3). AUC_{504} and C_{max} of N-desmethylvandetanib increased by 266.0% and 414.3%, respectively, in the presence of rifampicin compared with vandetanib alone; t_{max} was unaltered by rifampicin. Exposure to this metabolite, relative to the parent compound, increased by 506.0% when vandetanib was dosed in combination with rifampicin.

Vandetanib N-Oxide

Following a single oral dose of vandetanib 300 mg to healthy subjects, maximum plasma concentrations of vandetanib N-oxide were attained at a median time of 7 hours post-dose (table II; figure 4). In the majority of subjects, plasma concentrations of vandetanib N-oxide were nonquantifiable by 96–240 hours post-dose. AUC_{∞} and $t_{½}$ were not calculated as the terminal phases were poorly defined. Since it was not possible to calculate AUC_{504}, exposure to metabolite relative to parent compound was assessed by comparing AUC_{last} using a common timepoint for both vandetanib and vandetanib N-oxide (AUC_{ct}). Exposure to vandetanib N-oxide was very low compared with that of vandetanib. The AUC_{ct} of vandetanib N-oxide was ≈2% of the AUC_{ct} of vandetanib.

When vandetanib was coadministered with rifampicin, there was a 179% increase in the C_{max} of vandetanib N-oxide (table II). Plasma concentrations of vandetanib N-oxide then declined with an initial rapid phase, and were nonquantifiable in all subjects by 36 hours post-dose. AUC_{last} for vandetanib N-oxide following coadministration of vandetanib and rifampicin is not directly comparable to the value derived following dosing with vandetanib alone because these parameters were not determined using a common value of t. When AUC_{ct} was compared, a 126% increase was observed following vandetanib and rifampicin compared with vandetanib alone (gmean 44.26 vs 19.56 ng • h/mL). Exposure to vandetanib N-oxide relative to vandetanib was very similar when vandetanib was given in combination with rifampicin compared with vandetanib alone.

Study B (CYP3A4 Inhibition)

Itraconazole and Hydroxy-Itraconazole

Exposure to itraconazole and hydroxy-itraconazole was similar to that seen in other studies using the same dosing regimen.[15] On day 4, gmean (CV%) AUC from time 0 to 24 hours (AUC_{24}) and C_{max} of itraconazole were 5042 ng • h/mL (65.6) and 424.0 ng/mL (55.2), respectively. On day 4, gmean (CV%) AUC_{24} and C_{max} of hydroxy-itraconazole were 7688 ng • h/mL (56.8) and 412.6 ng/mL (40.6), respectively.

Vandetanib

Vandetanib was not detected in any pre-dose plasma samples. After a single dose of vandetanib 300 mg in healthy subjects, absorption was moderately slow with a median t_{max} of 5 hours both in the absence and presence of itraconazole (figure 5). Plasma concentrations of vandetanib declined in a biexponential manner, irrespective of treatment. Following vandetanib alone, plasma concentrations

Table II. Pharmacokinetic parameters of vandetanib, N-desmethylvandetanib, and vandetanib N-oxide following a single oral dose of vandetanib 300 mg alone or in combination with rifampicin[a,b]

Parameter	Vandetanib		N-desmethylvandetanib		Vandetanib N-oxide	
	vandetanib	vandetanib + rifampicin	vandetanib	vandetanib + rifampicin	vandetanib	vandetanib + rifampicin
AUC_{504} (ng • h/mL)	23 010 (23) [n = 12]	14 140 (16) [n = 12]	1681 (22) [n = 14]	6153 (20) [n = 15]	NC	NC
AUC_{last}[c] (ng • h/mL)	NA	NA	NA	NA	193.9 (84.6) [n = 15]	45.6 (66.8) [n = 13]
AUC_{∞} (ng • h/mL)	28 450 (30) [n = 12]	14 900 (18) [n = 12]	2208 (27) [n = 4][d]	6982 (22) [n = 15]	NC	NC
C_{max} (ng/mL)	170.2 (23.3) [n = 12]	186.1 (27.8) [n = 12]	7.4 (34.0) [n = 15]	38.1 (24.5) [n = 16]	2.0 (32.2) [n = 15]	5.6 (35.6) [n = 13]
t_{max} (h)	6 (3–10)[e] [n = 12]	5 (4–8)[e] [n = 13]	5 (3–7)[e] [n = 15]	5 (4–24)[e] [n = 16]	7 (4–12)[e] [n = 15]	5 (2–7)[e] [n = 13]
$t_{½}$ (h)	217.6 (37.1) [n = 12]	116.3 (34.4) [n = 12]	168.2 (28.5) [n = 4][d]	153.7 (21.8) [n = 15]	NC	NC
Ratio[f]	NA	NA	0.071 (25.3) [n = 11]	0.429 (16.4) [n = 12]	0.018 (53.5) [n = 13]	0.020 (33.3) [n = 13]

a Data are given as gmean (CV%), unless stated otherwise.
b The number of subjects varies depending on availability of adequate plasma concentration data.
c The vandetanib N-oxide metabolite data did not allow determination of AUC_{504}, so AUC_{last} was determined instead.
d Not calculable for 12 subjects because the terminal phase was poorly defined or >20% of the AUC was extrapolated.
e Median (range).
f Ratio of exposure (AUC_{504} for N-desmethylvandetanib : AUC_{ct} for vandetanib N-oxide) for metabolite to vandetanib.

AUC = area under plasma concentration-time curve; **AUC_{∞}** = AUC from time zero to infinity; **AUC_{504}** = AUC from time 0 to 504 hours; **AUC_{ct}** = AUC_{last} using a common timepoint for vandetanib and vandetanib N-oxide; **AUC_{last}** = AUC from time zero to t hours, where t is the last timepoint with a measurable result; **C_{max}** = maximum plasma concentration; **CV** = coefficient of variation; **gmean** = geometric mean; **NA** = not applicable; **NC** = not calculable; **$t_{½}$** = elimination half-life; **t_{max}** = time to C_{max}.

were near to or below the level of quantification in 12 of 15 subjects at 792 hours post-dose, while following vandetanib in combination with itraconazole, low plasma concentrations of vandetanib were still detectable in 11 of 12 subjects at this timepoint.

There was a statistically significant increase of 9% in the AUC_{504} (GLSmean ratio 1.09; 90% CI 1.01, 1.18) when a single dose of vandetanib 300 mg was given in combination with itraconazole compared with vandetanib alone (table III). The C_{max} of vandetanib was not significantly influenced by itraconazole (GLSmean ratio 0.96; 90% CI 0.83, 1.11; table III).

There was no change in vandetanib t_{max}, and only a small increase in vandetanib $t_{½}$, when vandetanib was coadministered with itraconazole compared with vandetanib alone (table IV).

Safety and Tolerability

In Study A, 9 of 18 subjects (50.0%) experienced at least one adverse event during the study. Three (20.0%) and five (31.3%) subjects reported adverse events following vandetanib in the absence and presence of rifampicin, respectively. Three subjects (16.7%) reported adverse events while receiving rifampicin alone. Headache was the most frequently reported adverse event (table V). One adverse event (mild abdominal pain) was considered by the investigator to be causally related to vandetanib. One subject had two serious adverse events (severe somnolence and drug toxicity requiring observation in hospital) while receiving rifampicin alone; this subject accidentally took an overdose of bromazepam during a period of stress due to examinations and was withdrawn from the study. A second subject was withdrawn from the study after 19 days due to varicella zoster virus infection (chickenpox).

In Study B, 6 of 16 subjects (37.5%) reported at least one adverse event during the study. Five (31.3%) and one (6.3%) subjects reported adverse events following vandetanib in the absence and presence of itraconazole, respectively. Only one adverse event (abdominal pain) was reported by more than one subject (table V). One adverse event (moderate abdominal pain) was considered

by the investigator to be causally related to vandetanib. There were no reports of serious adverse events or discontinuations due to adverse events.

In Study A, there were no clinically important changes in mean corrected QT (QT_C) interval or evidence of QT_C interval prolongation associated with vandetanib dosing, either alone or in combination with rifampicin. One subject showed an increase from baseline in QT_C interval of >60 ms after receiving vandetanib in combination with rifampicin. In Study B, mean QT_C interval increased after the dose of vandetanib by ≤20 ms at each timepoint. Three subjects had an increase from baseline in QT_C of >60 ms; one of these subjects also had episodes of sinus tachycardia. Two additional subjects had intermittent episodes of marked sinus bradycardia, which were considered to be a normal variation in healthy males. None of these changes was considered to be clinically important.

No clinically significant changes were observed in vital signs, hematology, clinical chemistry, or urinalysis, except for a trend towards small treatment-related increases in systolic and diastolic blood pressure, and mean arterial pressure in Study B.

Discussion

Two phase I, randomized, open-label, two-way crossover studies were carried out to investigate the potential for vandetanib to interact with a potent CYP3A4 inducer (rifampicin) or a potent CYP3A4 inhibitor (itraconazole). These studies were considered necessary because CYP3A4 is known to be involved in the metabolism of vandetanib, and any pharmacokinetic interactions with agents that induce or inhibit CYP3A4 may have clinical implications. In both studies, two single doses of vandetanib 300 mg were given to healthy subjects. Once daily dosing with vandetanib at 300 mg was well tolerated by patients with advanced solid tumors in previous phase I studies.[16,17] Single doses of vandetanib were used in the pharmacokinetic studies reported here because it was not considered possible to conduct multiple dose studies in healthy subjects due to safety and tolerability issues. However, multiple-

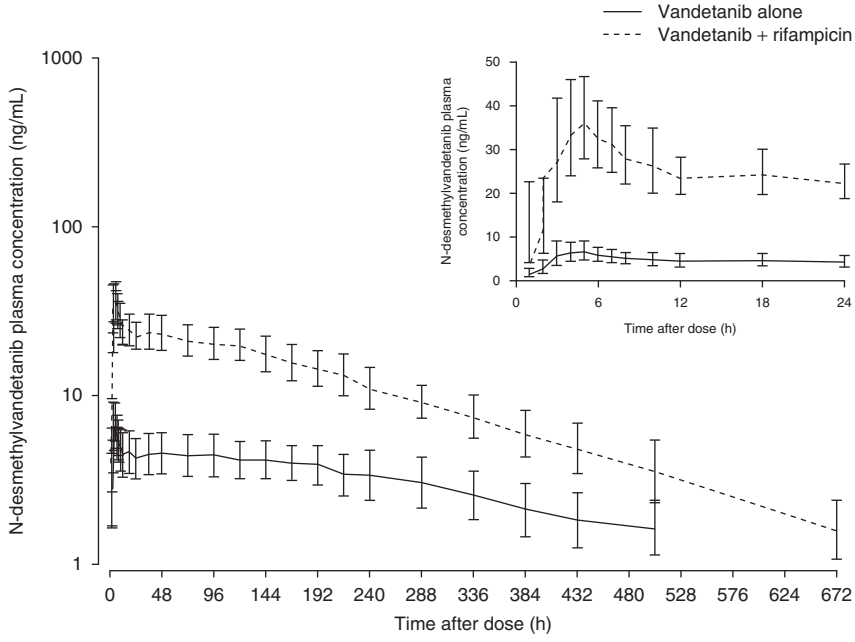

Fig. 3. Geometric mean (± SD) plasma concentrations of N-desmethylvandetanib following a single oral dose of vandetanib 300 mg alone or in combination with rifampicin. Insert shows more detailed plasma concentrations of N-desmethylvandetanib over the first 24 h.

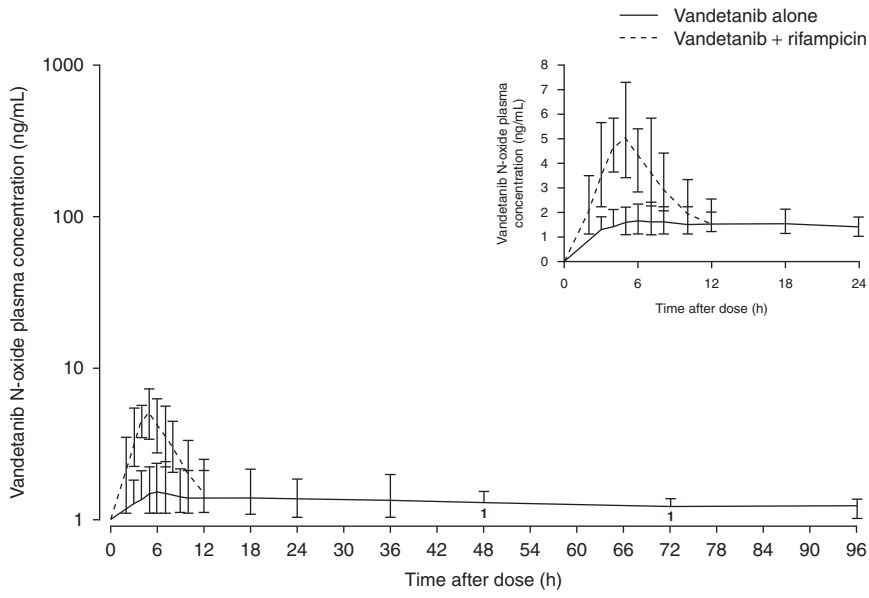

Fig. 4. Geometric mean (± SD) plasma concentrations of vandetanib N-oxide following a single oral dose of vandetanib 300 mg alone or in combination with rifampicin. Insert shows more detailed plasma concentrations of vandetanib N-oxide over the first 24 h. **1** = lower limit SD is not quantifiable <5 ng/mL.

dose pharmacokinetics can be accurately predicted by single-dose pharmacokinetics for vandetanib. AUC_{504} and C_{max} were selected as primary pharmacokinetic parameters for both studies. It was important to measure the AUC over a long time period because vandetanib is known to have a $t_{½}$ of around 10 days but the maximum number of doses of rifampicin and itraconazole that could be given to healthy subjects also had to be considered. Therefore, rifampicin was given for 10 days and itraconazole for 4 days before vandetanib was dosed. This allowed the maximal induction and inhibition effects of the agents to be achieved before vandetanib was administered. After vandetanib administration, rifampicin and itraconazole were continued for a further 20 days (approximately two vandetanib half-lives) so that the induction and inhibition effects were maintained over a sustained period during which the vandetanib pharmacokinetics were characterized. Plasma concentrations of vandetanib were below the level of quantification in all samples that were collected pre-dose, confirming that the washout periods between treatment arms were of sufficient length. Plasma concentrations of the metabolites of vandetanib were not measured in the CYP3A4 inhibition study because our understanding of the metabolism of vandetanib was incomplete when this study was planned. By the time the CYP3A4 induction study was initiated, the two main metabolites of vandetanib, N-desmethylvandetanib and vandetanib N-oxide, had been identified and it was considered important to investigate potential changes in the plasma levels of the metabolites together with the parent compound.

In both studies, vandetanib was absorbed slowly, reaching C_{max} at a median time of 5–6 hours after administration to healthy subjects. Exposure to vandetanib following a single 300 mg dose, assessed by AUC_{504} and C_{max}, was similar across the two studies. Plasma concentrations declined slowly with a biphasic disposition and a $t_{½}$ of about 9 days (216 hours). These results are consistent with those obtained previously in healthy subjects.

In Study A, CYP3A4 was induced by administration of rifampicin 600 mg/day for 10 days before dosing with vandetanib.[18] This regimen

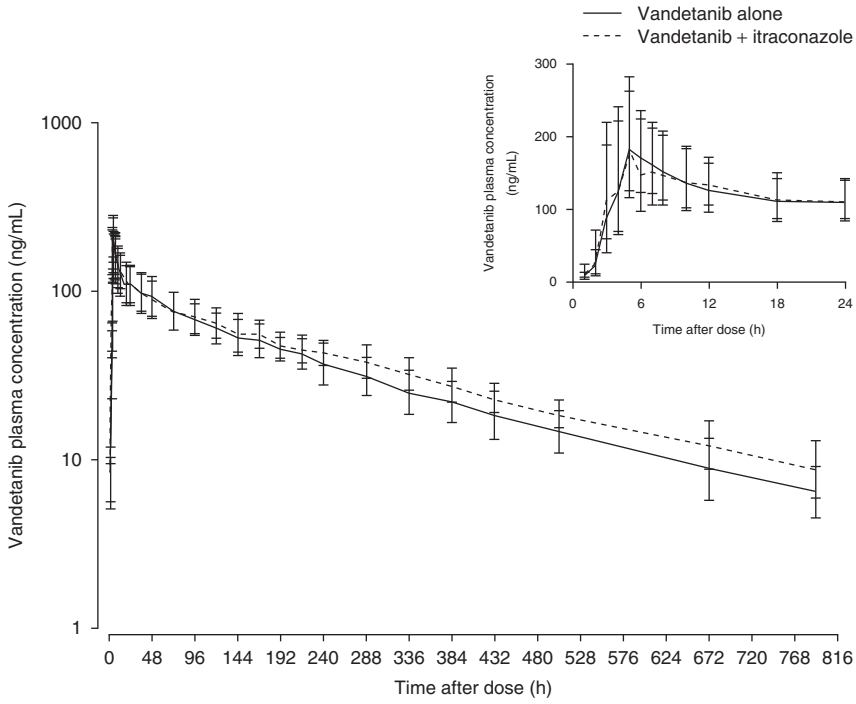

Fig. 5. Geometric mean (± SD) plasma concentrations of vandetanib following a single oral dose alone of vandetanib 300 mg alone or in combination with itraconazole. Insert shows more detailed plasma concentrations of vandetanib over the first 24 h.

has been shown to achieve maximal CYP3A4 induction within about 1 week[19] and has been used in previous drug-drug interaction studies.[20,21] It was noted that one subject had a significantly low plasma concentration of rifampicin on the day that vandetanib was administered compared with rifampicin concentrations measured before and in the days after vandetanib administration. However, this subject had adequate levels of rifampicin on all other occasions when it was measured, and there was no evidence to suggest that he had not taken the study medication. Therefore, data from this subject were included in the pharmacokinetic analysis. In all subjects, rifampicin dosing was continued for a further 21 days after administration of vandetanib to

Table III. Comparison of area under plasma concentration-time curve from time 0 to 504 hours (AUC_{504}) and maximum plasma concentration (C_{max}) of vandetanib following a single oral dose of vandetanib 300 mg alone or in combination with itraconazole

Parameter	GLSmean		GLSmean ratio[a] (90% CI)[b]
	vandetanib	vandetanib + itraconazole	
AUC_{504} (ng • h/mL)	22 702 (n = 15)[c]	24 678 (n = 14)[c,d]	1.09 (1.01, 1.18)
C_{max} (ng/mL)	195.6 (n = 15)[c]	188.2 (n = 15)[d]	0.96 (0.83, 1.11)

a Vandetanib in the presence of itraconazole : vandetanib in the absence of itraconazole.

b Coadministration with itraconazole is considered to have no statistically significant effect on the pharmacokinetics of vandetanib if the 90% CI for the ratio of exposure lay between 0.8 and 1.25.

c One subject was withdrawn during the first treatment period (vandetanib + itraconazole) and AUC_{504} was not calculable. This subject did not receive vandetanib alone.

d One subject did not receive vandetanib + itraconazole.

GLS = geometric least squares.

Table IV. Pharmacokinetic parameters of vandetanib following a single oral dose of vandetanib 300 mg alone or in combination with itraconazole[a]

Parameter	Vandetanib	Vandetanib + itraconazole[b,c]
AUC_{504} (ng • h/mL)	22 770 (20) [n = 15]	24 490 (21) [n = 14]
AUC_{∞} (ng • h/mL)	27 870 (21) [n = 15]	31 690 (23) [n = 14]
C_{max} (ng/mL)	191.3 (33.4) [n = 15]	189.1 (40.7) [n = 15]
t_{max} (h)	5 (3–7)[d] [n = 15]	5 (3–12)[d] [n = 15]
$t_{½}$ (h)	209.2 (25.9) [n = 15]	235.5 (19.4) [n = 14]

a Data are given as gmean (CV%), unless stated otherwise.

b One subject was withdrawn during the first treatment period (vandetanib + itraconazole) and AUC_{504}, AUC_{∞}, and $t_{½}$ were not calculable. This subject did not receive vandetanib alone.

c One subject did not receive vandetanib + itraconazole.

d Median (range).

AUC = area under plasma concentration-time curve; **AUC_{∞}** = AUC from time zero to infinity; **AUC_{504}** = AUC from time 0 to 504 hours; **C_{max}** = maximum plasma concentration; **CV** = coefficient of variation; **gmean** = geometric mean; **$t_{½}$** = elimination half-life; **t_{max}** = time to C_{max}.

ensure that enzyme induction was maintained throughout the pharmacokinetic sampling period. Although the plasma half-life of rifampicin is short (2–5 hours), and it is cleared from the body within about 24 hours of dosing, rifampicin may continue to exert an induction effect for up to 3 weeks after the last dose.[22] A washout period of at least 6 weeks was used in this study to ensure that the effects of rifampicin had been dispersed before crossover to the alternative treatment.

When vandetanib was administered in combination with rifampicin, vandetanib exposure, as assessed by AUC_{504}, was significantly reduced by 40%. The C_{max} of vandetanib was unchanged by rifampicin, and the AUC of vandetanib in the presence and absence of rifampicin showed little

Table V. Adverse events reported following a single oral dose of vandetanib 300 mg alone or in combination with rifampicin or itraconazole, or during the rifampicin or itraconazole dosing period prior to the vandetanib dose[a]

Adverse event	Vandetanib alone [n = 15]	Vandetanib + rifampicin [n = 16]	Rifampicin alone [n = 18]
Study A			
Headache	1 (6.7)	3 (18.8)	2 (11.1)
Abdominal pain	1 (6.7)	2 (12.5)	0
Epistaxis	1 (6.7)	0	0
Rhinitis	1 (6.7)	0	0
Diarrhea	0	1 (6.3)	0
Face injury	0	1 (6.3)	0
Nausea	0	1 (6.3)	0
Neck pain	0	1 (6.3)	0
Varicella	0	1 (6.3)	0
Drug toxicity	0	0	1 (5.6)
Somnolence	0	0	1 (5.6)
Stress	0	0	1 (5.6)
Study B	Vandetanib alone [n = 15]	Vandetanib + itraconazole [n = 15]	Itraconazole alone [n = 15]
Abdominal pain	2 (13.3)	0	0
Nasopharyngitis	1 (6.7)	1 (6.7)	0
Bronchitis	1 (6.7)	0	0
Tooth abscess	1 (6.7)	0	0

a Data are given as n (%).

difference for the first 24–48 hours post-dose. These observations indicate that the bioavailability of vandetanib was unaltered by CYP3A4 induction. Thus, the reduced AUC_{504} appeared to be due to increased metabolic clearance of vandetanib. Consequently, the vandetanib $t_{½}$ was reduced during administration of vandetanib in combination with rifampicin.

The AUC_{504} of N-desmethylvandetanib was increased by 266.0% in the presence of rifampicin, consistent with CYP3A4 induction. AUC_{∞} of N-desmethylvandetanib was not calculated for the majority of subjects as the accuracy of the estimate was limited by the amount of extrapolation that was required. Exposure to the metabolite relative to the parent drug, as assessed using AUC_{504} levels, increased from approximately 7% to 43% during coadministration of vandetanib with rifampicin, indicating that metabolism by this route was increased. Plasma concentrations of vandetanib N-oxide were very low, and comparison of exposure to this metabolite compared with that of the parent drug by measurement of AUC was not possible. Based on C_{max}, it appeared that exposure to vandetanib N-oxide was increased by around 179% following vandetanib dosing in combination with rifampicin compared with vandetanib alone. However, it should be noted that the change in absolute plasma levels of vandetanib N-oxide was small, and did not result in an obvious change in exposure relative to the parent drug (1.8% vs 2.0%). Overall, the results of this study are consistent with *in vitro* data, which indicate that vandetanib is a CYP3A4 substrate.[11] It is anticipated that coadministration of vandetanib with a potent CYP3A4 inducer could result in reduced steady-state exposure to vandetanib. Although reduced exposure to vandetanib has the potential to reduce its efficacy, a clear relationship between exposure and clinical effect has not been defined for vandetanib. Since N-desmethylvandetanib is of similar potency to vandetanib, increased exposure to the metabolite may compensate to some extent for reduced exposure to the parent compound.

In Study B, CYP3A4 was inhibited by administration of itraconazole 200 mg/day for 4 days before dosing with vandetanib. This itraconazole regimen is commonly used in drug-drug interaction studies.[15,23,24] Based on the $t_{½}$ of itraconazole (≈36 hours at steady state), it has been predicted that its CYP3A4 inhibitory effect continues for about 2 weeks after the last dose.[25] Thus, the extended washout period used in this study (3 months) was considered adequate to dissipate the action of itraconazole. Coadministration with itraconazole resulted in a small, statistically significant increase (9%) in exposure to vandetanib as assessed by AUC_{504}, probably due to reduced metabolic clearance consistent with CYP3A4 inhibition. There was no evidence of an effect on C_{max} or t_{max}. The vandetanib $t_{½}$ increased slightly when vandetanib was administered in combination with itraconazole. These minor pharmacokinetic changes are not considered to be clinically relevant. The results of this study indicate that coadministration of vandetanib with a potent CYP3A4 inhibitor is unlikely to have a clinically relevant effect on steady-state exposure to vandetanib and would not require contraindication or dosage adjustment.

In these studies, single doses of vandetanib 300 mg were well tolerated by healthy subjects, both alone and in combination with rifampicin or itraconazole. The tolerability profile of vandetanib was consistent with that observed in previous single-dose studies in healthy subjects.

Conclusions

Exposure to vandetanib, as assessed by AUC_{504} in healthy subjects, was reduced by 40% when a single dose was given in combination with the potent CYP3A4 inducer rifampicin. Because of this, it may be appropriate to avoid coadministration of potent CYP3A4 inducers with vandetanib. Vandetanib exposure was increased by about 9% when it was taken in combination with the CYP3A4 inhibitor itraconazole. It is unlikely that coadministration of vandetanib and potent CYP3A4 inhibitors will need to be contraindicated.

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