CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022405Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-405
Submission Date:	7 July 2010
Brand Name:	(b) (4)
Generic Name:	Vandetanib
Formulation:	100 and 300 mg tablets
IND:	60,042
OCP Reviewer:	Young Jin Moon, Ph.D.
Pharmacometrics Reviewer:	Pengfei Song, Ph.D.
QT Reviewer:	Anshu, Marathe, Ph.D.
OCP Acting Team Leader& Division Deputy Director:	Brian Booth, Ph.D.
Pharmacometrics Team Leader:	Christine Garnett, Pharm.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Sponsor:	AstraZeneca
Submission Type; Code:	Original NDA; 000
Dosing regimen:	300 mg once daily
Indication:	The treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer

OCP Briefing held on November 5, 2010.

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1 EXECUTIVE SUMMARY

To support the efficacy in patients with unresectable, locally advanced or metastatic medullary thyroid cancer (MTC), the applicant conducted one randomized, controlled phase 3 study. In this study patients were randomized to receive placebo or 300 mg of vandetanib daily. Progression free survival (PFS) was the primary endpoint and the median PFS for the vandetanib treatment arm was 30.5 months compared to 19.3 months for placebo.

No clear exposure-response relationship could be identified for the primary endpoint, PFS, for patients in the pivotal trial (D4200C00058). Dose reduction to 200 mg or 100 mg before or on Day 84 showed comparable PFS with dose of 300 mg, suggesting that lower doses might be effective.

Vandetanib caused substantial and sustained QTc prolongation, Torsades de Pointes, and sudden death. Even intensive ECG monitoring does not mitigate the risk of serious ventricular arrhythmia and sudden death. Given the long $t_{1/2}$ of the drug (19 days), withdrawal, dose interruption or dose-reduction due to QT prolongation still places the patient at increased risk for a prolonged period of time until the drug clears. The Interdisciplinary Review Team (IRT) deferred the risk-benefit considerations pertaining to drug approval to the review division.

Vandetanib is a CYP3A4 substrate. In healthy male subjects, the exposure to vandetanib was reduced by 48% when given together with rifampicin. The concomitant use of known strong CYP3A4 inducers should be avoided while receiving (b) (4) therapy.

A dedicated renal impairment study showed that the mean AUC of vandetanib increased by 40% in patients with moderate and severe renal impairment compared to those with normal renal function. A dose reduction to 200 mg for patients with moderate and severe renal impairment is recommended. Single dose pharmacokinetic data from healthy volunteers with hepatic impairment showed that there were no differences in pharmacokinetics compared to patients with normal hepatic function. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 times the upper limit of normal). (b) (4) is not recommended for use in patients with moderate and severe hepatic impairment, as safety and efficacy have not been established.

1.1 RECOMMENDATIONS

This application is acceptable from a clinical pharmacology perspective, provided that the applicant and the Agency come to a mutually satisfactory agreement regarding post marketing requirement and the language in the package insert.

Post Marketing Requirement

Conduct a trial to explore alternative vandetanib doses and/or dosage regimens that will reduce the toxicity profile but maintain the efficacy of the 300 mg dose. The exposure-response relationship for safety and efficacy endpoints should be used to simulate potential study designs, doses and outcomes of the new trial.

Protocol submission: (b) (4)

Study commencement: (b) (4)

Submission of study report: (b) (4)

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

Signatures

Young Jin Moon Reviewer Division of Clinical Pharmacology 5	Brian Booth, Ph.D. Deputy Director, Acting Team Leader Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **L Skarupa;** MTL - **V Maher**; **A Ibrahim** MO - **G Kim; K DeLorenzo**

DCP-5: Reviewer - **Y Moon, P Song, A Marathe;** TL**- C Garnett;** Deputy DD&ATL - **B Booth;** DD - **A Rahman**

1.2 CLINICAL PHARMACOLOGY SUMMARY

Vandetanib is a receptor tyrosine kinase inhibitor that inhibits VEGFR-2, RET receptor tyrosine kinase, VEGF receptor-3, and epidermal growth factor receptor (EGF) tyrosine kinases.

In the pivotal study, the primary endpoint was progression free survival. No clear exposure-response relationship for efficacy based on PFS was identified, although (b) (4) beat placebo. Significant exposure-response relationships were identified for diarrhea and fatigue, but not for hypertension or rash.

Substantial and sustained QTc prolongation was observed. The QTc prolongation is concentration-dependant. Based on the exposure-response relationship, the expected mean (90% CI) ΔQTcF at a dose of 300 mg was 35 (33-36) ms.

The applicant has conducted several phase 1 studies in healthy volunteers and patients with malignant tumors to evaluate the safety and pharmacokinetics of vandetanib. The T_{max} of vandetanib occurs 6 hours (range 4-10 hours) after the dose. The PK of vandetanib is linear over the range of 100 – 600 mg once daily dosing. A high-fat meal did not change the vandetanib exposure.

In the pivotal study, the clearance was 13 L/h, volume of distribution was 7450 L, and half-life was 19 days. There was high inter-individual variability. Vandetanib is 94% bound to human serum albumin and α1-acid-glycoprotein. Two metabolites – N-desmethyl vandetanib (active) and N-oxide vandetanib (inactive) - were identified in plasma, urine and feces. N-desmethyl vandetanib, which is produced by CYP3A4, is present at concentrations between 7 and 17% of vandetanib. N-desmethyl and N-oxide vandetanib have the potential to prolong QTc based on the human ether-a-go-go gene (hERG) assay with IC_{50} values that were 3- and 10-fold greater, respectively than that for vandetanib.

There was no clinically significant effect on exposure to vandetanib in the presence of the potent CYP3A4 inhibitor itraconazole in healthy volunteers. However, the potent CYP3A4 inducer rifampicin reduced exposure to vandetanib by 48% but increased exposure to the active N-desmethyl metabolite. Therefore, the effect of CYP3A4 inducers on the QTc effect is unclear. Patients receiving vandetanib should avoid the use of potent inducers of CYP3A4. After administration of radio-labeled vandetanib in healthy male subjects, both urine (25%) and fecal (44%) excretion are the major routes of elimination of vandetanib. Data from a single dose pharmacokinetic study in healthy volunteers with renal impairment resulted in a 40% increase in the mean AUC of vandetanib in patients with moderate and severe renal impairment. Also, higher proportions of patients with ΔQTc > 60 ms, or QTc > 480 ms or QTc > 500 ms were observed in patients with mild to moderate renal impairment as compared to patients with normal renal function in the pivotal study. A dose reduction to 200 mg for patients with moderate and severe renal impairment is recommended.

Single dose pharmacokinetic data from healthy volunteers with hepatic impairment suggests that there were no differences in pharmacokinetics compared to subjects with normal hepatic function. There is limited data in patients with hepatic impairment (serum bilirubin greater than 1.5 times the upper limit of normal). (b) (4) is not recommended for use in patients with hepatic impairment, as safety and efficacy have not been established.

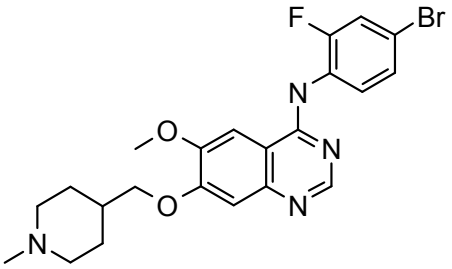
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Physico-chemical properties

1. Structural formula:



2. Established name: Vandetanib
3. Molecular Weight: 475.4 g/mol
4. Molecular Formula: $C_{22}H_{24}BrFN_4O$
5. Chemical Name: *N*-(4-bromo-2-fluorophenyl)-6-methoxy-7- [(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine
6. pKa: 5.2 for the aminoquinazoline moiety and 9.4 for the piperidine moiety
7. Partition coefficient (Log P): 4.7 at pH 11

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Vandetanib is a tyrosine kinase inhibitor with activity against the RET proto-oncogene, VEGFR-2, and EGFR. (b) (4) is indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.

2.1.3 What are the proposed dosage and route of administration?

The proposed dose of vandetanib is 300 mg orally taken, once daily. It may be taken with or without food.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Two Phase 1 studies conducted in 77 patients in the US and Australia (50 - 600 mg QD) and in 18 patients in Japan (100 - 400 mg QD), demonstrated a maximum tolerated vandetanib dose of 300 mg. Higher doses were limited by diarrhea, rash, and QT prolongation. The dose of vandetanib in the pivotal trial was 300 mg based on the results of Study 08. Study 08 was an open-label, single arm, monotherapy, phase 2 study, which showed efficacy and tolerability of

vandetanib 300 mg in patients with MTC. Most of the side effects at 300 mg were not life-threatening, although several patients required dose reduction, particularly for diarrhea.

Pivotal Study

The primary clinical efficacy and safety data for vandetanib 300 mg in support of the proposed indication are provided by Study 58: An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of vandetanib ([redacted] (b) (4)™) versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer. The primary endpoint was progression-free survival (PFS).

Patients were randomized in a 2:1 ratio to receive [redacted] (b) (4) 300 mg or placebo. Patients could receive up to 6 cycles of chemotherapy. The efficacy results are shown in Table 1.

Table 1 . Efficacy Results for vandetanib: Study 58

	N	Median PFS	HR[a]	95% CI	p-value
[redacted] (b) (4) 300 mg	73/231 (32%)	Not reached (predicted 30.5 months)	0.46	0.31, 0.69	0.0001
Placebo	51/100 (51%)	19.3 months			

(N: Number of events/number of randomized patients)

A phase 2 trial (Study 68) was conducted in parallel with the phase 3 trial to assess whether there is any efficacy of a lower 100 mg dose of vandetanib in patients with MTC. Study 68 had a similar design to another phase 2 trial, Study 08. However it had no control group and only patients with the hereditary form of MTC were enrolled. No formal comparison of data from these two phase 2 trials was conducted, but a side-by-side of major efficacy variables are shown in Table 2.

Table 2. Summary of results for common efficacy outcome variables in Study 08, Study 68, and Study 58

Variable		Study 08	Study 68	Study 58	
		Vandetanib 300 mg (N=30)	**Vandetanib 100 mg (N=19)**	**Vandetanib 300 mg (N=231)**	**Placebo (N=100)**
PFS	Median, months	27.9	16.2	30.5	19.3
ORR	Number of responses	6 (20.0%)	3 (15.8%)	104 (45.0%)	13 (13.0%)

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Clinical Endpoints

The clinical efficacy of vandetanib in combination with chemotherapy in patients with MTC has been demonstrated in the one phase 3 study (Study 58) and supported by two phase 2 studies. The design and endpoints from these studies are listed below in Table 3.

Table 3 . Efficacy endpoints of the dose finding and efficacy trials for MTC

Study	Number randomized/treated and type of subjects	Doses	Primary Endpoints
Study 8, Phase 2	0/30 Patients with locally advanced or metastatic hereditary MTC	vandetanib: 300 mg (once daily doses)	Objective response
Study 68, Phase 2	0/19 Patients with locally advanced or metastatic hereditary MTC	vandetanib: 100 mg (once daily doses)	Objective response
Study 58, Phase 3	331/231 Patients with MTC	vandetanib: 300 mg (once daily oral)	PFS

The pivotal efficacy trial used PFS as the primary endpoint. PFS was defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression), provided death was within 3 months from the last evaluable RECIST assessment.

Biomarkers

The most significant molecular event leading to both sporadic (spontaneous mutation) and hereditary MTC is the occurrence of RET activating mutation, and therefore inhibiting aberrant RET signaling is likely to have a significant impact on the disease. One of the secondary endpoints of the pivotal study was to determine the mutational status of the RET proto-oncogene in deoxyribonucleic acid (DNA) extracted from tumor samples. Also, it has been observed that EGFR and VEGFR (vascular endothelial growth factor receptor) are overexpressed in advanced MTC and activation of EGFR and VEGFR2 may be related to metastasis; therefore, inhibition of these receptors may impact the disease. One of the exploratory objectives was to investigate changes in tumor biomarkers of inhibition of RET, VEGFR, and EGFR signaling pathways.

In the pivotal study, all patients with sporadic (not inherited) MTC had to submit a tumor sample before randomization to establish the mutational status of the RET gene and to relate this to clinical outcome data. The optional procedure underwent both the pre and post dose vandetanib biopsies to characterize the effects of vandetanib on RET, EGFR, and VEGFR signaling pathways in tumors. RET mutation status was determined by AstraZeneca's Tissue Bank Reception (Alderley Park, Macclesfield, Cheshire UK) by (b) (4) and by evaluating for the M918T mutation using an amplification refractory mutation system (ARMS) analysis. (b) (4)

(b) (4)

Reductions in tumor biomarkers, such as calcitonin (CTN) or carcinoembryonic antigen (CEA) were assessed as secondary endpoints of the pivotal study. CTN is secreted by parafollicular cells ("C cells") of the thyroid gland, and exerts its biological effect by acting on 3 target organs: bone, kidney, and gastrointestinal (GI) tract. The exact effect of CTN on the GI tract is unknown, although abnormally high levels of serum CTN are associated with symptomatic diarrhea, which is a characteristic of advanced MTC. Intractable diarrhea usually occurs in patients with plasma CTN levels >30,000 pg/mL. Measurement of plasma CTN levels in the post-thyroidectomy period is useful in detecting residual or recurrent MTC. As with CTN, CEA increases progressively and in direct association with the tumor mass or the biosynthetic activity, making it a valuable, although non-specific, tumor marker. Small studies have shown that patients with elevated CTN levels and abnormal serum CEA are more likely to have disease progression and metastasis than patients with normal CEA. These data suggest that serial measurements of serum CEA levels may provide additional useful prognostic information.

One of the most important safety biomarkers for cardiac adverse events such as Torsades de Pointes and sudden death is QT prolongation. Especially, MTC patients has high risk of proarrythmic event because this patient population has a higher risk of electrolyte abnormalities (hypocalcemia and diarrhea) and also have longer than usual survival times for oncologic patients. A comprehensive population PK/QTc analyses are included throughout the clinical trials including the pivotal study. QTc prolongation was detected with electrocardiogram (ECG) monitoring.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the major circulating metabolites, N-desmethyl vandetanib and vandetanib-N-oxide, were measured in healthy volunteers (Study 16, 22, and 26; Table 9) and NSCLC patients (Study 57), but not in MTC patients. N-desmethyl vandetanib had a similar potency for inhibition of VEGF-induced proliferation, EGF- and basic Fibroblast Growth Factor compared with vandetanib itself (Table 4). The IC_{50} values of metabolites for RET is not reported. Vandetanib-N-oxide had relatively weak activity in cells (IC_{50} > 3.0 μM). Both metabolites were shown to prolong QTc using the human ether-a-go-go gene (hERG) assay. However, the IC_{50} values were 3- and 10-fold greater, respectively, than that for vandetanib, which indicates they are less likely to cause QT prolongation compared to the parent.

Table 4. The IC_{50} values of parent (ZD6474), N-desmethyl metabolite, and N-oxide metabolite (from Dr. Brenda Gehrke's pharmacology/toxicology review).

Compound	Mean IC_{50} μM (± S.E.)			
	VEGF-stimulated	EGF-stimulated	bFGF-stimulated	N
ZD6474	0.06 ± 0.02	0.17 ± 0.03	0.8 ± 0.07	5-6
N-desmethyl metabolite	0.02 ± 0.01	0.12 ± 0.03	0.95 ± 0.32	5
N-oxide metabolite	3.1 ± 1.9	8.8 ± 1.2	>10	6

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

PFS was the primary efficacy endpoint of the study 58 following 300 mg once daily oral dose of vandetanib. The observed steady-state plasma vandetanib concentrations at Day 56 after the first dose ($C_{ss,\ Day\ 56}$) from 98% patients (N=226) in vandetanib arm (N = 231) were used as an exposure variable to identify a relationship with PFS. The lack of a clear separation of the Kaplan-Meier curves indicates that there is no clear association between $C_{ss,\ Day\ 56}$ and PFS (Figure 1). Nevertheless, each quartile of $C_{ss,\ Day\ 56}$ demonstrated an improved PFS compared to the placebo arm. For unknown reasons, the quartile 4 (Q4) of $C_{ss,\ Day\ 56}$ demonstrated the worst PFS among the four quartiles.

Patients who had their doses reduced to 200 mg or 100 mg by Day 84 showed comparable PFS to patients who were consistently dosed with 300 mg of vandetanib, suggesting that lower doses may also provide effective therapy.

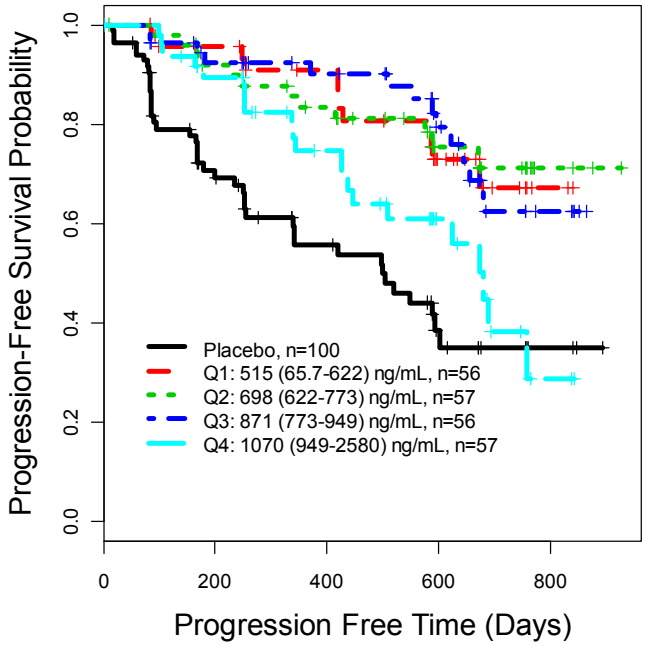


Figure 1. Kaplan-Meier curve of progression free survival for the vandetanib arm (N=226) by quartiles of $C_{ss,\ Day\ 56}$ and for the placebo arm (N=100) of the study 58. Quartile of $C_{ss,\ Day\ 56}$ was expressed as median (range) in the legend. All patients (N = 100) in the placebo arm are included in the Kaplan-Meier curve, regardless follow-up to Day 56 or not.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Significant exposure-response relationships were identified for diarrhea and fatigue, but not for hypertension or rash.

The probability of diarrhea grade 2 or higher is significantly associated with $C_{ss, Day 56}$ ($p = 0.025$) (Figure 2, left). Similarly, the probability of fatigue grade 2 or higher is significantly associated with $C_{ss, Day 56}$ ($p = 0.02$) (Figure 2, right), whereas no significant exposure-response relationships were identified for either hypertension or rash. The shallow slopes of the logistic regression models for diarrhea and fatigue project a minimal decrease in AE incidence for dose reductions at the population level, which is consistent with the relatively low incidence of these AEs in the pivotal trial.

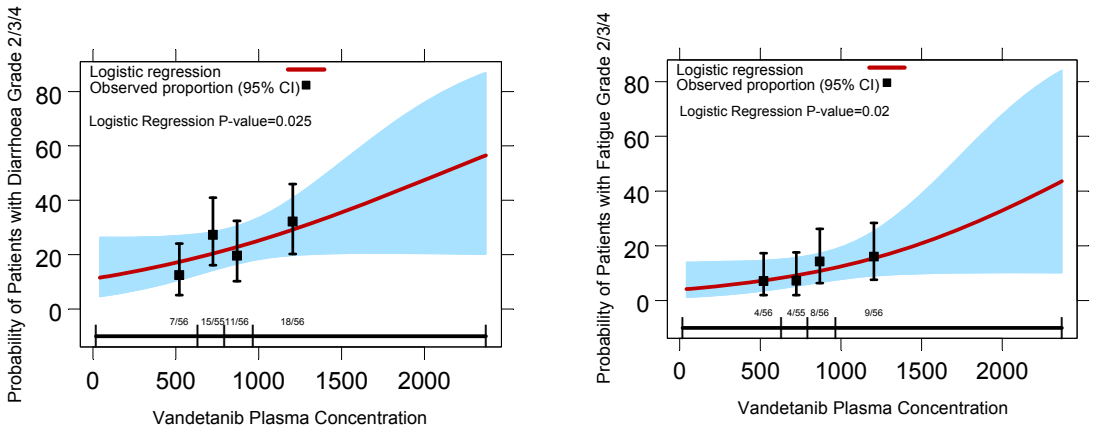


Figure 2. The relationship between $C_{ss, Day 56}$ and the incidence of grade 2 or higher diarrhea (left) and fatigue (right). Solid black symbols represent the observed proportion of patients experiencing ≥ grade 2 AEs in each quartile of $C_{ss, Day56}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of ≥ grade 2 adverse events. The exposure range in each quartile of $C_{ss, Day 56}$ is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Yes, substantial and sustained QTc prolongation was observed. The following results are from IRT review.

At the dose of 300 mg, vandetanib is associated with substantial and concentration-dependant QTc interval prolongation. As observed in 231 MTC patients receiving vandetanib from the pivotal trial, the mean QTc intervals were constantly higher than 30 ms at multiple visits beyond Week 4, with the upper bounds of two-sided 90% confidence intervals (CI) greater than 33 ms (Figure 3, left). The QTc prolongation is concentration-dependant. Based on log-linear relationship between concentration and ΔQTcF, the expected mean (90% CI) ΔQTcF at a dose of 300 mg was 35 (33-36) ms (Figure 3, right). In addition, about 36% of the patients in the vandetanib arm experienced greater than 60 ms increase in QTc interval.

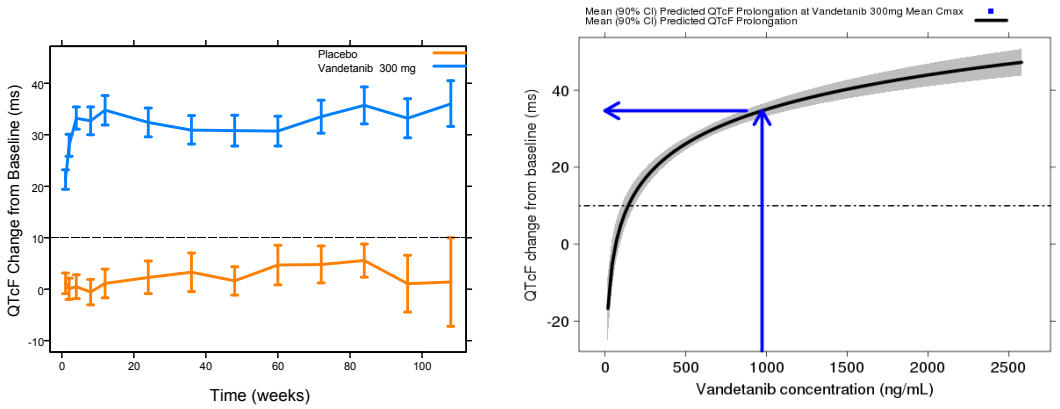


Figure 3. QTc prolongation observed in Study 58 using 300-mg dose; N=231.

Similar mean effect in QTcF prolongation from baseline is also predicted using a mechanistic Emax model (Figure 4). At the 300 mg dose, ΔQTcF is predicted to be 35 ms. The mean of the highest concentration observed among the subjects in the trial (973 ng/ml) was used for the prediction. ΔQTcF is predicted to be 30 and 21 ms for 200 and 100 m daily dosing (Table 5).

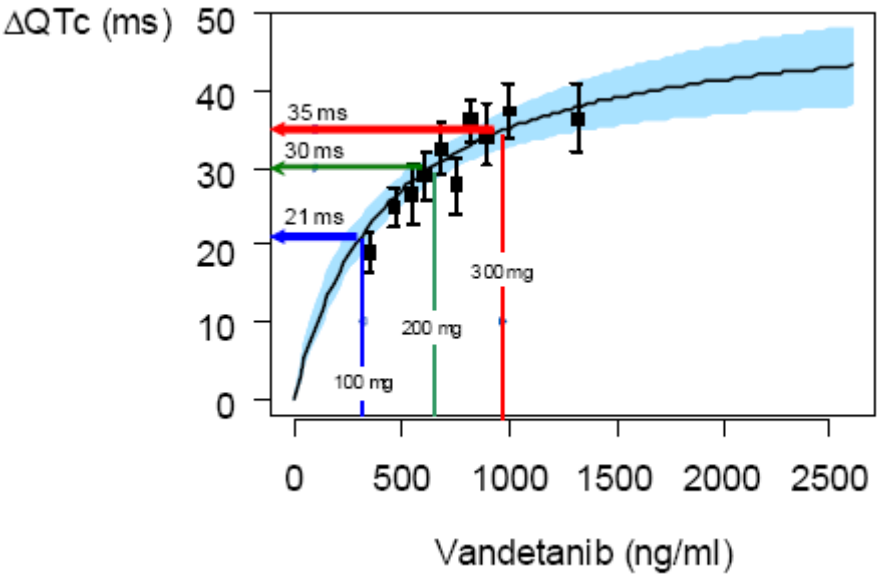


Figure 4. QTc prolongation observed (symbols) in Study 58 using 300-mg dose; N=231. The solid line represents the mean prediction using an Emax model.

Table 5. QTc prolongation predicted for various dose levels.

Dose (mg)	Concentration (ng/ml)	ΔQTcF (ms)
300	973	35
200	649	30
100	324	21

QTc prolongation is sustained over time. Following a single dose (700 mg) of vandetanib, QTc prolongation (with upper 90% CI greater than 10 ms and the mean at around 10 ms) was sustained over 28 days post-dose (the last observation time point) in Study 21 in 28 healthy subjects. The vandetanib exposure was 42.5% lower than the steady state exposure of vandetanib at 300-mg dose (Figure 5). The sustained, higher QTc prolongation is likely to be associated with the long half-life of vandetanib (19 days). As shown in Study 58, no meaningful reductions in the mean changes in QTc intervals (together with the 90% CIs) were observed following long-term treatment with vandetanib up to 108 weeks (around 2 years) (Figure 3, Left). This contradicts the applicant's assertions that the QTc effect is more tolerable with time.

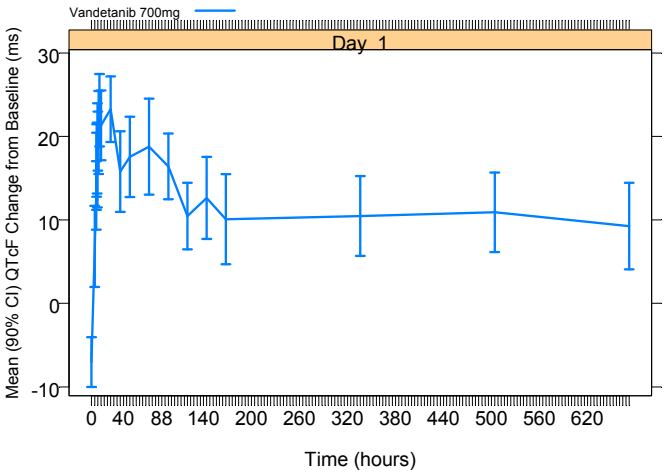


Figure 5: Δ QTcF versus Time in Study 21

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

No. The 300 mg daily dose may not be optimal based on the long-half life of the drug.

The sponsor's rationale for the 300 mg dose was based on:

(1) preclinical data, which demonstrated that the greatest benefit (in terms of maximizing inhibition against key targets) is seen when vandetanib is used at the maximum tolerated dose (MTD),
(2) the MTD of 300 mg was concluded from data in the phase 1 ascending-dose in US/Australia and Japanese patients
(3) in phase 2 study of 300 mg vandetanib in hereditary MTC patients, 20% of the patients demonstrated a confirmed partial objective response.

In isolated enzyme assays, vandetanib inhibits VEGFR-2 tyrosine kinase activity (IC_{50} = 40 nM), and shows inhibitory activity against RET receptor tyrosine kinase (IC_{50} = 100 nM), VEGF receptor-3 (IC_{50} = 110 nM), and epidermal growth factor receptor (EGFR) (IC_{50} = 500 nM) tyrosine kinases. The $C_{max,ss}$ in MTC patients following 300 mg daily dose was 857 ng/mL (385 -

2241 ng/mL). Since free drug in plasma is 6% of the total drug (see 2.2.5.4), the free drug concentration is about 51 ng/mL (≡ ~100 nM), which is higher than IC_{50} for VEGFR2 inhibition, similar to IC_{50} for RET receptor and VEGFR-3 inhibition, and lower than IC_{50} for EGFR inhibition.

The sponsor selected 300 mg daily dose to maximize the efficacy. However, at the expense of efficacy, patients in vandetanib arm experienced serious adverse events.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

Single dose

The single dose PK data of vandetanib in malignant tumor patients were found in Study 1, 4, 43, and 50. Study 1, 4, and 43 were phase 1, dose escalation study conducted in U.S. and Australia (Study 1, 50 - 600 mg QD), in Japan (Study 43, 100 - 400 mg QD), and in China (Study 4, 100 mg QOD - 300 mg QD). The drug was given orally as a single dose and when given daily until tumor progression. Study 50 is a phase 1, randomized study to assess the effect of vandetanib on vascular permeability in patients with advanced colorectal cancer and liver metastases. Table 6 shows the single dose PK parameters following 300-mg dose of vandetanib.

Table 6. Single dose PK parameters following 300-mg dose of vandetanib in different studies.

	Study 1	Study 43	Study 4	Study 50
Study	Dose rising	Dose rising	Dose rising	PK/PD for permeability
Subjects	Malignant tumors	Malignant tumors	Malignant tumors	Colorectal cancer and liver metastases
Race	Caucasian 85.7% Black 6.5% Asian 2.6% Other 5.2%	Japanese	Chinese	Caucasian
Formulation	Phase I formulation	Phase I formulation	Commercial (100 mg X 3)	Commercial (300 mg x 1)
Sampling	dense	dense	dense	dense
Food intake	fast from midnight	feed (before breakfast)	no restriction	not shown
N	6-8	5-6	12	12
T_{max} (Median, (range)), h	7.5 (4-24)	5 (4-6)	8 (2-10)	4 (4 - 24)
C_{max} (Gmean) ng/mL (CV%)	213 (40.4)	392 (50.5)	330 (70.0)	269 (53.7)
$T_{1/2}$	109 ± 29.8 h	90.2 ± 13.7 h	—	—
AUC, ng·h/mL (CV%)	13929[a] (98.84)	29400[b] (40.1)	—	—
AUC_{0-24h}, ng·h/mL (CV%)	3019 (43.6)	5580 (44.4)	5643 (58.8)	4913 (55.5)

a: 50% of AUC was extrapolated; b: 40% of AUC was extrapolated;
—: values are not reported

In Study 1, following a single dose of vandetanib, absorption was slow, with median t_{max} times across the doses ranging from 4 to 7.5 hours (Figure 6); individual patients had a prolonged absorption phase with a C_{max} occurring as late as 24 hours after dosing. Following the peak,

plasma concentrations declined very slowly, such that by Day 7 post dose, levels had only fallen between one-third and one-half of the C_{max}. Because up to 50% of the total AUC was extrapolated beyond Day 7, the exact terminal half-life is unknown.

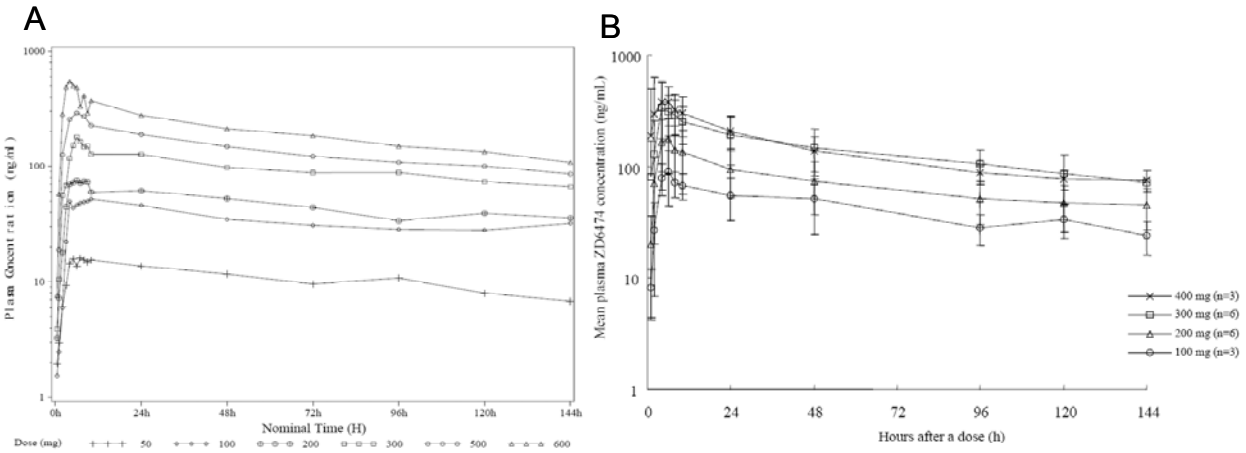


Figure 6. Mean plasma concentrations of vandetanib after a single oral dose in malignant tumor patients (A-from Study 1, 85.7% was Caucasian; B- from Study 43, 100% was Japanese).

Following single, oral doses of vandetanib ranging between 300 mg to 1200 mg in healthy volunteers, less than 5% of the dose was excreted in the urine as unchanged vandetanib over the first 72 hours post-dose. The geometric mean CL_R ranged from 0.89 L/h to 1.60 L/h (Study 12).

Multiple doses

Table 7 shows the multiple dose PK parameters in patients following 300-mg dose of vandetanib. The accumulation index showed a median value of about 5-fold (range 3- to 10-fold) for 300 mg once-daily dosing on Day 29. Mean plasma concentrations of vandetanib after 28 day multiple doses are shown in Figure 7.

Table 7. Multiple dose PK parameters in patients following 300-mg dose of vandetanib in different studies

	Study 1	Study 43	Study 4	Study 50
Race	Caucasian 85.7% Black 6.5% Asian 2.6% Other 5.2%	Japanese	Chinese	Caucasian
N	9-10 (Day 29)	3 (Day 29)	7 (Day 43)	7 (Day 56)
T_{max} (Median, range), h	5 (0-24)	6	4 (0-24)	4 (4 - 24)
C_{max} (Gmean), ng/mL (CV%)	919.8 (60.70)	1580 (19.1)	2024 (39.1)	853 (38.5)
$T_{1/2}$, day	—	—	7.6 ± 1.76[a]	—
$AUC_{0\text{-}24h}$, ng·h/mL (CV%)	17926 (58.35)	29900 (15.4)	38611 (38.4)	18260 (41.4)
Accumulation	5 (3-10)	5.3 (4.1-6.5)	8.1	4.5 (3.2-8.4)

[a]data from population PK analysis; —: values are not reported

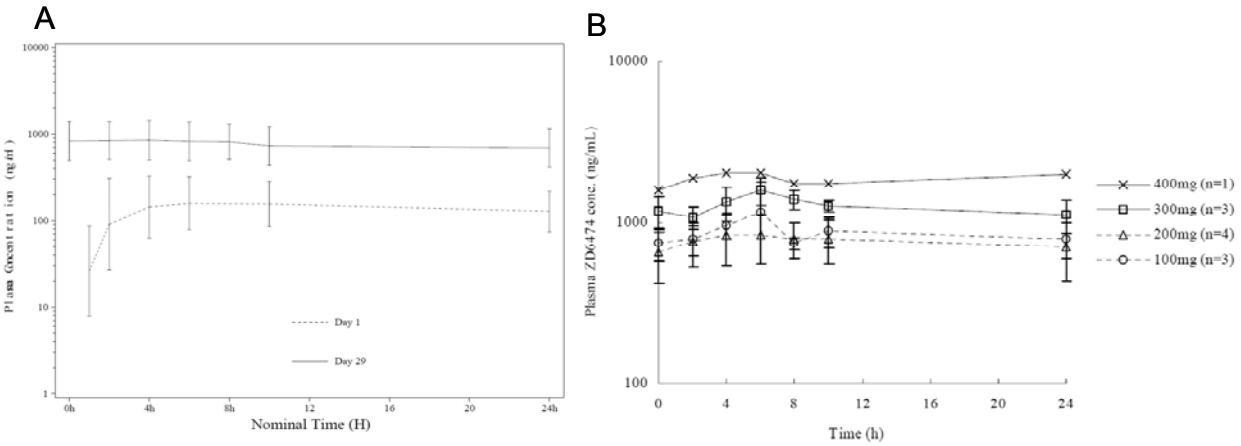


Figure 7. Mean plasma concentrations of vandetanib after 28-day multiple oral doses of 300 mg/day (A-from Study 1) and 100 to 400 mg/day (B- from Study 43).

Marked accumulation seen on once daily dosing was consistent with a long half-life. The exposure after 28-day multiple doses increased about 5 times more than after a single dose in the 300 mg/day group.

In the pivotal study, a total 191 MTC patients were dosed to steady state (Day 56) with 300 mg daily. PK parameters were obtained using population PK modeling. Mean C_{max} at steady state was 857 ng/mL (385 - 2241 ng/mL). $C_{min,ss}$ on Day 56 was 795 ng/mL and AUC_{ss} was 19829 ng·h/mL.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK parameters of vandetanib following a 300-mg single dose in the healthy volunteers could be found in studies shown in Table 8.

Table 8. Single dose PK parameters of 300-mg vandetanib in healthy volunteers

	Study 12	Study 15	Study 24	Study 26	Study 30
Study	Dose rising	DDI with itraconazole	Food effect (fast/fed)	DDI with rifampicin	Relative BA
Subject	HV	HV	HV	HV	HV
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Formulation	Phase I formulation	commercial	commercial	commercial	commercial
Sampling	dense	dense	dense	dense	dense
Food intake	fast from midnight	fast from 8 hours before	fast from midnight/ 30 min after meal	not shown	fast from midnight
N	6	14	15	12-13	10
T_{max} (Median, range), h	6 (4-8)	5 (4-7)	6 (5-18)/8 (3-18)	6 (3-10)	8 (6 -18)
C_{max} (Gmean), ng/mL (CV%)	130 (27.9)	194 (33.5)	131 (29.4)/117(30.9)	170 (23.3)	184 (29.4)
$T_{1/2}$ (h) (CV%)	204 (14.0)	208 (31.0)	204 (20.1) /215 (20.0)	218 (37.1)	228 (18.4)
AUC, ng·h/mL (CV%)	22030 (8.42)	28314 (19.8)	20880 (18.6)/20860 (19.9)	28450 (30.2)	34530 (23.0)
AUC_{0-t}, ng·h/mL (CV%)	2170 (24h[a]) (22.0)	22449 (504h[a]) (19.9)	5437 (21.4)/ 5313 (22.8) (72h[a])	23010 (504h[a]) (22.5)	31560 (864h[a]) (22.5)

[a]:last sampling time point

Mean C_{max} values from healthy volunteers in different studies (Table 8) appear consistently lower than the values in cancer patients (Table 6). Mean AUC_{0-24} in healthy volunteers (2170 ng·h/mL) was also lower than AUC_{0-24} in patients. Multiple dose data were not obtained from the healthy volunteers.

N-desmethyl vandetanib and vandetanib-N-oxide were measured in healthy volunteers (Study 16, 22, and 26; Table 9) and NSCLC patients (Study 57), but not in MTC patients.

Table 9. The percent exposure to N-desmethyl vandetanib and vandetanib-N-oxide relative to that to vandetanib.

	Study 16	Study 22	Study 26	Study 57
Study, Dose	Hepatic imp, 800 mg	Renal imp, 800 mg	DDI with rifampicin, 300 mg	Phase 3 in NSCLC, 300 mg
N-desmethyl/ parent	8%	10%	7%	17.1%
N-oxide/ parent	1.40%	1.50%	1.80%	2.2%

The appearance and subsequent disposition of N-desmethyl-vandetanib and vandetanib-N-oxide was similar to vandetanib. The apparent half-lives of N-desmethyl-vandetanib and vandetanib-N-oxide were similar to that for vandetanib itself, suggesting formation-rate limited metabolism.

2.2.5.3 What are the characteristics of drug absorption?

Following oral administration of vandetanib absorption is slow with peak plasma concentration achieved at a median of 6 hours, range 4 to 10 hours after dosing.

A relative bioavailability study (Study 30) was conducted with an oral solution and to-be-marketed tablet formulation (TBM). The PK parameters for the TBM formulation were available in 10 subjects.

Table 10. Ratios of Geometric means (test/reference) and 90% confidence intervals for primary PK parameters (N=10).

PK parameter	Formulation	GMean	ratio of GMean	90% CI	
				Lower	Upper
AUCinf (ng.h/mL)	Oral solution	31196.26	1.11	0.93	1.32
	TBM	34528.69			
Cmax (ng/mL)	Oral solution	174	1.06	0.87	1.28
	TBM	184			

Although the upper bounds of the 90% CI were higher than 1.25, it may be due to the small number of subjects. Since both formulations show similar exposures, the absorption of vandetanib is probably not dissolution rate limiting.

2.2.5.4 What are the characteristics of drug distribution?

Ex-vivo Protein Binding

The protein binding of vandetanib was determined *ex-vivo* in healthy subjects and subjects with hepatic impairment in Study 16, in healthy subjects and subjects with renal impairment in Study 22 and in patients with advanced colorectal cancer and liver metastases in Study 50. The *ex-vivo* plasma protein binding of vandetanib assessed in this study was found to be higher than that determined *in vitro* with a geometric mean binding of 94.0%, range 91.6 to 96.0%. It appears that there is no difference in the mean percentage binding of vandetanib between cancer patients and healthy volunteers, regardless of renal/hepatic function, except that there was a trend a trend towards reduced binding in subjects with severe hepatic impairment.

In-vitro plasma protein binding

The protein binding of [^{14}C]-vandetanib was determined by equilibrium dialysis at 37°C, over concentrations (0.05, 0.2, 1, 4 and 6 μg/mL) in the plasma of male and female healthy volunteers (D6474 KPJ010). Vandetanib was found to be moderately bound (83%-90%) to plasma proteins. There was no apparent difference in the plasma protein binding between males and females.

The protein binding of [^{14}C]-vandetanib was also determined in solutions of human serum albumin and α-1 acid glycoprotein over similar concentrations to those in plasma. The binding of [^{14}C]-vandetanib to human serum albumin (40 mg/mL) was 76%. At all three concentrations of α-1 acid glycoprotein (0.4, 0.8 and 1.6 mg/mL) the binding of [^{14}C]-vandetanib declined over the range 0.05 to 6 mg/ml suggesting that the binding to this specific protein could be saturated. The binding of [^{14}C]-vandetanib to α-1 acid glycoprotein (0.4 mg/mL) in the presence of human serum albumin (40 mg/mL) was 77% and did not decline with the increasing concentrations of [^{14}C]-vandetanib.

Blood distribution

The *in vitro* blood distribution study was not conducted.

The ratio of the concentration of total radioactivity in the plasma: concentration of total radioactivity in the blood was measured in ADME study (Study 25). The concentrations of radioactivity in blood were initially slightly lower than in plasma (plasma:blood ratio 1.1 at 6 hours) then slightly higher than plasma, thereafter (plasma:blood ratio 0.8 at 72 hours).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Both urinary and fecal excretion are the main routes of elimination of vandetanib.

An ADME study (Study 25) with a single dose of 800 mg ^{14}C-vandetanib (10 mg/mL solution) was conducted in healthy male subjects. This study included analysis of metabolites in plasma, urine and feces. During the collection interval of 21 days, 44.1 ± 11.5 %, 25.2 ± 3.2 %, and 69.3 ± 9.1% of the administered radioactive dose were recovered in feces, urine, and in total, respectively. Fecal radioactivity could represent unabsorbed dose or biliary excretion of absorbed radioactivity. However, an average of 6.5% of the dose was recovered in feces in the first 2 days when unabsorbed radioactivity would be expected. The elimination of radioactivity was very slow, with approximately 1% to 3% of the dose excreted daily from 192 hours (Day 8) to 504 hours (Day 21).

2.2.5.6 What are the characteristics of drug metabolism?

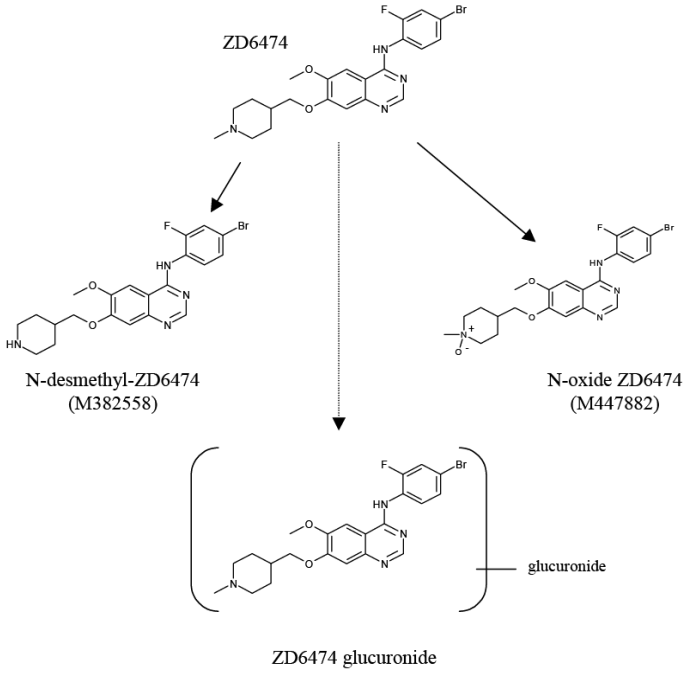


Figure 8: Proposed metabolic pathways of vandetanib in humans (Sponsor's figure)

In vitro study showed that vandetanib is metabolized to an N-desmethyl metabolite by CYP3A4

(Study KMX038) and to an N-oxide metabolite by FMO1 and FMO3 (Study KMX046). A human ADME study (Study 25) indicated that vandetanib was eliminated unchanged, as an N-desmethyl metabolite, as an N-oxide metabolite, and as a glucuronide. In this study, it was not possible to quantify the metabolites due to the long half-life of vandetanib and the radioactive dose.

Metabolism of vandetanib by UGT was very limited with the formation of two minor metabolites (Study KMN091). Metabolite 1 formation was catalyzed by UGT1A1, 1A3, and 1A9 and metabolite 2 formation was catalyzed by UGT1A4 and 2B4.

The levels of radioactivity in plasma, urine and feces were very low and did not allow the use of standard methods for metabolite profiling based on radioactivity detection. However, qualitative analysis was carried out by HPLC-MS on a single quadrupole Micromass ZQ mass spectrometer. Unchanged vandetanib and 2 known metabolites (vandetanib N-oxide and N-desmethyl vandetanib) were detected in plasma. The same metabolites were found in both urine and feces, where an additional minor metabolite was also present. This was shown by mass spectroscopy to be a glucuronide conjugate of vandetanib.

Thin layer chromatography (TLC) of the fecal extract showed that there were 2 major component; vandetanib and N-desmethyl vandetanib in the ratio 5:1. The N-oxide of vandetanib was only detected in 1 sample, the 3-9 day sample from one subject. Vandetanib glucuronide was not detected using TLC, suggesting that it is a minor metabolite which is only detectable by the more sensitive technique of mass spectrometry (MS). The results of the analysis are summarized in Table 11.

Table 11. Summary of the metabolites identified following HPLC-MS analysis of plasma, urine, and fecal extract (N=4).

	Time (hr)	Vandetanib	N-desmethyl	N-oxide	Vandetanib-glucuronide
Plasma	6, 24	✓	✓	✓	Not detected
Urine	0-3 3-9 9-15 15-21	✓	✓	✓	✓ (trace amount)
Feces	0-3 3-9 9-15 15-21	✓	✓	✓	✓ (trace amount)

2.2.5.7 What are the characteristics of drug excretion?

Both urine and fecal excretion are the major routes of elimination of vandetanib. In the human ADME study (Study 25), 44.1 ± 11.5 % and 25.2 ± 3.2 % of the administered radioactive dose (800 mg ^{14}C-vandetanib) were recovered in feces and urine, respectively.

Population PK analysis showed that vandetanib has a long half-life (~19 days) and an apparent oral clearance of ~ 13.2 L/h in MTC patients (Study 58).

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

The PK of vandetanib is linear between 50 to 600 mg single dose, and 50 to 300 mg daily dose in cancer patients.

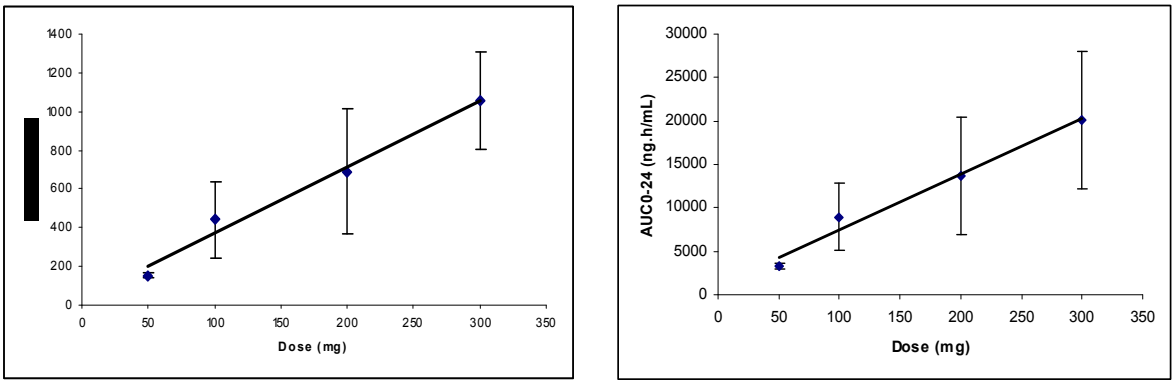


Figure 9. C_{max} (Left) and AUC (Right) values of vandetanib after daily administration for 14 days (multiple doses).

Following single, oral doses of vandetanib of 300 mg to 1200 mg in healthy volunteers, mean AUC and C_{max} both increased with dose in a dose-proportional manner and, at each dose level. Oral clearance of vandetanib appeared to be independent of dose.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

After multiple daily doses, the AUC and C_{max} of vandetanib increased and achievement of steady state exposure to vandetanib on once-daily dosing required a minimum of 95 days of dosing.

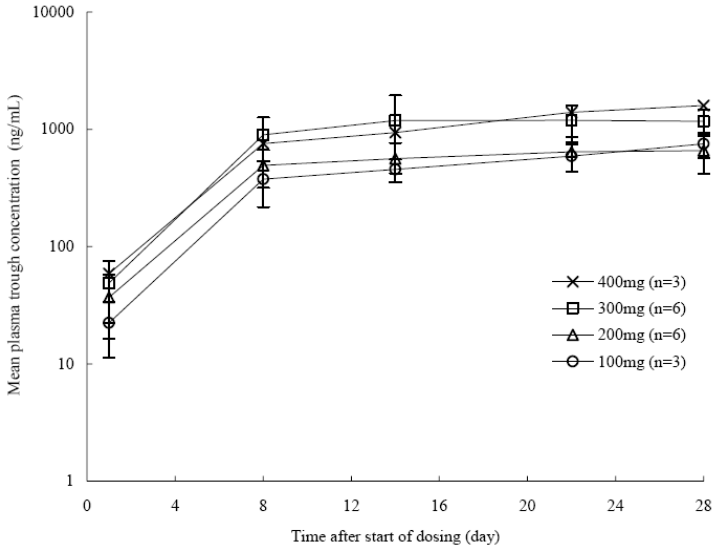


Figure 10. Plasma trough concentration profiles of vandetanib (mean ± SD) in Japanese patients during 28-day multiple oral doses of 100 to 400 mg/day (Study 43)

Please see Section 2.2.5.1 for more information on the pharmacokinetics of vandetanib following multiple doses.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In healthy subjects the inter-subject variability (CV%) for AUC ranged from 8.4% to 25.8%, with a similar CV range for C_{max}. The observed within-subject variability (CV%) of the primary PK parameters was within 20% for AUC and within 10% for C_{max}. In patients with cancer patients there was a higher inter-subject variability compared to healthy subjects in CV% of 40% to 77% for C_{max} and 57.44% to 175.9% % for AUC at a single dose, and 60.7% for C_{max} and 58.4% for AUC at Day 29 in Study 1.

Vandetanib is metabolized by CYP3A4, FMO1 and FMO3, and UGTs (minor). The expression of CYP3A4 is known to be highly variable between individuals (Forrester et al., 1992). FMO1 is known to be polymorphic and could account for up to a 2- to 3-fold decrease in FMO1 expression. The expression of FMO1 and FMO3 is also known to be highly variable between individuals.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Race

The PK of vandetanib in the phase 1 dose escalation studies conducted in US and Australia (Study 01), Japanese (Study 43), and Chinese (Study 4) patients with solid tumors were evaluated using a non-compartmental analysis approach. Based on a cross-study comparison in a limited number of patients, Japanese and Chinese patients had on average exposures that were up to two-fold higher than other patients receiving the same dose, following single (Table 6) and multiple (Table 7) doses of vandetanib. In the pivotal trial, no conclusion could be reached on the effect of race on PK, as 95% of the patients were Caucasians.

Weight

The body weight was included as a significant covariate for clearance and central volume of distribution (Figure 11) in the final population PK model. The inclusion of the covariates resulted in a decrease in the inter-individual variability in the clearance, central and total volume of distribution from 32.9, 54.9, and 106% to 30.9, 52.0, and 101%, respectively. However, given a narrow range of BSA (1.2–2.5 m^2) and small magnitudes of decrease of inter-individual variability in the final model, the reviewer agrees to the applicant's conclusion that the effects of body weight are not clinically important.

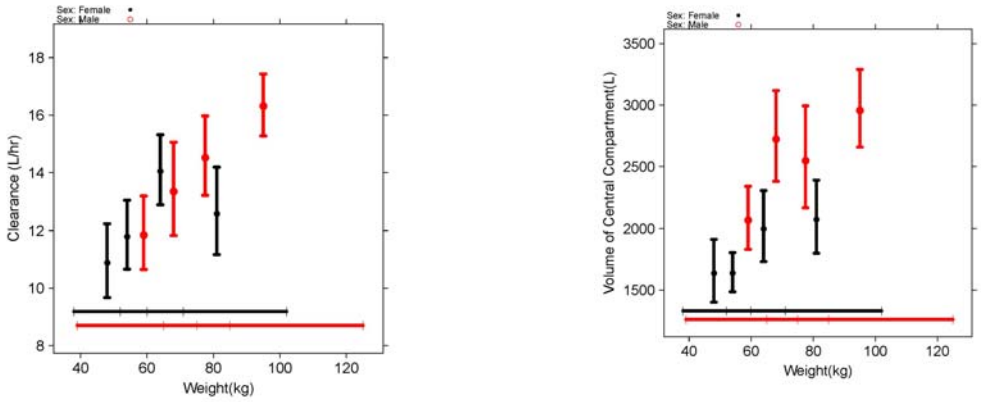


Figure 11. The fixed effect of body weight on the clearance (left) and central volume of distribution (right) of vandetanib for male (in red) and female (in black). The body weight quartiles are denoted by the horizontal black line. The clearance and central volume of distribution are the post-hoc estimates for 231 patients in the pivotal trial Study 58.

Also, body weight did not appear to influence QTc prolongation (see IRT review posted in DARRTS).

Gender

A slightly larger QTc effect was observed in female patients as compared to male patients (Table 12).

Table 12. Categorical Analysis for ΔQTcF and QTcF Based on Gender (IRT review)

	N	ΔQTcF >60 (ms)	QTcF >480 (ms)	QTcF >500 (ms)
Male	134	44 (32.8%)	18 (13.4%)	6 (4.5%)
Female	97	38 (39.2%)	21 (21.6%)	4 (4.1%)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

Safety and efficacy of vandetanib in pediatric patients have not been established. An uncontrolled, single-arm, dose escalation study is ongoing in pediatric patients with hereditary MTC.

2.3.2.2 Renal impairment

Dedicated study

A study (Study 22) was conducted in healthy subjects with normal function (N = 10; estimated creatinine clearance >80 mL/min), mild (N = 6; ≥50 to ≤80 mL/min), moderate (N = 8; ≥30 to <50 mL/min) and severe renal impairment (N = 6; <30 mL/min) according to their creatinine clearance at screening, estimated using the Cockcroft-Gault equation. All subjects received a single 800 mg dose of vandetanib. AUC was modeled using linear regression, fitting measured creatinine clearance as a variable. The creatinine clearance values of 10, 30, 50, and 125 mL/min were used in the applicant's calculations to represent the severe, moderate, mild, and normal groups, respectively (Table 13). These are extreme values and do not represent the mean creatinine clearance of each group in this study (23.0, 39.6, 62.4, and 98.9 mL/min in severe, moderate, mild and normal group, respectively). Therefore, the reviewer re-analyzed the data (Table 14).

Table 13. Creatinine clearance values used for grouping, actual mean creatinine clearances in each renal function group, and the values used in the applicant's AUC calculation.

group	creatinine clearance (mL/min)		
	grouping based on creatinine clearance	actual mean values in each group (range)	applicant's values used for AUC calculation
normal	> 80	98.9 (83-128.8)	125
mild	≥50 to ≤80	62.4 (54.1-69.9)	50
moderate	≥30 to <50	39.6 (30.4-49.5)	30
severe	<30	23.0 (18.6-27.9)	10

There was no significant effect of renal function on the C_{max}; in addition there was no apparent difference in the time to C_{max} observed in any of the subject groups with renal impairment. For the moderate and severe renal impairment groups there were significant increases in AUC of 39% and 41%, respectively (Table 14). Mean CL/F for vandetanib was slower in subjects with mild, moderate and severe renal impairment compared to in subjects with normal renal function (Table 14). Figure 12 shows the AUC of vandetanib versus the calculated creatinine clearance.

Table 14. Geometric mean ratio for C_{max} and AUC of total vandetanib in healthy subjects and subjects with renal impairment (N: Normal = 10, Mild = 6, Moderate = 8, Severe = 6).

	Mild/Normal	Moderate/Normal	Severe/Normal
C_{max}	1.02	1.18	0.93
AUC	1.14	1.39	1.41
CL/F	0.88	0.72	0.71

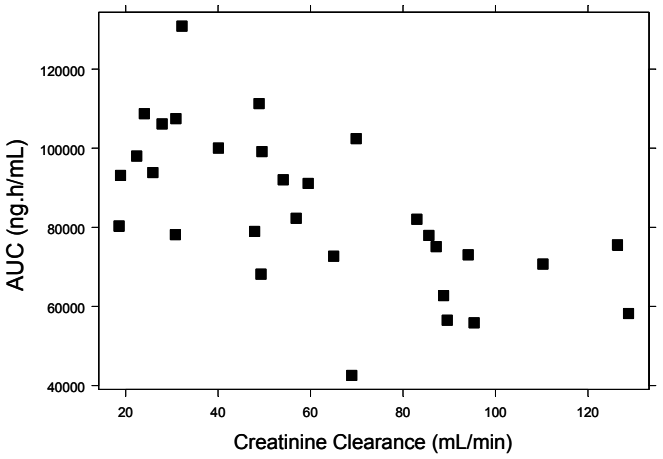


Figure 12. The vandetanib AUC versus the baseline creatinine clearance. The creatinine clearance was estimated using the Cockcroft-Gault equation.

There was no apparent difference in the volume of distribution of vandetanib. Plasma protein binding assessed *ex vivo* in subjects with normal renal function was 94%, and this was unaltered in subjects with renal impairment.

Exposure to the N-desmethyl and N-oxide metabolites increased in subjects with renal impairment, by up to 2-fold and 4-fold respectively in subjects with severe renal impairment. This increased exposure may be a consequence of a shift to an increased metabolic clearance of vandetanib, which compensates for some of the reduced intrinsic clearance due to renal impairment. It may also be due to the fact that renal impairment also compromises the intrinsic clearance, as both metabolites have been shown to be eliminated by the renal route.

In conclusion, a dose reduction to 200 mg for patients with moderate and severe hepatic impairment is recommended.

Population PK analysis

Population pharmacokinetic analysis of the pivotal trial also supports the conclusion of the dedicated study. Clearance in each patient in the pivotal trial was estimated using population pharmacokinetic modeling. Clearance values in patients with moderate renal impairment were lower compared to the ones in patients with normal renal function or mild renal impairment (Figure 13). In this study, patients with severe renal impairment were excluded.

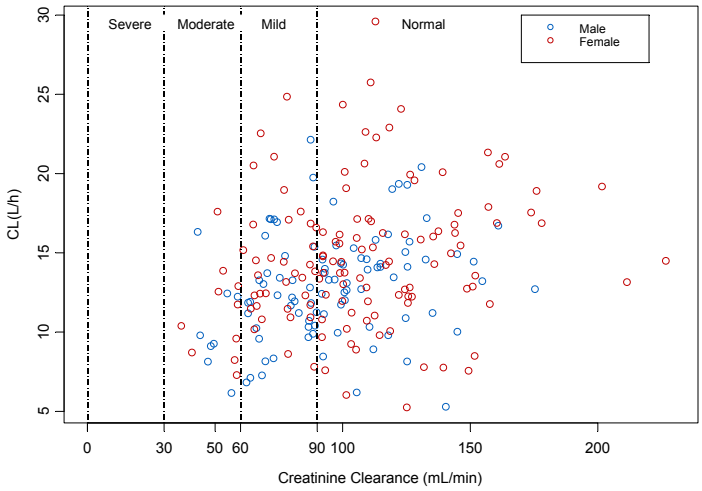


Figure 13. Estimated plasma vandetanib clearance vs creatinine clearance in patients (N=231) with MTC in the vandetanib arm of Study 58. The plasma vandetanib clearance is presented in red for females and black blue for males. The renal function was classified as normal (> 90 mL/min), mild impairment (60-90 mL/min), moderate impairment (30-60 mL/min), and severe impairment (< 30 mL/min).

Using the estimated clearance, the steady state AUCs following 300 mg daily dose were calculated, and shown in the left panel of Figure 14. When 200 mg daily dose is given to the patients with moderate renal impairment, the AUCs in these patients will become similar as those with normal renal function (Figure 14, right). No dose reduction is needed for patients with mild renal impairment.

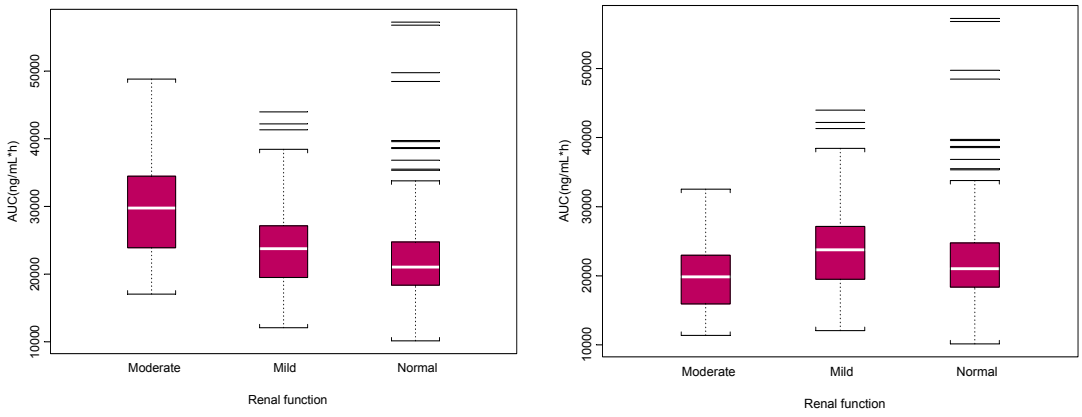


Figure 14. Box-plots for model-predicted AUCs with a 300 mg oral daily dose (left) and with a 200 mg oral daily dose of vandetanib (right) in patients with moderate renal impairment. AUCs were based on post-hoc estimates of clearance for patients (N=231) in the vandetanib arm of Study 58. In patients with mild impairment or normal renal function, the dose of vandetanib is 300 mg oral daily.

QT data also support a dose reduction in patients with renal impairment. A higher proportion of patients with ΔQTcF > 60 ms, or QTcF > 480 ms or QTcF > 500 ms was observed in patients with mild to moderate renal impairment as compared to patients with normal renal functions (Table 15).

Table 15. Categorical analysis for ΔQTcF and QTcF based on renal function

	N	ΔQTcF >60 (ms)	QTcF >480 (ms)	QTcF >500 (ms)
Normal (CRCL ≥ 80)	167	57 (34.1 %)	25 (15 %)	6 (3.6 %)
Mild (50 ≥ CRCL < 80)	56	21 (37.5 %)	12 (21.4 %)	3 (5.4 %)
Moderate (30 ≥ CRCL < 50)	7	4 (57.1 %)	2 (28.6 %)	1 (14.3 %)

Dialysis

On 05 November 2010, the FDA sent the following request for information to the sponsor:
We are concerned that the prolonged half-life of vandetanib may make the treatment of patients with marked prolongations in their QTc interval difficult. Please develop a plan to assess the ability to remove vandetanib, through hemodialysis, etc., from the patient's circulation. Please provide a timeline for development and completion of this plan (in vitro, in vivo, or patient testing, as needed) within 2 weeks.

The sponsor's response to the request is as follows:

It is AstraZeneca's belief that dialysis would not be an effective or rapid means of removing vandetanib from patients' circulation.

Based on the pharmacokinetic properties of vandetanib (protein binding of 90% and volume of distribution of 7450L) and estimating the fraction of drug that could be dialyzed using the method evaluated by Tang and Mayersohn 2004 (AAPS poster abstract), we estimate that approximately 0.05% of the drug would be removed in a 6-hour dialysis session.

Substituting into the formula 1/Fr = 1.3Vu + 2.14, where Vu is (7450L/50 kg)/ 0.10 and simplifying Fr = 0.05%.

When using this formula for drugs that are reliably removed by hemodialysis a value for Fr is typically > 30%. Based on the value obtained from this predictive formula, we conclude that there is no additional benefit to experimentally determining (either non-clinically or clinically) whether vandetanib clearance can be increased from the circulation by hemodialysis. Other methods of removal of drug from the circulation, such as hemoperfusion, would also be predicted to be ineffective.

Reviewer's comments
The formula was derived in another abstract (Tang and Mayersohn, 2004 AAPS poster abstract). The formula 1/Fr = 1.3Vu + 2.14 was obtained from the data of 20 drugs which have V_u (L/kg) values ranged from 0 to ~22 (Figure 15). However, V_u of vandetanib is much larger (1064 L/kg).

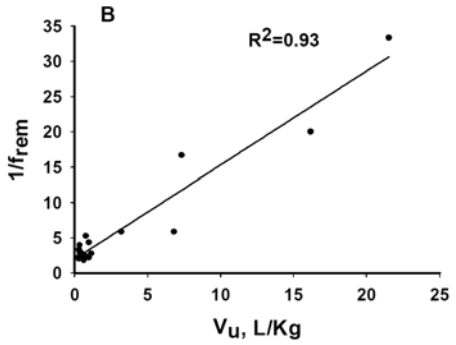


Figure 15. The inverse relationship between f_{rem} and V_u (f_{rem} : the amount of drug in the body removed)

To decide the appropriateness of this extrapolation, the reviewer searched literature data. A drug with a large volume of distribution is distributed widely throughout tissues and is present in relatively small amounts in the blood. Drugs with a high degree of protein binding will have a small plasma concentration of unbound drug available for dialysis. Therefore, given that high volume of distribution, long half-life, and high protein binding of vandetanib, it is concluded that *in vivo* dialysis of vandetanib is unlikely to be successful.

References

1. Johnson and Simmons, 2000 Dialysis of drugs. Nephrology Pharmacy Associates, Inc.
2. Tomita et al, 2004. Clin Pharmacokinet 43 (8): 515-527
3. John Francis Maher, 1989. Replacement of renal function by dialysis

2.3.2.3 Hepatic impairment

Dedicated study

A study (study 16) was conducted in healthy subjects (N = 5) and subjects with mild (N = 8), moderate (N = 7) and severe renal impairment (N = 6) were included. All subjects received a single 800 mg dose of vandetanib. The subjects were classified using the Child-Pugh system. There was no significant effect of hepatic function on the C_{max} and AUC (Table 16).

Table 16 . Mean ratio for C_{max} and AUC in healthy subjects and subjects with hepatic impairment

	Mild/Normal	Moderate/Normal	Severe/Normal
C_{max}	0.868	0.909	0.709
AUC	1.04	0.943	0.930
CL/F	0.96	1.06	1.08

Exposure to the N-desmethyl metabolite decreased (~2-fold to 6-fold) in subjects with hepatic impairment; an increase in the exposure to the N-oxide metabolite was observed (~2-fold) only in subjects with severe hepatic impairment.

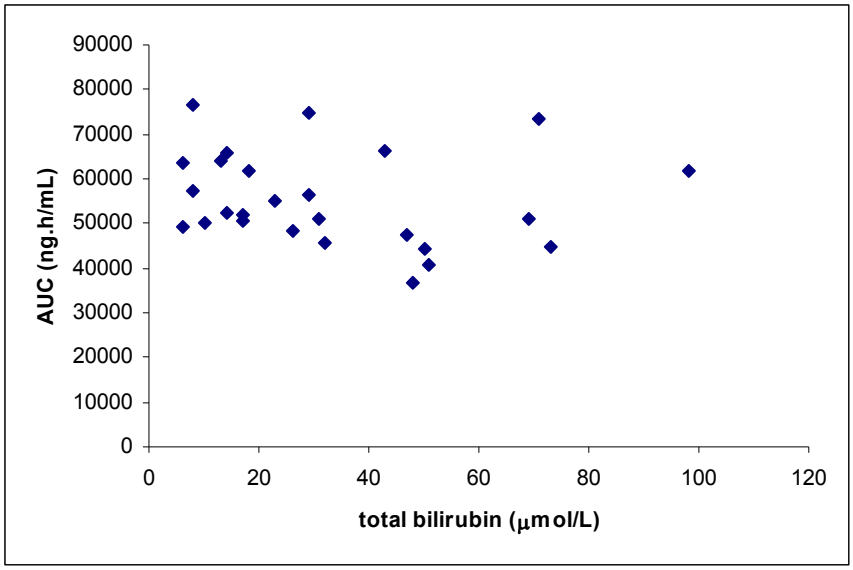


Figure 16. No effect of baseline total bilirubin on AUC of vandetanib

Reviewer's comment

- In the applicant's proposed label, (b) (4) is not recommended for use in patients with hepatic impairment, even though dedicated hepatic impairment study showed no difference in AUC and C_{max} between subjects with hepatic impairment and subject with normal hepatic function. Therefore, Information Request was sent on September 10, 2010 and September 24, 2010 to ask the sponsor's justification. The applicant's response is as follows:

  There is limited data in cancer patients with liver impairment (serum bilirubin greater than 1.5 times the upper limit of normal). Vandetanib is not recommended for use in patients with hepatic impairment, as safety and efficacy have not been established.

  We would be willing to discuss specific labeling statements to provide further guidance to patients, given our finding in the volunteer study that PK are not affected by hepatic impairment.

For future studies, we would consider broadening the eligibility criteria so that patients with hepatic impairment are not excluded.

Population PK analysis

In the pivotal trial, patients with normal hepatic function and mild hepatic impairment were included (total bilirubin ≤ 1.5 × ULN). No effect of mild hepatic impairment observed on model-estimated clearance of vandetanib (data not shown).

In conclusion, subjects with mild, moderate or severe hepatic impairment, based on Child-Pugh criteria, showed no significant difference in the exposure to vandetanib in healthy volunteers. However, as there are limited data in patients with moderate and severe hepatic impairment, (b) (4) is not recommended for use in patients with moderate and severe hepatic impairment.

2.3.2.4 What pregnancy and lactation use information is there in the application?

There are no adequate and well-controlled studies in pregnant women using (b) (4) and no data on the use of (b) (4) in nursing mothers.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate to the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of vandetanib.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes, vandetanib is a substrate of CYP3A4. Vandetanib is also an inhibitor of CYP2D6 and an inducer of CYP1A2, 2C9, and 3A4.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Yes, the drug is a substrate of CYP3A4. The in vitro metabolism study in human liver microsomes was conducted (Study KMX038). N-desmethyl vandetanib formation was extensively inhibited in the presence of ketoconazole (IC_{50} was not calculated in the report) in a concentration-dependent manner, indicating the involvement of CYP3A4 in the N-desmethylation: this was confirmed in the experiment where vandetanib incubated in the presence of heterologously expressed human CYP3A4.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

***In vitro* inhibition**

Yes, vandetanib is a weak inhibitor of CYP2D6 and 2C8. It is not an inducer of CYP enzymes.

Human hepatic microsomal protein was incubated with selective CYP450 substrates (bufuralol for CYP2D6) in the presence of vandetanib at a range of concentrations between 0.025 and 100 μg/mL (Study KMX020). IC_{50} and Ki values for vandetanib were 25 μg/mL and 12.6 μg/mL, respectively. The inhibition was not time-dependent (Study KMX095). As the vandetanib mean steady state C_{max} following 300 mg daily oral dose was 0.857 μg/mL in the pivotal trial, [I]/Ki is less than 0.1.

Another study (KMX054) was conducted to investigate the potential of vandetanib to directly inhibit CYP2C8. Human hepatic microsomes were incubated with paclitaxel (selective probe substrate of CYP2C8) in the presence of vandetanib at a range of concentrations between 0.025 and 100 μg/mL. At highest concentration of vandetanib (100 μg/mL), a 57% reduction was observed in the formation of 6α-hydroxypaclitaxel. It is concluded that vandetanib is a weak inhibitor of 2C8.

Study KMX095 showed that the N-desmethyl metabolite produced little or no reversible inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5 activities (100, 98.9, 100, 112, 104, 77.3, 88.9, 112 and 89.9% of vehicle control activity remained, respectively, at 10 μM N-desmethyl metabolite). Since N-desmethyl metabolite concentration was up to 517 ng/mL at steady state in NSCLC patients (Study 57), the possibility that the N-desmethyl metabolite inhibits CYPs *in vivo* is low.

***In vitro* induction**

Induction was measured by catalytic activity assays selective for CYP isozymes 1A2, 2C9 and 3A4 in fresh human hepatocytes (Study KMX067). Vandetanib was incubated with hepatocytes at concentrations of 0.5, 2, 10, and 25 μM for donor HH185 and 0.5, 2, 10, and 15 μM for donors HH186 and HH187.

Vandetanib caused induction of CYP1A2, CYP2C9 and CYP3A4 in hepatocytes from all 3 donors when incubated at 0.5 μM (≡ 0.24 μg/ml) and 2 μM (≡ 0.95 μg/ml). Maximal induction of CYP1A2 activity increased 28% of the positive control [β-naphthoflavone] response). CYP2C9 activity increased 38% of the positive control [rifampicin] effect), and CYP3A4 activity increased 33% of the positive control [rifampicin] effect), occurred at 2 μM (0.95 μg/ml) vandetanib. The Western blot results supported the results of activity assays: induction of all 3 enzymes was shown at 0.5 μM and 2 μM. A decrease in enzyme activity occurred at higher concentrations (15 and 25 μM). Since the inductive effect was less than 40%, the possibility that vandetanib induces CYPs *in vivo* is low (Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling).

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Vandetanib is not a substrate or an inhibitor of p-glycoprotein (P-gp). The effect of P-gp and *in vitro* permeability was determined using MDCKII cells transfected with human MDR1 (Study KMN070). A concentration-dependent transport of vandetanib was observed in both MDCKII

control and MDCKII-MDR1 cells. Permeability of vandetanib was moderate. At a concentration of 1 µM, the transport to the apical side was higher than the basolateral side in both cell lines, indicating possible transport by endogenous canine (dog) transporter proteins. P_{app} b→ a values were low and uncorrected efflux ratios were in the range of 1.4-2.2; corrected efflux ratios ranged from 0.8 to 1.1 (Table 17).

Table 17. Permeability of vandetanib in MDCKII-MDR1 cells

Permeability data ZD6474 and Efflux Ratio's							
	MDCKII-control			MDCKII-MDR1			
ZD6474 concentration	P_{app} a-b	P_{app} b-a	P_{app} b-a/ a-b	P_{app} a-b	P_{app} b-a	P_{app} b-a/a-b	MDCKII corrected Efflux Ratio
1 µM	4.56	8.69	1.91	3.65	7.87	2.15	1.13
SD	0.58	0.16	0.04	0.93	0.37	0.10	0.05
10 µM	9.60	9.84	1.02	5.65	11.45	2.03	1.06
SD	1.96	0.74	0.08	2.31	1.53	0.27	0.14
25 µM	10.04	9.94	0.99	6.13	11.54	1.88	0.99
SD	1.02	1.26	0.13	2.58	1.38	0.23	0.12
50 µM	15.79	14.94	0.95	10.55	15.17	1.44	0.75
SD	2.89	0.47	0.03	0.68	0.33	0.03	0.02

Data are mean P_{app} values in $cm*10^{-6}$/sec and SD of three determinations.

Addition of the MDR1 inhibitor, verapamil (50 µM), produced a minor reduction (0 - 10%) in the P_{app} a → b values (Table 18), indicating that vandetanib is not a substrate for P-gp.

Table 18. Permeability of vandetanib in MDCKII-control and MDCKII-MDR1 cell

Permeability values of ZD6474 in the absence and presence of verapamil			
	MDCKII-MDR1		
ZD6474 concentration	P_{app} b-a	P_{app} b-a + verapamil	% of P_{app} Without verapamil
1 µM	8.69	8.34	96.0
SD	0.16	0.49	5.6
10 µM	9.84	9.05	92.0
SD	0.74	1.20	12.2
25 µM	9.94	10.11	101.7
SD	1.26	1.23	12.4
50 µM	14.94	13.48	90.2
SD	0.47	0.43	2.9

Data are mean P_{app} values in $cm*10^{-6}$/sec and SD of three determinations.

The effect of vandetanib on the stimulation of the basal vanadate-sensitive ATPase activity was determined, to indicate whether vandetanib is a possible substrate of MDR1. In addition, the effect of vandetanib on the MDR1 activated ATPase activity stimulated by a model substrate (40 µM verapamil hydrochloride) was determined to indicate whether vandetanib is a possible

inhibitor or a slowly transported substrate of the MDR1 transporter. At a high concentration (100 μM), vandetanib enhanced the basal vanadate-sensitive ATPase activity of MDR1. This suggests that vandetanib may be a low affinity substrate of P-gp at high concentrations, which are not attainable under clinical conditions. In the presence of verapamil the vanadate-sensitive ATPase activity was enhanced from 6 to approximately 18 nmol Pi/mg protein/min. The MDR1-ATPase inhibition experiment showed that vandetanib did not reduce verapamil-stimulated MDR1-ATPase activity. Values for verapamil-stimulated MDR1-ATPase activity were generally increased and variable in the presence of vandetanib. There was no evidence that vandetanib was an inhibitor of P-gp.

The effect of vandetanib (0.1 - 100 μM) on MDR1-mediated transport of the substrate [^{3}H]-digoxin is shown in Table 19 (Study KMN096).

Table 19. The effect of vandetanib on the permeability of the model substrate [^{3}H]-digoxin across MDCKII-control and MDCKII-MDR1 cell monolayers.

Cell Type	[ZD6474] (μM)	P_{app} a - b (cm·10^{-6}/sec)	P_{app} b - a (cm·10^{-6}/sec)	Efflux ratio P_{app} b - a / a - b	Corrected Efflux Ratio[a]	% Inhibition[b] of Transport (P_{app} b– a)	Papp b-a (% of control)
MDCKII-control	No inhibitor	1.48 ± 0.28	8.51 ± 0.59	5.75	na	na	100 ± 6.93
MDCKII-control	0.1	1.38 ± 0.22	9.33 ± 0.33	6.77	na	nc	110 ± 3.89
MDCKII-control	0.3	1.19 ± 0.09	9.91[d]	8.36	na	nc	116[c]
MDCKII-control	1	1.22 ± 0.03	8.85 ± 3.59	7.28	na	nc	104 ± 42.1
MDCKII-control	2	1.33 ± 0.15	9.10 ± 0.32	6.82	na	nc	107 ± 3.71
MDCKII-control	5	2.03 ± 0.55	7.67 ± 0.37	3.78	na	9.91 ± 4.31	90.1 ± 4.31
MDCKII-control	10	1.76 ± 0.19[e]	6.03 ± 0.65	3.42	na	29.2 ± 7.60	70.8 ± 7.60
MDCKII-control	33	4.67 ± 0.31[c]	5.98 ± 0.25	1.28	na	29.8 ± 2.97	70.2 ± 2.97
MDCKII-control	100	6.95 ± 0.42[c]	6.38 ± 0.35	0.92	na	25.1 ± 4.07	74.9 ± 4.07
MDCKII-MDR1	No inhibitor	0.41 ± 0.02	15.5 ± 0.49	37.9	6.59	na	100 ± 3.15
MDCKII-MDR1	0.1	0.74 ± 0.38	16.3 ± 1.01	21.9	3.24	nc	105 ± 6.50
MDCKII-MDR1	0.3	1.23 ± 0.45	15.9 ± 0.96	12.9	1.54	nc	103 ± 6.21
MDCKII-MDR1	1	1.38 ± 0.81	16.0 ± 1.82	11.6	1.59	nc	103 ± 11.8
MDCKII-MDR1	2	2.61 ± 0.68	17.5 ± 1.24	6.71	0.98	nc	113 ± 8.03
MDCKII-MDR1	5	0.54[e]	13.7[e]	25.5	6.75	11.5[e]	88.5[e]
MDCKII-MDR1	10	0.66 ± 0.09	12.6 ± 0.72	19.0	5.56	18.6 ± 4.64	81.4 ± 4.64
MDCKII-MDR1	33	1.67 ± 0.27	9.81 ± 0.99	5.89	4.60	36.6 ± 6.40	63.4 ± 6.40
MDCKII-MDR1	100	3.88 ± 0.42[c]	6.83 ± 0.44	1.76	1.92	55.9 ± 2.85	44.1 ± 2.85

Mean transport data are the mean (N=3) Papp values ± standard deviation, except for d (N=1) and e (N=2). Individual data are presented in Table C3
a Corrected efflux ratio = (Papp b - a / a – b from MDCKII-MDR1)/(Papp b - a / a – b from MDCKII-control)
b % Inhibition = 100 – ([(Papp b– a (+ZD6474) from MDCKII-control or MDR1)/ average (Papp b – a (No inhibitor) from MDCKII-control or MDR1))
c mass balance data of [^{3}H]digoxin < 80%
na not applicable ; nc not calculates as no inhibition observed

In MDCKII-MDR1 cells, the b → a transport of [^{3}H]-digoxin showed dose-dependent inhibition by vandetanib to 44.1% of control values at 100 μM, with rates decreasing from 15.5 ± 0.49 cm·10^{-6}/sec to 6.83 ± 0.44 cm·10^{-6}/sec, to give a calculated IC_{50} value of 18.3 μM. Inhibition of the b→ a transport of [^{3}H]-digoxin in MDCKII-control cells was also observed, with the rate decreasing from 8.51 ± 0.59 cm·10^{-6}/sec to 6.38 ± 0.35 cm·10^{-6}/sec at 100 μM vandetanib, indicating possible inhibition of endogenous transporters. It was not possible to observe a clear

dose-dependent inhibition of transport in the MDCKII-MDR1 cells using the corrected efflux ratio, probably because of the higher variability in the a → b dataset.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

FMO1 and FMO3 were involved in the metabolism of vandetanib to N-oxide vandetanib (Study KMX046**)**. Human liver microsome pre-incubated at 45°C, in the absence of NADPH, showed that the rate of formation of the N-oxide metabolite was reduced compared to controls pre-incubated at 37°C and the rate of formation of N-desmethyl vandetanib was unaffected. Using the same pre-incubation procedure, but in the presence of NADPH, the rate of formation of the N-oxide metabolite was greatly enhanced, whereas the rate of formation of the N-desmethyl metabolite was still unchanged. This pattern of metabolism under modified conditions strongly indicates the involvement of heat-sensitive FMO enzymes in the N-oxidation of vandetanib. N-oxide vandetanib formation was extensively inhibited in a concentration-dependent manner in the presence of methimazole (FMO inhibitor). The involvement of FMOs in vandetanib metabolism was confirmed using heterologously expressed human FMOs: both FMO1 and FMO3 metabolized vandetanib to the N-oxide metabolite with no N-desmethyl vandetanib formation detected.

The FDA asked the below question to the sponsor regarding in the June 8, 2005 correspondence and the sponsor relied in the August 23, 2006 correspondence.

Is inhibition of ZD6474 (vandetanib) metabolism by concomitantly administered FMO inhibitors likely? Is inhibition of the metabolism of concomitantly administered FMO substrates by ZD6474 likely? Is the FMO system inducible?

AstraZeneca Reply: ZACTIMA has been shown in vitro to be metabolised to an N-oxide metabolite by FMOI and FM03. An excretion balance study in humans indicated that ZACTIMA was eliminated unchanged, as an N-desmethyl metabolite (by 3A4), as an N-oxide metabolite (by FMOI & FM03) and as a glucuronide. It was not possible to quantify the metabolites in excreta and thereby quantify the contribution of different clearance mechanisms due to the long half-life of ZACTIMA and the radioactive dose.

Based on a recent review ofFMO metabolism (Cashman JR, Zhang J. Human flavin-containing monooxygenases. Annu. Rev. PharmacoL.Toxicol 2006; 46: 65-100.), we believe there is low likelihood of clinically significant inhibition ofFMO mediated ZACTIMA metabolism by co-administered drugs. This is in part due to there being few drugs that produce clinically relevant inhibition ofFMOs but also due to the fact that there are other clearance routes for ZACTIMA including CYP3A4 and glucuronidation.

Inhibition of FMO metabolism by ZACTIMA has not been studied. Again we believe there is low likelihood of ZACTIMA causing clinically significant drug-drug interactions via FMOs as few drugs are solely dependent on FMOs for clearance.

Cashman's review alludes to the FMOs not being induced though no specific studies are referenced to support this claim. The existing phase II/III studies have ZD6474 concentration monitoring which, when analysed, could identify any reductions in exposure indicative of significant induction of FMO mediated metabolism of ZACTIMA.

The FDA accepts the sponsor's response (communication date: September, 8, 2006).

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

The label does not specify co-administration of another drug.

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Vandetanib is a substrate of CYP3A4. Absorption and elimination of vandetanib may be influenced by drugs which inhibit or induce CYP3A4. Below in Table 20 is an outline of all the drug-drug interaction studies conducted.

Table 20. Drug-Drug interaction studies

Study	CYP450	Patient	Results
itraconazole	3A4 strong inhibitor	healthy volunteers	vandetanib: AUC ↑14%; C_{max} ↔
rifampin	3A4 strong inducer	healthy volunteers	vandetanib: AUC ↓ 48%; C_{max} ↔
ondansetron	3A4 substrate	healthy volunteers	vandetanib: AUC ↔; C_{max} ↔
pemetrexed	*oncology co-med*	NSCLC	vandetanib: AUC ↔; C_{max} ↔ pemetrexed: AUC ↔; C_{max} ↔
docetaxel	*oncology co-med* 3A4 substrate	NSCLC	vandetanib: AUC ↓15%; C_{max}↓17% docetaxel: AUC ↔; C_{max}↑14%
FOLFIRI (Irinotecan, 5-FU, and leucovorin)	*oncology co-med*	Metastatic colorectal adenocarcinoma	combination not relavant to current NDA not reviewed

CYP3A4 inhibitor- Intraconazole

The effect of itraconazole, a potent CYP3A4 inhibitor on vandetanib PK was investigated in Study 15. In the August 3, 2006 correspondence, the Agency agreed that only itraconazole will be used as the inhibitor in CYP3A4 inhibition study. In the package insert, dosage recommendations for itraconazole vary (100-400 mg/day) according to the infection treated. In this study, a dose of 200 mg itraconazole daily for 24 days was to be administered to ensure complete inhibition of CYP3A4 over the period of time that characterizes 80% of the AUC of vandetanib under monotherapy conditions, i.e., 504 hours. According to the FDA drug-drug interaction guidance, the study design and choice of CYP3A4 inhibitor appear appropriate. Vandetanib pharmacokinetic parameters were determined following a single oral dose of vandetanib 300 mg on Day 4 administered alone and in combination with oral itraconazole 200 mg once daily for 24 days in 14 healthy subjects.

Table 21. Effect of itraconazole on the vandetanib PK

PK parameter		Vandetanib	Vandetanib + Itraconazole	Ratio (90% CI)
AUC_{0-504h} (ng.h/mL)	GMean	22449	24490	1.09 (1.01-1.20)
	CV(%)	19.89	20.86	
AUC_{inf} (ng.h/mL)	GMean	27314	31690	**1.16 (1.08-1.26)**
	CV(%)	19.80	23.42	
C_{max} (ng/mL)	GMean	193.7	189.1	**0.94 (0.82-1.15)**
	CV(%)	33.48	40.73	
T_{max} (h)	Median	5	5	1
	Range	4 - 7	3 - 12	
$T_{1/2}$ (h)	GMean	208.1	235.5	1.13
	CV(%)	30.96	19.39	
CL/F (L/h)	GMean	10.98	9.467	0.86 (0.81-0.93)
	CV(%)	20.08	23.42	
V_{ss}/F (L)	GMean	3030	3115	1.03
	CV(%)	28.49	22.23	(0.96-1.14)

There was little difference in the mean C_{max} following vandetanib alone compared with vandetanib plus itraconazole (Table 21). Mean AUC_{0-504h} and AUC both increased in the presence of itraconazole, although the increases were both small (9% and 16%, respectively). Mean $t_{1/2}$ showed a 12.6% increase in the presence of itraconazole compared with vandetanib alone (235.5 hours and 209.2 hours, respectively) and mean CL/F showed a 12% reduction in the presence of itraconazole compared with vandetanib alone (9.467 L/h and 10.77 L/h, respectively). There was little difference in vandetanib V_{ss}/F between the 2 treatments.

Six volunteers reported AEs; 5 (2 Abdominal pain, 1 Bronchitis, 1 Nasopharyngitis, 1 Tooth abscess) were receiving vandetanib alone and 1 (Nasopharyngitis) was receiving vandetanib plus itraconazole. No events were serious or led to discontinuation. One event (moderate abdominal pain) was considered by the investigator to be related to vandetanib and itraconazole treatment although the event was reported during Period 1 when the volunteer was receiving vandetanib alone. The mean QTcF increase at each time point was <15 ms.

In conclusion, no clinically relevant PK interaction was shown between vandetanib and itraconazole.

CYP3A4 induction- Rifampicin

The effect of rifampicin, a potent CYP3A4 inducer on vandetanib PK was investigated in Study 26. According to the FDA drug-drug interaction guidance, the study design and choice of CYP3A4 inducer are appropriate. This cross-over study was completed using steady state administration of rifampicin 600 mg (daily for 31 days) and a single dose of vandetanib on Day 10 in 16 healthy subjects. The PK parameters were obtained from 12 subjects.

Table 22. Effect of rifampicin on the vandetanib PK

PK parameter		Vandetanib	Vandetanib + Rifampicin	Ratio (90% CI)
AUC_{0-504h} (ng.h/mL)	GMean	23005	14136	0.59 (0.56-0.63)
	CV(%)	22.50	16.00	
AUC_{inf} (ng.h/mL)	GMean	28452	14895	**0.52 (0.48-0.56)**
	CV(%)	30.20	18.10	
C_{max} (ng/mL)	GMean	170.2	186.1	**1.09**
	CV(%)	23.30	27.80	
T_{max} (h)	Median	6	5	0.83
	Range	3 - 10	4 - 8	
$T_{1/2}$ (h)	GMean	217.6	116.3	0.53
	CV(%)	37.10	34.40	
CL/F (L/h)	GMean	10.54	20.14	1.91
	CV(%)	30.20	18.10	
V_{ss}/F (L)	GMean	3033	2935	0.97
	CV(%)	23.20	22.20	

Following a single 300 mg oral dose of vandetanib to healthy subjects on Day 10 of the 31 day rifampicin dosing period (vandetanib in combination with rifampicin), there was no apparent difference in t_{max}, and no difference in the C_{max} compared with vandetanib alone (Table 22). Co-administration of vandetanib with rifampicin lowered the exposure of vandetanib by 48% for AUC_{inf} compared to when vandetanib was administered alone. In Subject 15, the AUC_{0-504h} characterized only 52% of the AUC when vandetanib was administered alone. Therefore, this AUC_{inf} value was not included when the ratio is calculated (ratio = 0.52). There was a 91.1% increase in the CL/F of vandetanib in combination with rifampicin compared with vandetanib alone. The increased clearance resulted in a shorter $t_{½}$ for vandetanib in combination with rifampicin. There was no apparent difference in V_{ss}/F in the presence or absence of rifampicin.

The PK parameters for the plasma N-desmethyl metabolite of vandetanib, in the presence and absence of rifampicin, are summarized in Table 23. No $t_{½}$ or AUC were calculable for 12 of the 16 subjects as either the terminal phase was poorly defined or the percentage AUC extrapolated was greater than 20%. The exposure to the N-desmethyl metabolite relative to vandetanib was low for vandetanib alone, with a mean ratio of N-desmethyl metabolite AUC_{0-504h} to vandetanib AUC_{0-504h} of 0.07086.

Table 23. Effect of itraconazole on the N-desmethyl vandetanib PK

PK parameter		Vandetanib	Vandetanib + Rifampicin	Ratio
AUC_{0-504h} (ng.h/mL)	GMean	1681	6153	3.66
	n	14	15	
AUCinf (ng.h/mL)	GMean	2208	6982	3.16
	n	4	15	
C_{max} (ng/mL)	GMean	7.401	38.06	5.14
	n	15	16	
T_{max} (h)	Median	5 (3-7)	5 (4-24)	1
	n	15	16	
$T_{1/2}$ (h)	GMean	168.2	153.7	0.91
	n	4	15	
Ratio[a]	GMean	0.07086	0.4294	6.06
	n	11	12	

There was a 414.3% (5.14 fold) increase in the Cmax of the N-desmethyl metabolite. A terminal phase was defined in 15 subjects and, from the Cmax, plasma concentrations declined slowly with a mean $t_{½}$ of 153.7 hours. There was a 266.0% increase in the AUC0-504h of the N-desmethyl metabolite for vandetanib in combination with rifampicin compared with vandetanib alone, and the C_{max} of N-desmethyl relative to vandetanib increased by 506.0%, for vandetanib in combination with rifampicin compared with vandetanib alone.

The PK parameters for the N-oxide metabolite of vandetanib were also determined. Following a single 300 mg oral dose of vandetanib alone to healthy subjects, C_{max} of the N-oxide metabolite was attained at a median time of 7 hours post dose (range: 4 to 12 hours). Plasma concentrations of the N-oxide metabolite were very low (mean C_{max}: 2.005 ng/mL) and, in some subjects, very flat concentration-time profiles were observed, with plasma concentrations just above the assay LOQ of 1 ng/mL observed up to 384 hours post dose; however, for the majority of subjects N-oxide metabolite plasma concentrations were not quantified by 96 to 240 hours post dose when treated with vandetanib alone. Terminal phases were poorly defined and thus no t½ or AUC were calculable, and the data did not allow the determination of the AUC_{0-504h}.

Following a single 300 mg oral dose of vandetanib in combination with rifampicin, the plasma concentration-time profile of the N-oxide metabolite was altered compared with vandetanib alone. There was a 178.9% increase in the C_{max} (mean: 5.591 ng/mL) and, from the C_{max}, plasma concentrations declined with an initial rapid phase and were non quantifiable in all subjects by 36 hours post dose. A 126.0% increase in AUC_{0-t} is observed for vandetanib in combination with rifampicin (mean: 44.26 ng.h/mL) compared with vandetanib alone (mean: 19.56 ng.h/mL). The exposure to the N-oxide metabolite relative to vandetanib was similar when dosed with vandetanib in combination with rifampicin (mean ratio: 0.02041) compared with vandetanib alone (mean ratio: 0.01774).

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Vandetanib is a BCS Class II compound (low solubility, high permeability) at above pH 6.

Solubility

Vandetanib exhibits pH dependent aqueous solubility and is defined as 'low solubility' under the Biopharmaceutics Classification System (BCS). The equilibrium solubility data (see Table 24) were measured at standard temperature (20 ± 5°C) in aqueous buffer systems.

Table 24. Solubility of vandetanib (in aqueous media)

Buffer	Dissolved vandetanib (mg/ml)
(b) (4)	

Permeability

Bi-directional permeability coefficient at three concentrations (1, 10 and 50 μM) was determined in the Caco-2 cell culture system (Study 02-ASTR-UK.P01R1). Caco-2 monolayers were grown in 12-well Transwell plates. The permeability assay buffer was Hank's Balanced Salt Solution containing 10 mM HEPES and 15 mM glucose at a pH of 7.4. These incubations were performed for 2 hours at 37°C with vandetanib administered in the apical (A→B) or basolateral (B→A) compartment and results and are listed below in Table 25.

Table 25. Permeability Coefficient (P_{eff}) of vandetanib in Caco-2 monolayers (N = 3)

vandetanib (uM)	P_{eff} (A to B), x 10^{-6} (cm/sec)	P_{eff} (B to A), x 10^{-6} (cm/sec)	(B to A) / (A to B) Ratio
1	17.9 ± 0.87	33.2 ± 3.27	0.78
10	23.8 ± 0.17	45.0 ± 0.08	0.75
50	31.2 ± 1.00	16.8 ± 2.00	0.54

Vandetanib was classified as having high permeability coefficients at each concentration evaluated; its absorption in human is not expected to be permeability limited.

Dissolution

(b) (4)

(b) (4)

[redacted]

2.5.2 What is the composition of the to-be-marketed formulation?

What is the composition of the to-be-marketed formulation? Table 27 shows the composition of the to-be-marketed formulation.

Table 27 Quantitative composition of vandetanib 100 and 300 mg white film-coated tablets

Ingredients	100 mg Amount per tablet Amount (mg)	100 mg Amount per tablet Amount (% of tablet core)	300 mg Amount per tablet Amount (mg)	300 mg Amount per tablet Amount (% of tablet core)
Tablet core				
Vandetanib	100.0	(b) (4)	300.0	(b) (4)
Dibasic calcium phosphate dihydrate[a]	(b) (4)			
Microcrystalline cellulose				
Crospovidone				
Povidone				
Magnesium stearate				
(b) (4)				
Core tablet weight (mg)				
Tablet coating				
Hypromellose 2910[c, d]	(b) (4)			
Polyethylene glycol 300[c, e]				
Titanium dioxide[c]				
(b) (4)				
Nominal coated tablet weight (mg)				

[a] An alternative name is calcium hydrogen phosphate dihydrate.
[b] (b) (4)
[c] Coating constituents may be applied using a proprietary mixture, eg, (b) (4) Relative ratios will remain constant.
[d] An alternative name is hydroxypropyl methylcellulose.
[e] An alternative name is Macrogol.
[f] Total tablet weight gain after coating should b (b) (4)
NA Not applicable.

2.5.3 What moieties should be assessed in bioequivalence studies?

The tablets in the pivotal trial have identical quantitative composition to the vandetanib tablet intended for commercial supply. Therefore, no bioequivalence study was required to bridge between the pivotal trial and commercial supply.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A food effect study was completed (Study 24). This was a randomized, open-label, 3-period crossover study. Total sixteen healthy volunteers were randomly allocated to 1 of 2 treatment groups, each of which had 3 study periods with a minimum of 6 weeks between doses of vandetanib:

- **Group 1**: 1 oral dose of vandetanib 300 mg in a fasted state and 2 oral doses of vandetanib 300 mg 30 minutes after consuming a standard high fat breakfast (Treatment order: fasted-fed-fed)

or

- **Group 2**: 1 oral dose of vandetanib 300 mg 30 minutes after consuming a standard high fat breakfast and 2 oral doses of vandetanib 300 mg in a fasted state (Treatment order: fed-fasted-fasted)

The representative PK profiles are shown in Figure 17. The vandetanib exposure appears to be affected by treatment order (Figure 17). This is probably because washout-period was not long enough, although concentrations at pre-dose in second and third sequences are below LLOQ except one subject (ID 5, 5.31 ng/mL at pre-dose in second sequence).

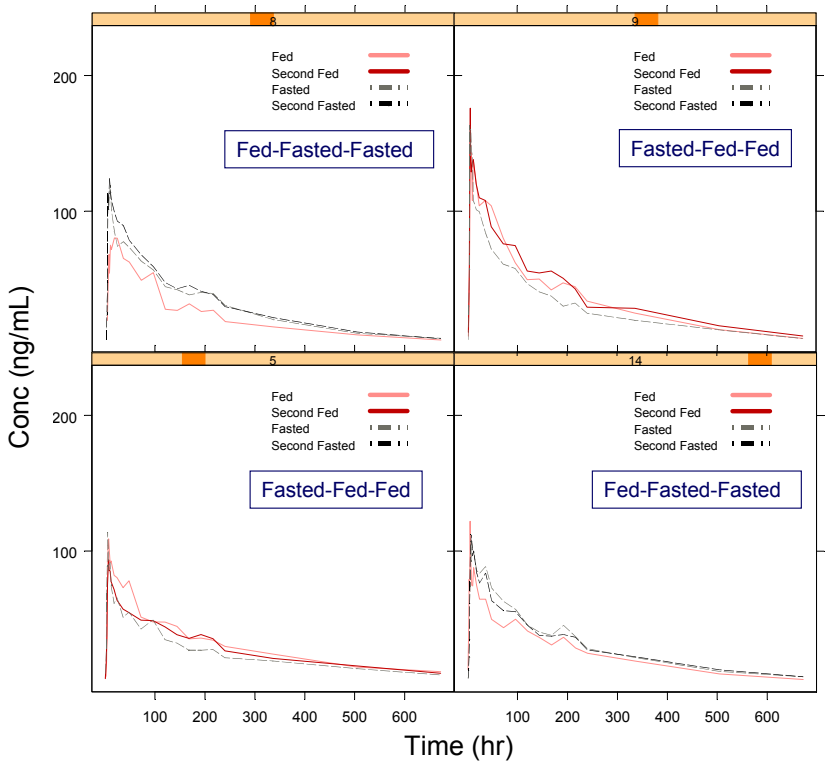


Figure 17. Representative concentration-time profiles from four subjects (ID 5, 8, 9, and 14; FDA Analysis).

Therefore, it is not appropriate to pool all the data regardless of treatment order as the applicant did. The applicant concluded that there was no significant effect on the AUC of vandetanib when dosed with food compared to without (Fed/Fasted ratio = 1.0), and that there was a small (11%) reduction in the mean C_{max} with food, but this was not considered to be clinically significant because the estimated ratios of fed compared with fasted for AUC and C_{max}, and their confidence intervals (CIs), fell within the bioequivalence limits set for this study (0.8, 1.25).

The FDA reviewer analyzed data from only first sequence. The overall food effect on the extent of absorption was a reduction of 10% (Table 28). Mean C_{max} was lower by 17% under the fed condition. Although the lower bounds of the 90% CI were lower than 0.80, it may be due to the small number of subjects. Under the fasted state, C_{max} was achieved at a median of 6 hours post-dose, ranging from 5 to 10 hours. In the fed state, C_{max} was achieved a little later, at a median of 8.5 hours post-dose with a range from 5 to 18 hours. The mean CL/F, V_{ss}/F, and $t_{1/2}$ were comparable between fed and fasted conditions.

Table 28. Ratios of Geometric means (Fed (N=8)/Fasted (N=7); FDA analysis).

PK parameter		GMean	Ratio (90% CI)
$AUC_{0\text{-last}}$ (ng.h/mL)	Fed	18701.69	0.91 (0.79-1.06)
	Fasted	20386.19	
AUC_{inf} (ng.h/mL)	Fed	20511.01	**0.90 (0.78-1.03)**
	Fasted	22709.23	
C_{max} (ng/mL)	Fed	112	0.83 (0.64-1.07)
	Fasted	134	

In conclusion, food has a minimal effect. In the proposed label the applicant suggests that vandetanib tablets be taken with or without food. This is the same dosing instruction that was given to the patients enrolled in the pivotal trial (Study 58).

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Please refer to Biopharmaceutics review posted on DARRTs.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

An assay was developed to determine the concentrations of active metabolites N-desmethyl-vandetanib and vandetanib-N-oxide in plasma and their PK was assessed in Studies 16, 22 and 26 (healthy volunteers) and in Study 57 (NSCLC patients).

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes. Vandetanib was found to be stable in plasma for 24 hours at room temperature (D6474

(b) (4)

[redacted]

3 DETAILED LABELING RECOMMENDATIONS

Labeling recommendations are being communicated directly to the review team. The major recommendation is as follows:

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	**22-405**
Compound	**Vandetanib (300 mg oral once daily) for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC)**
Submission Date	**July 7, 2010**
Clinical Division	**DDOP**
Primary PM Reviewer	**Pengfei Song, Ph.D.** **Anshu Marathe, Ph.D.**
Secondary PM Reviewer	**Christine Garnett, Pharm.D.**

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 Is there an exposure-response relationship for progression free survival (PFS)?

No clear exposure-response relationship could be identified for the primary endpoint, PFS, for patients in the study 58 (D4200C00058). However, the quartile 4 (Q4) of $C_{ss,\ Day\ 56}$ demonstrated the worst PFS among the quartiles. Dose reduction to 200 mg or 100 mg before or on Day 84 showed comparable PFS with dose of 300 mg, suggesting that lower doses might be effective.

PFS was the primary efficacy endpoint of the study 58 following 300 mg once daily oral dose of vandetanib. The observed steady-state plasma vandetanib concentrations at Day 56 after the first dose ($C_{ss,\ Day\ 56}$) from 98% patients (N=226) in vandetanib arm (N = 231) were used as an exposure variable to identify a relationship with PFS. The lack of a clear separation of the Kaplan-Meier curves indicates that there is no clear association between $C_{ss,\ Day\ 56}$ and PFS (Figure 1). Nevertheless, each quartile of $C_{ss,\ Day\ 56}$ demonstrated an improved PFS compared to the placebo arm. For unknown reasons, the quartile 4 (Q4) of $C_{ss,\ Day\ 56}$ demonstrated the worst PFS among the four quartiles.

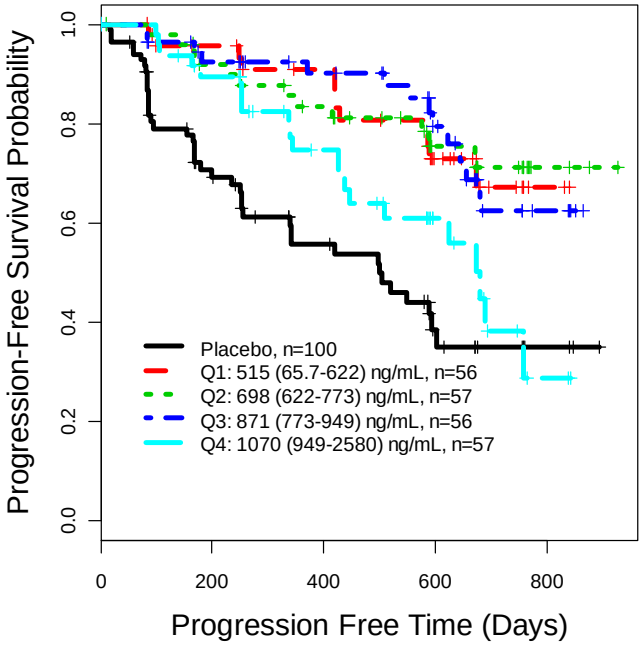


Figure 1. Kaplan-Meier curve of progression free survival for the vandetanib arm (N=226) by quartiles of $C_{ss,\ Day\ 56}$ and for the placebo arm (N=100) of the study 58. Quartile of $C_{ss,\ Day\ 56}$ was expressed as median (range) in the legend. All patients (N = 100) in the placebo arm are included in the Kaplan-Meier curve, regardless follow-up to Day 56 or not.

It is unclear why the Q4 of $C_{ss,\ Day\ 56}$ demonstrated the worst PFS among the quartiles. The key covariates at baseline were compared across quartiles (Table 1), but no clear imbalance in each of these covariates is a reasonable explanation for the poor PFS of the Q4.

Table 1. Summary of demographics of patients (N=226) in vandetanib treatment arm by quartiles of $C_{ss,\ Day\ 56}$ in the study 58

	$C_{ss,\ Day56}$			
Baseline Characteristic	**Q1**	**Q2**	**Q3**	**Q4**
	N	**N**	**N**	**N**
Sex				
Female	18	17	29	33
Male	38	40	27	24
Ethnic origin	5	2	3	3
Caucasian	51	55	53	54
WHO Performance status				
PS = 0	34	39	40	39
PS ≥ 1	22	18	16	18
MTC status				
Sporadic or unknown mutation	53	51	46	48
Hereditary or germline mutation	3	6	10	9
Extent of Disease				
Locally advanced	1	1	5	7
Metastatic	55	56	51	50
Number of prior therapies				
0	36	37	30	36
>=1	20	20	26	21
Response to most recent prior therapy				
NE/unknown BOR to prior therapy	42	50	41	49
Response to prior therapy	1	0	3	0
No response to prior therapy	13	7	12	8
BSA Mean (SD) (m^2)	1.89 (0.25)	1.90 (0.27)	1.78 (0.24)	1.70 (0.19)
Age	51	46	52	52
Death	4	7	8	9
Dose Modifications				
Dose reduction before Day 56	8	2	2	1
Dose of 300 mg unchanged	42	54	54	56
Dose discontinuation	6	1	.	.
Voluntary withdrawal by subject	6	3	1	8
Renal Function				
Creatinine Clearance <90 mL/min	23	16	22	29
Creatinine Clearance < 50 mL/min	1	1	1	3

A sensitivity test suggested that there are no changes in the trend of Kaplan-Meier curves of $C_{ss,Day\ 56}$ quartiles using data from patients who did not undergo any dose modification. As dose modifications (dose reductions to 200 mg or 100 mg, dose discontinuation, dose interruptions) prior to Day 56 may result in lower concentrations on Day 56 and then bias the analysis, a sensitivity test was conducted using all patients (N=189) who did not undergo any dose modification. Results suggested that there are no changes in the trend of Kaplan-Meier curves and the Q4 remains as the worst among quartiles (Figure 17).

Furthermore, an exploratory landmark analysis was conducted to evaluate whether lower doses such as 200 mg or 100 mg demonstrated comparable PFS with those patients who did not

undergo any dose modification prior to Day 84. Results suggested that patients who underwent dose reductions to 200 mg (N=26) or 100 mg (N=3) prior to Day 84 showed comparable Kaplan-Meier curves with patients (N = 180) who are treated by 300 mg of vandetanib once daily (Figure 2).

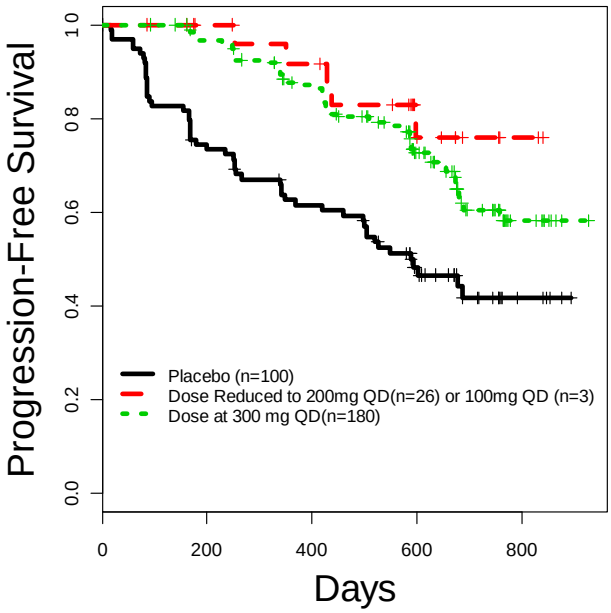


Figure 2. Kaplan-Meier curve of progression free survival for 300 mg once daily (n=180) and those patients who underwent dose reduction to 200 mg (n=26) or 100 mg (n=3) once daily prior to Day 84 after the first dose. Patients whose treatment were permanently discontinued and those who were not followed up to Day 84 are excluded from the analysis. All patients (N = 100) in the placebo arm are included in the Kaplan-Meier curve, regardless of follow-up to Day 84 or not.

1.1.2 Is there an exposure-response relationship for the best calcitonin response?

Yes. Logistic regression analysis indicated that the best calcitonin response is significantly associated with $C_{ss,\ Day\ 56}$ (P=0.0011) (Figure 3), based on the data from 223 patients in the vandetanib arm of the study 58. However, it is difficult to interpret this finding as the relationship between the best calcitonin response and PFS or overall survival has not been established in this patient population to date.

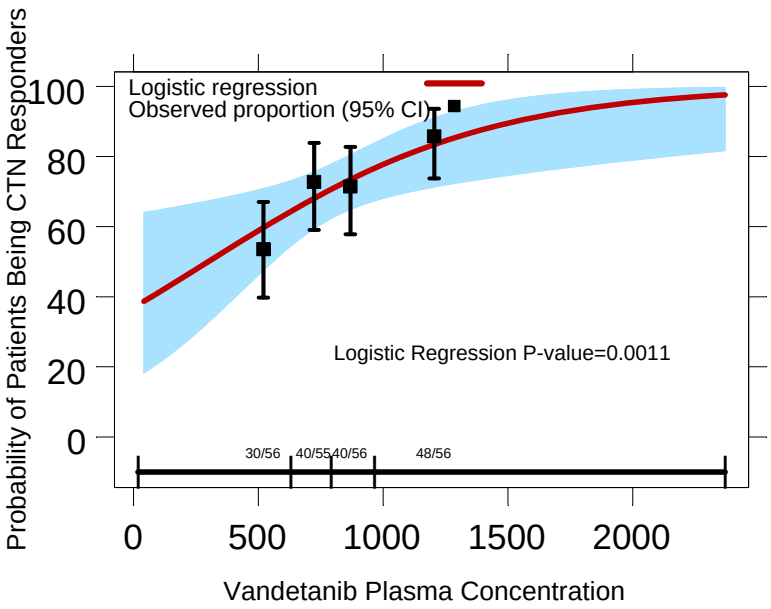


Figure 3. The relationship between the best calcitonin response and the steady-state plasma vandetanib concentrations at Day 56 ($C_{ss,\ Day\ 56}$). Solid black symbols represent the observed proportion of best calcitonin response (CR+PR) in each quartile of $C_{ss,\ Day\ 56}$ from 223 patients in vandetanib arm in the study 58. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represents the mean and 95% confidence interval for the probability of the best calcitonin response. The exposure range in each quartile of $C_{ss,\ Day\ 56}$ is denoted by the horizontal black line along with the number responders/total number of patients in that quartile.

1.1.3 Are there exposure-response relationships for safety (QTc prolongation, diarrhea, fatigue, hypertension, and rash)?

Significant exposure-response relationships were identified for diarrhea and fatigue, but not for hypertension or rash. More importantly, substantial and sustained QTc prolongation was vandetanib concentration-dependent (see QT-IRT review for details).

The most common adverse events that led to dose reductions were QT prolongation, diarrhea, rash, fatigue, and hypertension in the study 58. Due to the low incidence of ≥ grade 3/4 AEs, AEs ≥ grade 2 were used for logistic regression analysis. Results suggested that the probability of diarrhea ≥ grade 2 is significantly associated with $C_{ss,\ Day\ 56}$ (P = 0.025) (left panel of Figure 4). Similarly, the probability of fatigue ≥ grade 2 is significantly associated with $C_{ss,\ Day\ 56}$ (P = 0.02) (right panel of Figure 4). Whereas, no significant exposure-response relationships were identified for either hypertension (left panel of Figure 5) or rash (left panel of Figure 5).

The shallow slopes of the logistic regression models for diarrhea and fatigue project a minimal decrease in AE incidence for dose reductions at a population level, which is consistent with the relatively low incidence of these AEs in the pivotal trial.

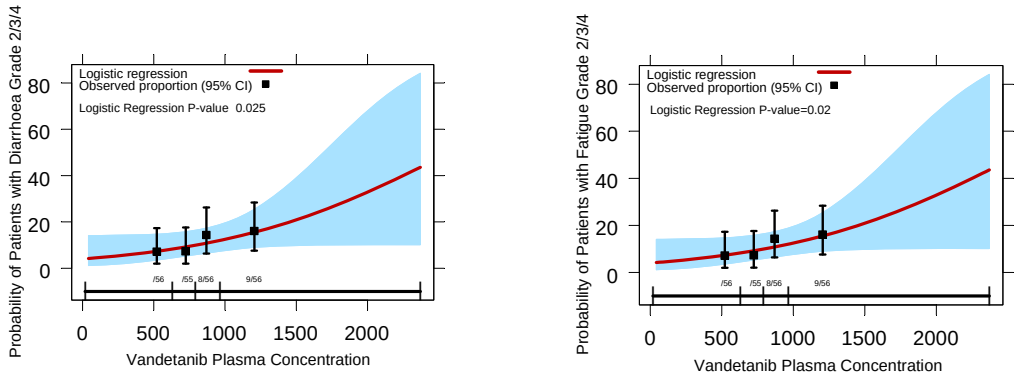


Figure 4. The relationship between $C_{ss,\ Day\ 56}$ and the incidence of ≥ grade 2 adverse events (AEs): diarrhea (left panel) and fatigue (right panel). Solid black symbols represent the observed proportion of patients experiencing ≥ grade 2 AEs in each quartile of $C_{ss,\ Day56}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of ≥ grade 2 adverse events. The exposure range in each quartile of $C_{ss,\ Day\ 56}$ is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

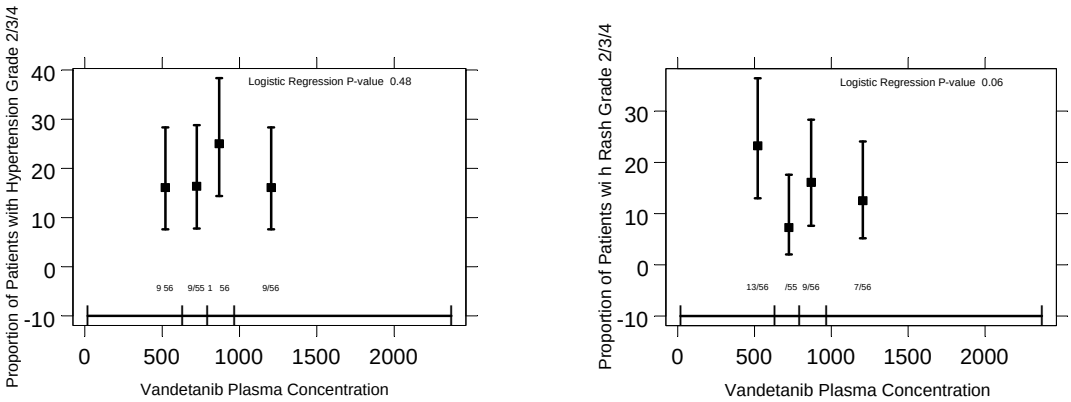


Figure 5. The relationship between $C_{ss,\ Day\ 56}$ and the incidence of ≥ grade 2 adverse events (AEs): hypertension (left panel) and rash (right panel). Solid black symbols represent the observed proportion of patients experiencing ≥grade 2 AEs in each quartile of $C_{ss,\ Day\ 56}$. The vertical black bars represent the 95% confidence interval. The exposure range in each quartile of $C_{ss,\ Day\ 56}$ is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

1.1.4 Does renal function affect the clearance of vandetanib?

Yes. Post-hoc estimates of plasma clearance from the final population pharmacokinetic model suggested that a decrease of clearance in patients with moderate renal impairment (Figure 6). To ensure similar AUCs in patients with moderate renal impairment and those with normal renal function (Figure 7), a reduction of the starting dose from 300 mg oral daily vandetanib to 200 mg oral daily dose is recommended for patients with moderate renal impairment accordingly. No dose reduction is needed for patients with mild renal impairment. This conclusion is

consistent with that from the dedicated renal impairment study (see Clinical Pharmacology review by Dr. Moon). As patient with severe renal impairment were excluded from the pivotal trial, no recommendations can be made for these patients from the population PK approach.

The steady state concentrations of the drug in expected to be higher in patients with renal impairment due to the decrease in drug clearance in these patients. This is likely to increase the QTc prolongation in renal impaired patients because QTc prolongation is shown to be concentration dependent (see the QT-IRT review). The steady state concentrations of vandetanib in renal impaired patients were not available. Thus, simulations were performed to calculate the drug concentrations at steady state in patients with normal renal function and patients with renal impairment (see Section 3.2 for details). With the simulated concentrations, the ΔQTcF for patients with severe renal impairment at steady-state C_{max} was predicted to be higher (39 ms) than patients with normal renal function (35 ms) (see the QT-IRT review for details).

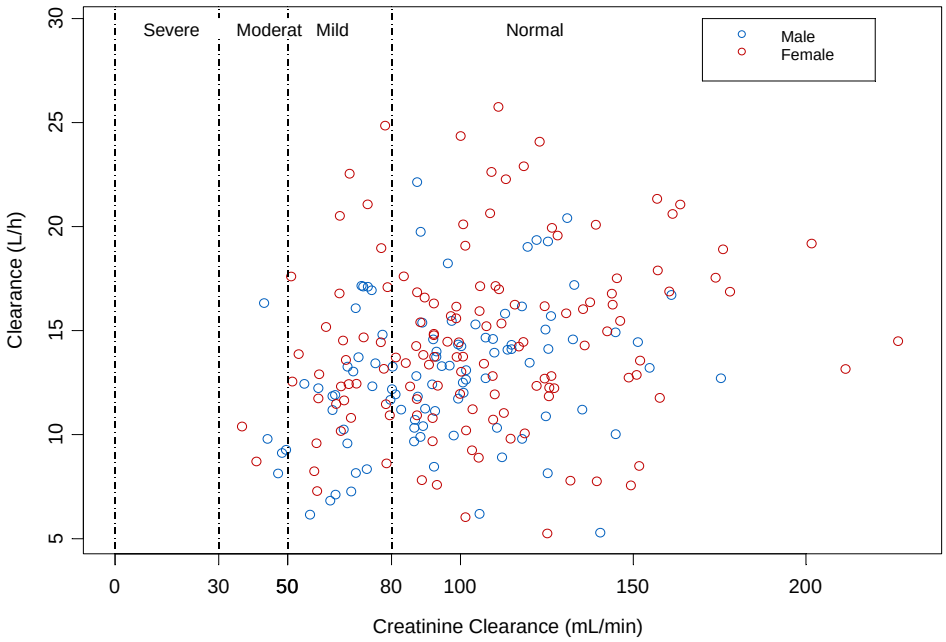


Figure 6. Estimated plasma vandetanib clearance vs. creatinine clearance in patients (N=231) with meduallary thyroid cancer in the vandetanib arm of the study 58. The plasma vandetanib clearance is presented in red for females and black blue for males. The renal function was classified as normal (> 90 mL/min), mild impairment (60-90 mL/min), moderate impairment (30-60 mL/min), and severe impairment (< 30 mL/min). Patients with severe renal impairment were excluded from the study 58.

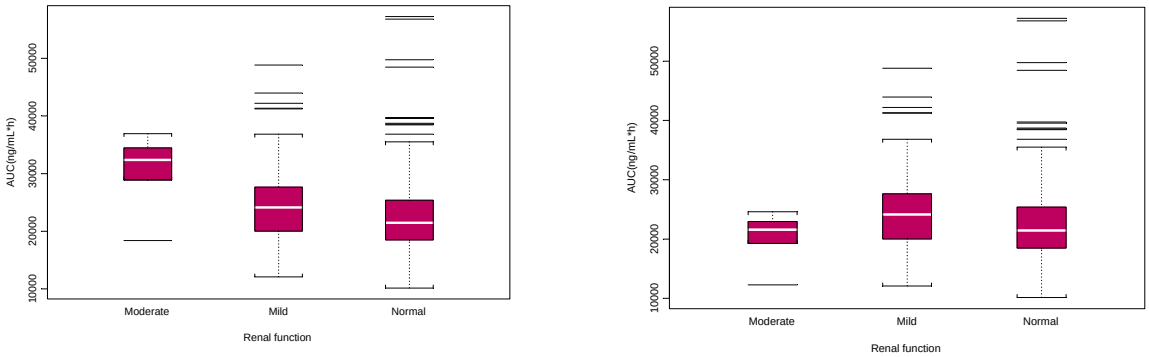


Figure 7. Boxplots for model-predicted AUCs with a 300 mg oral daily dose (left panel) and with a 200 mg oral daily dose of vandetanib (right panel) in patients with moderate renal impairment. AUCs were based on post-hoc estimates of clearance for patients (N=231) in the vandetanib arm of the study 58. In patients with mild impairment or normal renal function, the dose of vandetanib is 300 mg oral daily. The renal function was classified as normal (> 80 mL/min), mild impairment (50-80 mL/min), moderate impairment (30-50 mL/min), and severe impairment (< 30 mL/min). Patients with severe renal impairment were not available as these patients were excluded from the study 58.

1.1.5 Does BSA affect the pharmacokinetics of vandetanib?

Yes. Body weight was included as a significant covariate for clearance and central volume of distribution (Figure 8) in the final population PK model. The inclusion of the covariates resulted in a decrease in the inter-individual variability in clearance, central and total volume of distribution from 32.9, 54.9, and 106% to 30.9, 52.0, and 101%, respectively.

In addition, the reviewer conducted a linear regression analysis to explore the relationship between body weight and $C_{ss,\ Day56}$. Results suggested that body weight contributed significantly to the variability of in $C_{ss,\ Day56}$ (R^2=0.0724, P < 0.0001) (Figure 9, left). Median of the lowest and highest quartiles of body weight showed 19.9% higher and 14.5% lower of $C_{ss,\ Day56}$, respectively, than the overall median of body weight (Figure 9, right).

Therefore, the reviewer agrees to the applicant's conclusion that the effect of body weight is not considered to be of clinical importance, given the small decrease of inter-individual variability in the final population PK model with body weight as covariate, and the small increase of $C_{ss,\ Day56}$ in patients with low body weight.

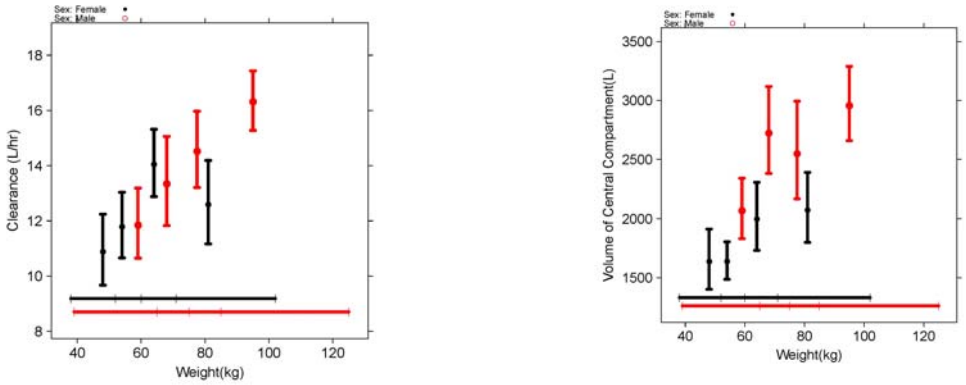


Figure 8. The fixed effect of body weight on the clearance (left) and central volume of distribution (right) of vandetanib for male (in red) and female (in black). The body weight quartiles are denoted by the horizontal black line. The clearance and central volume of distribution are the post-hoc estimates for 231 patients in Study 58.

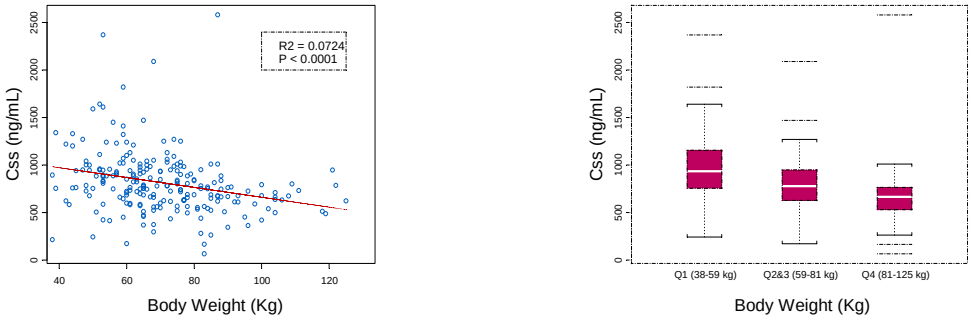


Figure 9. The relationship between body weight and $C_{ss,\ Day\ 56}$ in 226 patients who took 300 mg of vandetanib once daily orally in the study 58.

1.2 Recommendations

Division of Pharmacometrics finds that the NDA 22405 is acceptable from a clinical pharmacology perspective provided that a satisfactory agreement is reached between the Applicant and the Agency regarding labeling language.

1.3 Label Statements

Only relevant clinical pharmacology sections are included. Double underlines indicate content that was added by the agency and ~~strikethroughs~~ indicate content taken out by the agency.

12.3 Pharmacokinetics

A population pharmacokinetic analysis of vandetanib was conducted in 231 patients with MTC following oral administration of 300 mg daily dose. The pharmacokinetics of vandetanib at the 300 mg dose in MTC patients are characterized by a mean clearance of approximately 13.2 L/h, a mean volume of distribution of approximately 7,450 L, and a mean plasma half-life of 19 days.

2 APPLICANT'S ANALYSES

The applicant performed population PK and PK-PD analyses using data from all 231 patients in the vandetanib treatment arm in pivotal study 58. The key findings from the Applicant's analyses are summarized below:

2.1 Population Pharmacokinetic Analysis

The objectives were to summarize the pharmacokinetics of vandetanib and investigate the influence of fixed effects on pharmacokinetic parameters describing the observed concentration in this patient population.

2.1.1 Method

Study 58 is a Phase 3 randomized trial to support the efficacy of vandetanib for metastatic medullary thyroid cancer. A total of 331 patients were actually randomized with 231 randomized to receive vandetanib (oral administration of 300 mg vandetanib once daily) and 100 patients to receive the placebo. Sparse pharmacokinetic samples were obtained between 4 and 8 hours post dose during weeks 1, 2, 4, 8, 12, and then every 12 weeks up to and including discontinuation of vandetanib/placebo. During preliminary PK evaluation, 1 patient (Patient 178) was identified as a PK outlier and was subsequently excluded from all analyses. Therefore, a total of 1617 concentration observations from 230 patients collected over up to 515 days were used for model development.

The demographic of 231 patients were summarized in Table 2.

Table 2. Summary of demographics of 231 patients in vandetanib arm in Study 58

Racial group (Caucasian n=218, American Black n=1, Asian=8, Other n=4)
Gender: 97 Females, 134 Males

	Mean	Median	SE	SD	Highest	Lowest	Number of patients
Age (years)	50.7	50.0	0.9	14.1	83	18	231
Weight (kg)	70.4	68.0	1.1	17.3	125	38	231
BSA (m^2)	1.82	1.80	0.02	0.26	2.5	1.2	227
CrCL (mL/min)	101.4	98.9	2.1	32.5	227	37	231
ALT (IU)	23.11	18.00	1.15	17.42	150	6	231
AST (IU)	24.8	21.0	0.8	12.0	91	7	231
AP (IU)	94.9	75.0	4.6	69.5	535	29	231
Albumin (g/dL)	45.2	46.0	0.3	3.8	54	28	231
Bilirubin (mg/dL)	11.79	10.00	0.36	5.44	46	3	231

BSA=Body surface area, CrCL=Creatinine clearance, ALT= Alanine aminotransferase, AST=Aspartate aminotransferase, AP=Alkaline phosphatase

Source: Table 2 on Page 18 of the Study report entitled "Population Pharmacokinetic (PK) and Pharmacokinetic-Pharmacodynamic (PK-PD) Analysis"

The population PK analysis was performed using NONMEM (Version 6.1) running under the Digital Visual Fortran compiler (FORTRAN 90, Version 5.0) on a Dell PC (Microsoft Windows 2003). The program PDx-Pop (Version 3.0, ICON Development Solutions) was used as an interface with NONMEM.

Log-transformed concentration data and a proportional error model were used for model development. All runs were performed using first order conditional estimate (FOCE) method with the interaction option. The relationships between the individual estimates and the

covariates were investigated. Demographic characteristics such as age, sex, race, weight, body surface area (BSA), liver function (bilirubin, albumin, ALT, AST, and AP), and renal function (creatinine clearance, CLCR) were tested as potential model covariates.

2.1.2 Conclusions

A two-compartment open model with first order absorption and first order elimination from the central compartment, with Ka fixed to that estimated from previous studies with rich data was found to best describe the vandetanib concentration-time data following multiple doses of 300 mg vandetanib in cancer patients.

The effect of weight on clearance and weight on initial and peripheral volume of distribution were identified as significant. The mean estimated clearance for median weight (68 kg) was 13.2 ± 0.306 L/h. However, the reduction in interindividual variability relative to the model without covariates was only 2.0% for CL/f, while inter-individual variability was reduced by 2.9% for V2/f and by 5% for V3/f. As the percentage of variability explained by these covariates was minimal, these effects are not considered to be of clinical importance.

The mean effective half-life was 19.0 days (Table 4). There was no discernable difference between male and female patients in their pharmacokinetics. The vast majority of the patients were Caucasians (95%), therefore differences between racial groups could not be conclusively evaluated.

Parameter estimates for fixed effect and random effects with standard errors are presented in Table 3. Basic goodness of fit plots from the sponsor's final model are presented in Figure 10.

Table 3. Applicant's population PK parameter estimates using base and final models

		Basic					Final				
Parameter		**Mean**	**SE**	**%CV**	**η(%)**	**η[1](%)**	**Mean**	**SE**	**%CV**	**η(%)**	**η[1](%)**
CL/f (L.hr^{-1})		θ_1					θ_1 * (weight/67) $^{\theta 4}$				
	θ_1	13.3	0.321	2.44	32.9	8	13.2	0.306	2.32	30.9	9
	θ_6						0.428	0.0796	18.6	-	
V_2/f (L)		θ_2					θ_2 *(weight/67)				
	θ_2	2090	105	5.07	54.9	24	2100	104	4.95	52.0	25
V_3/f (L)		θ_3					θ_3				
	θ_3	5330	544	10.2	106	32	5350	536	10.0	101	32
Q/f (L.hr^{-1})		θ_4					θ_4				
	θ_4	11.0	0.783	7.07	-		10.7	0.778	7.27	-	
Ka (h^{-1})		θ_5					θ_5				
	θ_5	0.3 (fixed)					0.3 (fixed)				
Residual error ($100*\sqrt{\sigma^2}$)				17.9					17.9		
Minimisation				FOCEI					FOCEI		
Obj				-2921.318					-2959.415		

[1] Eta Shrinkage
Mean The population mean parameter value
SE The standard error of the mean
%CV The SE/Mean * 100 (percentage of the mean)
η The inter-subject variability
Obj NONMEM objective function

Source: Table 20 on Page 33 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf'

Table 4. Applicant's secondary population PK parameter estimates using final model for all patients

	Accumulation ratio	Steady state C_{max} 4 hours post dose day 56 ($ng.mL^{-1}$)	Clearance ($L.h^{-1}$)	Steady state trough day 56 ($ng.mL^{-1}$)	Half-life (days)	Steady state exposure day 56 ($ng.h.mL^{-1}$)
Mean	7.70	810	13.84	754	18.95	18782
SE	0.218	19.3	0.267	18.2	0.747	451
Median	6.94	794	13.44	731	15.90	18377
SD	3.31	293	4.05	276	11.33	6842
Minimum value	0.509	61	5.24	61	4.18	1445
Maximum value	20.39	2241	29.59	2105	84.77	52714
Number of patients	230	230	230	230	230	230

Source: Table 24 on Page 35 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf'

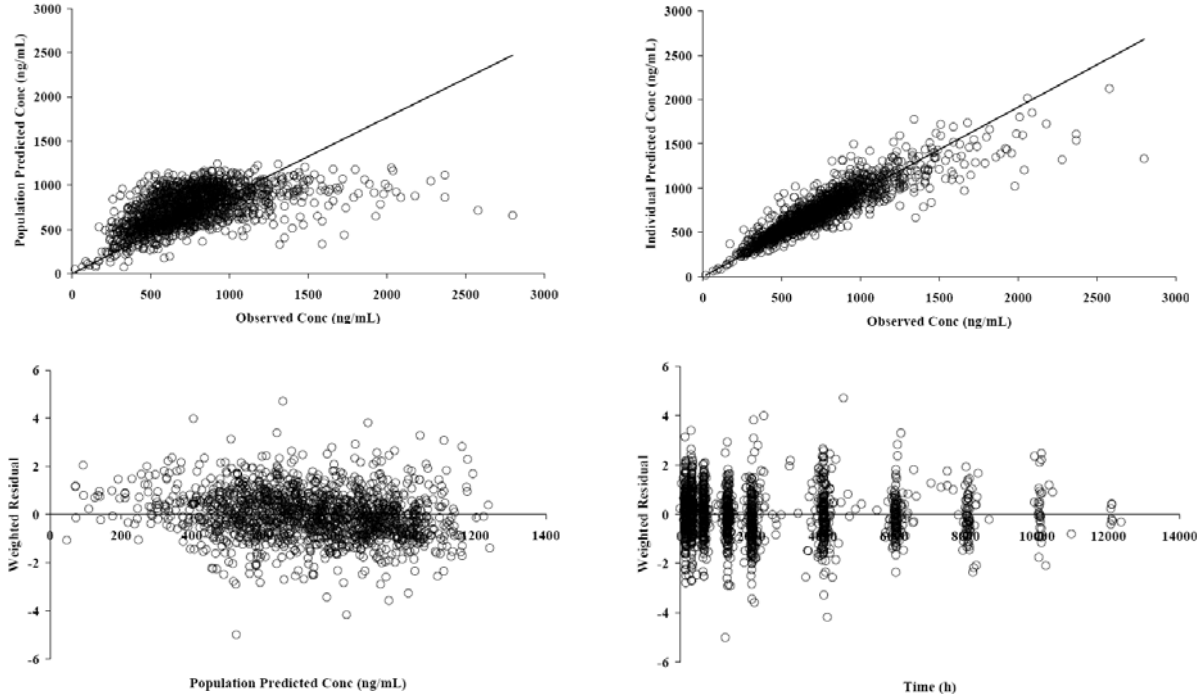


Figure 10. Basic goodness of fit plots for the Applicant's final model**.**

Source: Figure 69-72 on Page 88-89 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf'

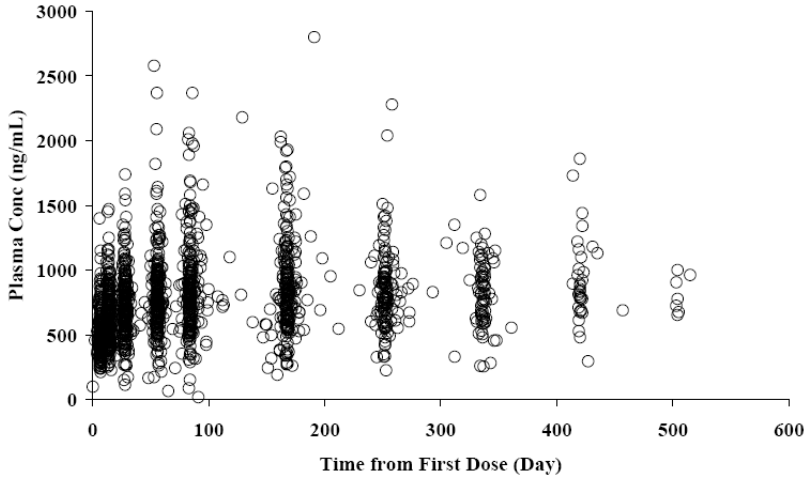


Figure 11. Observed vandetanib plasma concentrations over time (0–597 days) post first dose

Reviewer's comments:

The applicant's population PK analysis followed reasonable model selection and optimization in describing the pharmacokinetics of vandetanib in patients with unresectable locally advanced or metastatic medullary thyroid cancer.

The reviewer obtained identical results by repeating the Applicant's population PK analysis using NONMEM under a Linux cluster. The reviewer agrees that the effects of body weight are not considered to be of clinical importance, given the small magnitudes of decrease of inter-individual variability in the final population PK model and the small increase of $C_{ss,Day56}$ *in patients with low body weight.*

In addition, though the renal function was not identified as a significant covariate (possibly due to few number of patients with moderate renal impairment), post-hoc estimates suggested a trend of lower clearance in patients with moderate renal impairment when compared to patients with normal renal function. This finding is consistent with the conclusion of the dedicated renal impairment study.

2.2 Exposure-Response Analysis

The objective was to provide a PK/PD (descriptive or statistical) evaluation of vandetanib using predicted concentrations and drug exposure in relation to the relevant efficacy (progression-free survival and response), pharmacodynamic (QTc), and adverse event (incidence of rash, hypertension, diarrhea etc) parameters.

2.2.1 Method

PK parameter estimates

Individual PK parameter estimates (predicted concentration at time of progression, predicted concentration or steady-state exposure at Day 56) were computed for each patient from the population parameters obtained in the final population PK model.

PK/PD analysis

The exploratory PK/PD analysis was conducted for the efficacy and safety data obtained from pivotal study 58. Exposure-response relationship were explored for the primary endpoint PFS, secondary endpoints including best objective response and biochemical response (calcitonin and carcinoembryonic antigen). Furthermore, the exposure-response relationships were explored for safety variables including QTc prolongation, rash, diarrhea, hypertension, interstitial lung disease.

2.2.2 Conclusions

Efficacy

1. PFS

No clear relationships between pharmacokinetics and progression-free survival (Figure 12) or overall survival (Figure 13) were identified.

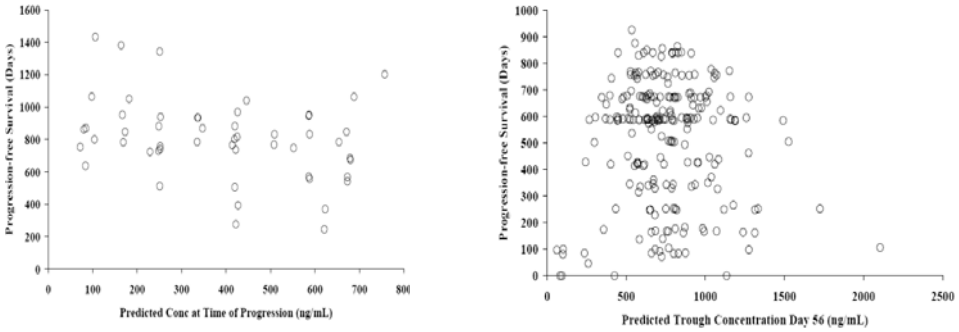


Figure 12. Relationship of progression-free survival to predicted concentration at the time of progression (left panel) and trough concentration at Day 56 (right panel).

Source: Figure 120 and 121 on Page 114 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf';

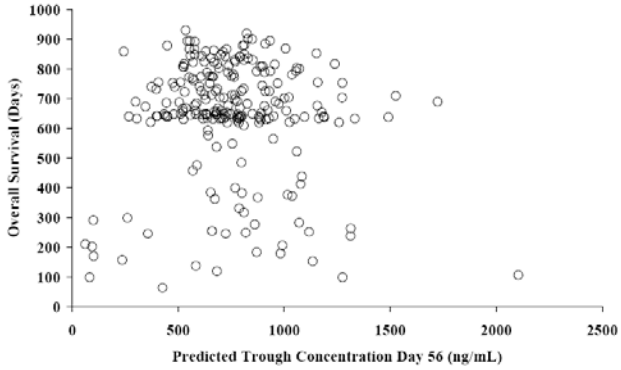


Figure 13. Relationship of overall survival to predicted trough concentration at Day 56.

Source: Figure 123, on Page 115 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf';

2. Best biochemical response (calcitonin, carcinoembryonic antigen)

A non-linear relationship was observed between predicted plasma concentrations and serum calcitonin. No clear relationships could be established between predicted plasma concentrations and serum carcinoembryonic antigen.

Calcitonin (CTN) concentrations appear to decrease over the course of the study (Figure 14). Additionally, CTN concentrations appear to decrease with increasing predicted vandetanib concentration (Figure 15). PD parameters from a sigmoidal Emax model that best fits the log-transformed CTN data are shown in Table 5.

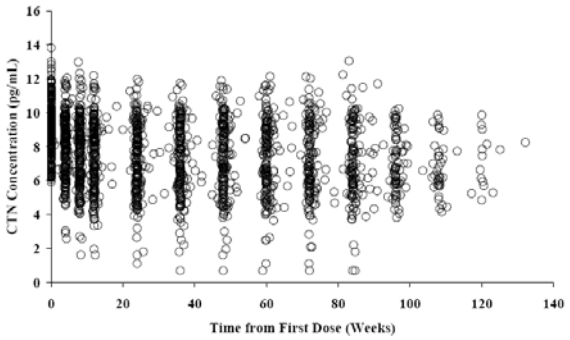


Figure 14. Individual log-CTN concentrations as a function of time from the first dose

Source: Figure 101, on Page 104 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf';

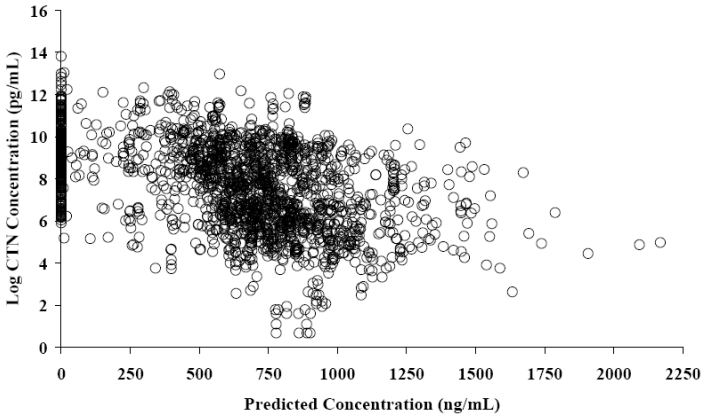


Figure 15. Individual log-CTN concentrations as a function of the patients predicted plasma concentrations

Source: Figure 103, on Page 105 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf';

Table 5. Pharmacodynamic parameter estimates from the final sigmoidal calcitonin Emax model for vandetanib

Parameter estimate	Mean	% SE	95% confidence limit	
			Upper	Lower
Baseline	8.90	1.11	9.09	8.71
Emax	3.01	11.2	3.67	2.35
EC_{50} ($ng.mL^{-1}$)	816	8.39	950	682
γ	3.25	15.7	4.25	2.25
η Baseline (%CV)	14.9			
η Emax (%CV)	57.4			
η EC_{50} (%CV)	44.7			
σ (% CV)	8.18			

Confidence intervals based on inter-individual variance

3. Best response

The relationship of the best response was analyzed as a function of the observed or predicted steady-state (Day 56) exposure using a probability model. Based upon the observed data using the steady-state (day 56) exposure as a predictor, results indicate that a steady-state AUC of 7.4 µg.h/mL is required for the probability of stable disease to be 50% or more while a steady-state AUC of >19 µg.h/mL is required for the predicted probability of partial response to be 50% or more. Similarly, results indicate that a steady-state AUC of at least 7.05 µg.h/mL is required for the probability of stable disease to be 50% or more while a steady-state AUC of 20.77 µg.h/mL or greater is required for the predicted probability of partial response to be 50% or more.

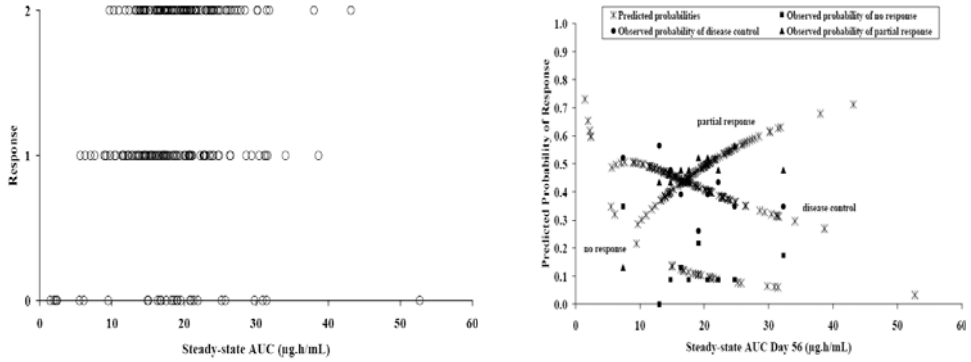


Figure 16. Observed response versus steady-state exposure on Day 56 (0: no response, 1: disease control, 2: partial response) (left panel) and Predicted probabilities of response as a function of predicted steady-state exposure on Day 56

Source: Figure 125-126, on Page 116-117 of the study report entitled 'd4200c00058-12-1-13-population-pk-pd-report.pdf';

Safety

- A concentration-dependent increase in QTcF was observed. See sections 4.2.8.4.2 and 5.3 of the QT-IRT review for details._
- No clear relationship between pharmacokinetics and adverse events were determined in this study. This may be the result of the limited number of patients experiencing adverse events at CTC grade ≥3 during the course of the study, with only 6.5% reporting rash, 10.9% diarrhea and 7.0% hypertension at CTC grade ≥3, whilst only 0.87% had an ILD (pneumonitis) and 15.2% had QTc related adverse events.

3 REVIEWER'S ANALYSIS

3.1 Exposure-Response Analysis

3.1.1 Objectives

The objectives of the reviewer's analyses are:

- To explore the exposure-efficacy relationship using the primary endpoint, progression-free survival (PFS) and the secondary endpoints, best calcitonin response in the pivotal trial
- To explore exposure-safety relationships for diarrhea, rash, fatigue, and hypertension

3.1.2 Methods

The observed steady-state plasma vandetanib concentrations at Day 56 ($C_{ss, Day56}$) from 226 patients in Vandetanib arm (N= 231) were used as a drug exposure variable for all the exposure-response analyses. Kaplan Meier analysis was applied to establish a relationship between quartiles of $C_{ss, Day56}$ and PFS. Logistic regression method was applied to analyze the relationships between $C_{ss, Day56}$ and calcitonin response, diarrhea, fatigue, or hypertension.

3.1.2.1 Data Sets

Data sets used in the analysis are summarized in Table 6.

Table 6.: Analysis datasets

Study Number	Name	Link to EDR
D4200C 00058	alldata.xpt fdareq9.xpt r-ex.xpt r-lb.xpt reclana1.xpt	(b) (4)

3.1.2.2 Software

SAS 9.2 and S-PLUS 7 (Version 7.0) and NONMEM (Version 6.2) were used for the reviewer's analyses.

3.1.3 Results

3.1.3.1 Efficacy

No significant exposure-response relationship could be identified for PFS. The probability of the best calcitonin response is significantly related with $C_{ss, Day56}$ (P=0.0011). However, it is difficult to interpret this significance as the relationship between the best calcitonin response and PFS or overall survival has not been established in this patient population to date.

PFS:

PFS was the primary efficacy endpoint of the study 58 following 300 mg once daily oral dose of vandetanib. The observed steady-state plasma vandetanib concentrations at Day 56 after the first dose ($C_{ss, Day 56}$) from 98% patients (N=226) in vandetanib arm (N = 231) were used as an exposure variable to identify a relationship with PFS. The lack of a clear separation of the Kaplan-Meier curves indicates that there is no clear association between $C_{ss, Day 56}$ and PFS (Figure 1). Nevertheless, each quartile of $C_{ss, Day 56}$ demonstrated an improved PFS compared to the placebo arm. For unknown reasons, the quartile 4 (Q4) of $C_{ss, Day 56}$ demonstrated the worst PFS among the four quartiles.

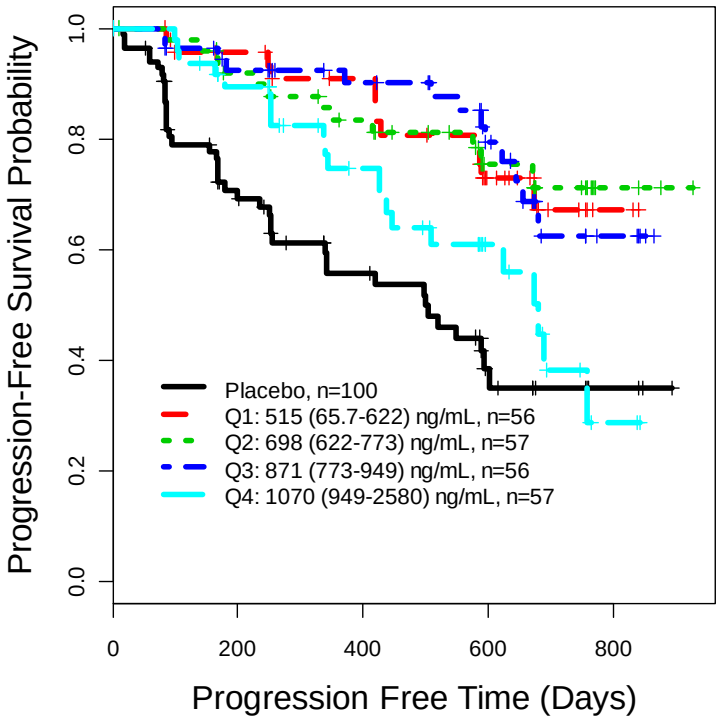


Figure 1. Kaplan-Meier curve of progression free survival for the vandetanib arm (N=226) by quartiles of $C_{ss, Day 56}$ and for the placebo arm (N=100) of the study 58. Quartile of $C_{ss, Day 56}$ was expressed as median (range) in the legend. All patients (N = 100) in the placebo arm are included in the Kaplan-Meier curve, regardless follow-up to Day 56 or not.

A sensitivity test suggested that there are no changes in the trend of Kaplan-Meier curves of $C_{ss, Day\ 56}$ quartiles using data from patients who did not undergo any dose modification. As dose modifications (dose reductions to 200 mg or 100 mg, dose discontinuation, dose interruptions) before or on Day 56 may result in lower concentrations at Day 56 and then bias the analysis, a sensitivity test was conducted using all patients (N=189) who did not undergo any dose modification. Results suggested that there is no change in the trend of Kaplan-Meier curves of $C_{ss, Day\ 56}$ quartiles and the Q4 remains as the worst among quartiles (Figure 17).

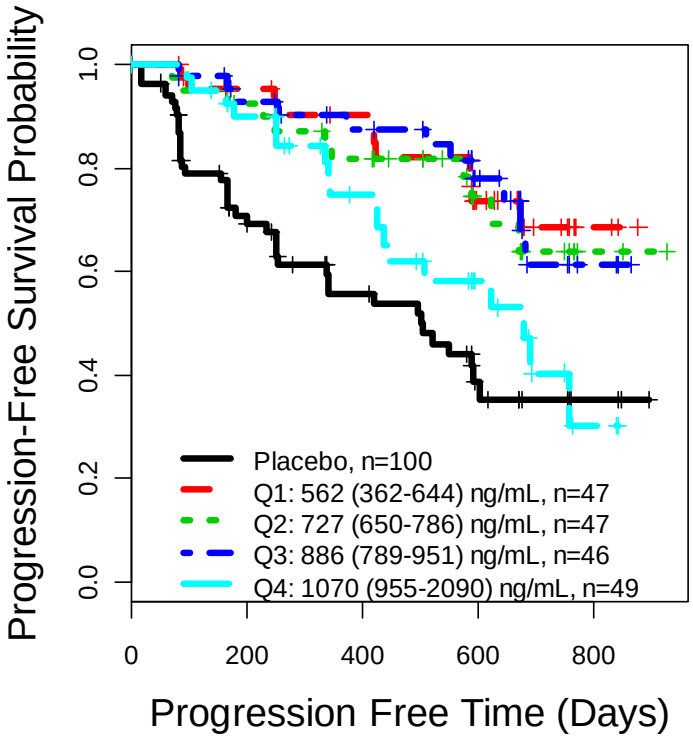


Figure 17. Kaplan-Meier curve of progression free survival by quartiles of $C_{ss, Day\ 56}$ for patients who did not undergo dose modifications (dose reductions, dose interruptions, or discontinuation) in the vandetanib arm (N=189) and for the placebo arm (N=100) of the study 58. Quartile of $C_{ss, Day\ 56}$ was expressed as median (range) in the legend. All patients (N = 100) in the placebo arm are included in the Kaplan-Meier curve, regardless follow-up to Day 56 or not.

Any exploratory analysis suggested that lower doses such as 200 mg or 100 mg may demonstrate comparable PFS using landmark analysis at Day 84 (Figure 2). Patients who underwent dose reductions to 200 mg or 100 mg before or on Day 84 showed comparable Kaplan-Meier curve with those who are treated by 300 mg once daily vandetanib.

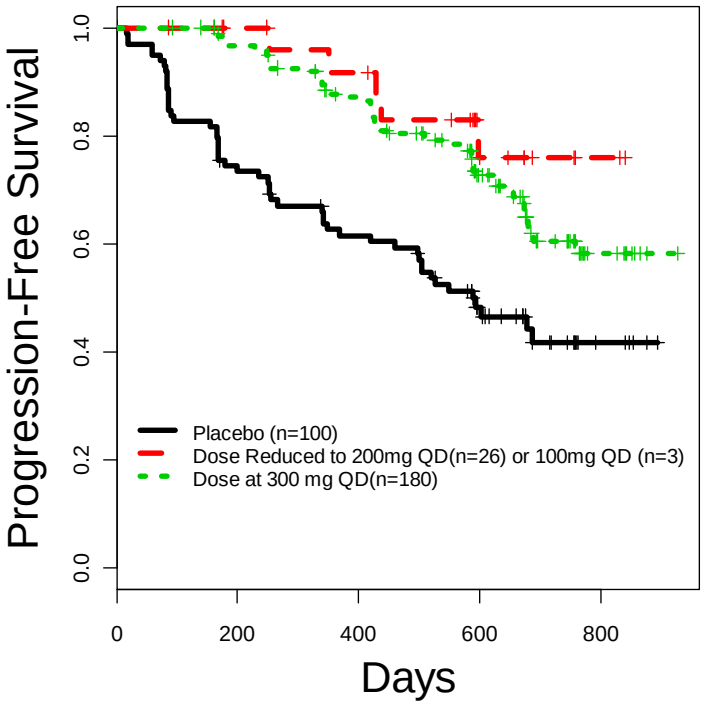


Figure 2. Kaplan-Meier curve of progression free survival for 300 mg once daily (n=180) and those patients who underwent dose reduction to 200 mg (n=26) or 100 mg (n=3) once daily on Day 84 after the first dose, using a landmark analysis. All patients in the placebo arm are included in the Kaplan-Meier curve, regardless follow-up to Day 84 or not. Patients whose treatment were permanently discontinued and those who were not followed to Day 84 are excluded from the landmark analysis.

Best calcitonin response:

Serum calcitonin is a tumor biomarker of MTC. Measurement of calcitonin is routinely used in clinical practice to monitor the progression of disease, as CTN levels are associated with tumor burden. High levels of calcitonin are also associated with diarrhea and flushing, common symptoms in patients with metastatic MTC.

In the pivotal trial study 58, calcitonin ≥ 500 pg/mL is used as one of the inclusion criteria. As a secondary efficacy endpoint, the best calcitonin response is defined as complete response (CR) plus partial response (PR). Specifically, CR was defined as complete normalization of serum calcitonin, confirmed by a repeat assessment > 4 weeks later. PR was defined as a decrease of > 50% in serum calcitonin from baseline, confirmed by a repeat assessment > 4 weeks later.

Data of the best calcitonin response and $C_{ss,\ Day56}$ were available in 223 patients out of 231 patients in the vandetanib arm of the pivotal trial following 300 mg once daily dose of vandetanib (Figure 3).

Logistic regression analysis suggested that the probability of the best calcitonin response is significantly related with $C_{ss, Day56}$ (P=0.0011) (Figure 3). However, it is difficult to interpret this significance as the relationship between the best calcitonin response and PFS or overall survival has not been established in this patient population to date.

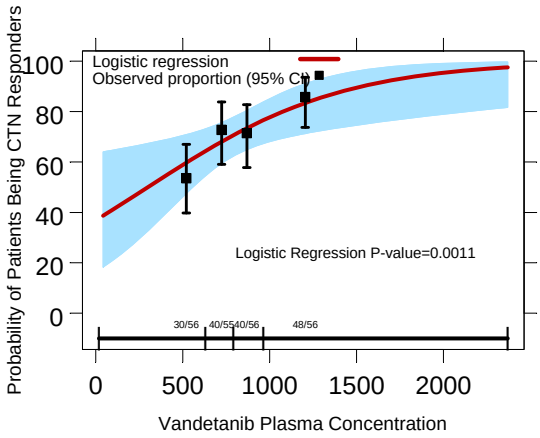


Figure 3. The relationship between the best calcitonin response and the steady-state plasma vandetanib concentrations at Day 56 ($C_{ss, Day 56}$). Solid black symbols represent the observed proportion of best calcitonin response (CR+PR) in each quartile of $C_{ss, Day 56}$ from 223 patients in vandetanib arm in the study 58. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represents the mean and 95% confidence interval for the probability of the best calcitonin response. The exposure range in each quartile of $C_{ss, Day 56}$ is denoted by the horizontal black line along with the number responders/total number of patients in that quartile.

3.1.3.2 Safety

Significant exposure-response relationships were identified for diarrhea and fatigue, but not for hypertension or rash. More importantly, substantial and sustained QTc prolongation was vandetanib concentration-dependent (see QT-IRT review for details).

The most common adverse events that led to dose reduction were diarrhea, QT prolongation, and rash and hypertension and fatigue in the pivotal study 58. Due to the low incidence of ≥ grade 3 of the above AEs, AEs ≥ grade 2 were used for logistic regression analysis. Results suggested that the probability of diarrhea ≥ grade 2 is significantly related with $C_{ss, Day56}$ (P = 0.025) (left panel of Figure 4). Similarly, the probability of fatigue ≥ grade 2 is significantly related with $C_{ss, Day 56}$ (P = 0.02) (right panel of Figure 4). However, no significant exposure-response relationships were identified for hypertension or rash (Figure 5).

The shallow slops of the logistic regression models for diarrhea and fatigue project a minimal decrease in AE incidence for dose adjustments, which is consistent with the relatively low incidence of these AEs in the pivotal trial.

In the pivotal trial, dose reductions to 200 mg and then 100 mg were practiced for AEs. Of the 231 patients who started treatment with 300 mg vandetanib, 70 (30.3%) remained on the starting dose of 300 mg daily until the date of data cutoff; 51 (22.0%) stopped 300 mg vandetanib because of disease progression; and 27 (11.7%) stopped 300 mg vandetanib for AEs or other reasons. Of the 83 (35.9%) patients who required a dose reduction, 81 (35.1%) had their dose reduced to 200 mg daily, and 2 (0.9%) were reduced directly to 100 mg daily. Of the 81 patients

who received the 200 mg dose, 24 (10.4%) remained on the 200 mg dose until the date of data cutoff; 15 (6.5 %) stopped because of disease progression; and 12 (5.2%) stopped for AEs or other reasons. A total of 30 (13.0%) patients required further dose reduction, 29 (12.6%) patients were reduced directly to 100 mg daily, and 1 (0.4%) patient was reduced to 200 mg every other day before receiving 100 mg daily.

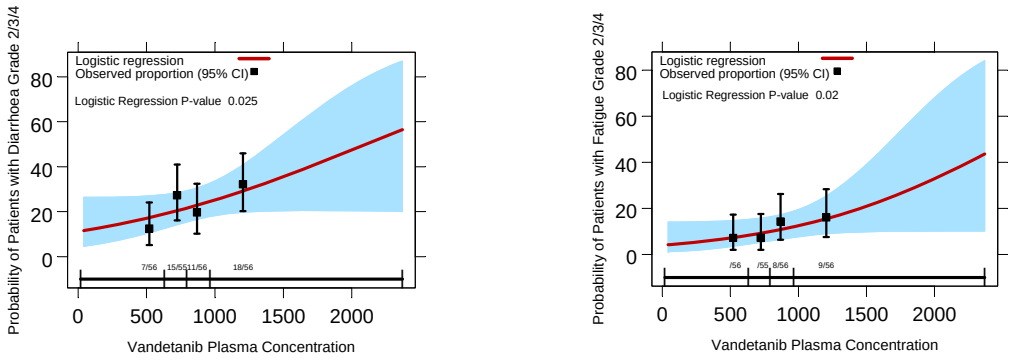


Figure 4. The relationship between $C_{ss,\ Day\ 56}$ and the incidence of ≥ grade 2 adverse events (AEs): diarrhea (left panel) and fatigue (right panel). Solid black symbols represent the observed proportion of patients experiencing ≥ grade 2 AEs in each quartile of $C_{ss,\ Day56}$. The vertical black bars represent the 95% confidence interval. The solid red line and shaded area represent the predicted mean and 95% confidence interval for the probability of ≥ grade 2 adverse events. The exposure range in each quartile of $C_{ss,\ Day\ 56}$ is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

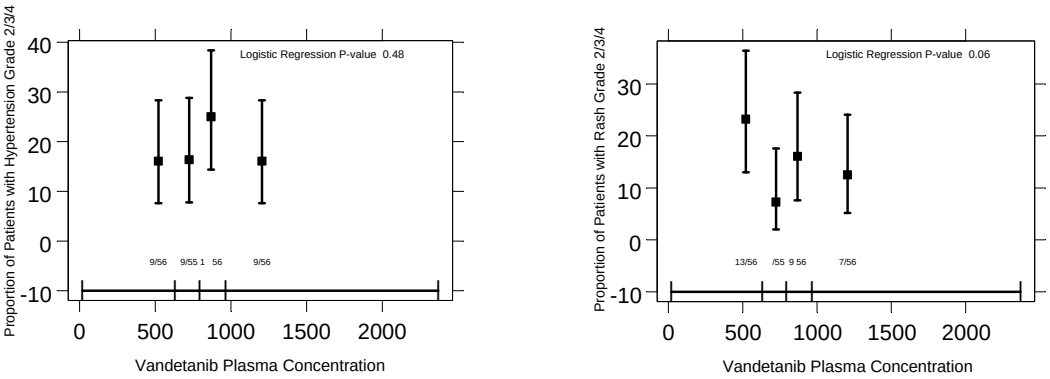


Figure 5. The relationship between $C_{ss,\ Day\ 56}$ and the incidence of ≥ grade 2 adverse events (AEs): hypertension (left panel) and rash (right panel). Solid black symbols represent the observed proportion of patients experiencing ≥grade 2 AEs in each quartile of $C_{ss,\ Day\ 56}$. The vertical black bars represent the 95% confidence interval. The exposure range in each quartile of $C_{ss,\ Day\ 56}$ is denoted by the horizontal black line along with the number of patients with AEs/total number of patients in each quartile.

3.2 Effect of Renal Impairment on Steady State Vandetanib Concentration

Population PK parameters from the sponsor's final model were used to simulate the profile for normal patients (Table 3). The drug clearance (CL/F) for patients with mild, moderate and severe renal impaired patients were calculated using the ratio of clearance in renal impaired patients to clearance in normal subjects observed in the dedicated study. For example, the clearance in patients with mild renal impairment was 11.6 (=10.3/11.7*13.2) L/h. The clearance parameters utilized for the simulation are shown in Table 7. All other parameters remained constant across groups. The simulated concentration-time profiles are shown in Figure 18. The steady state C_{max} and C_{min} for normal patients and patients with severe renal impairment are shown in Table 8.. The corresponding increase in ΔQTcF for renal impaired patients was also calculated (see the QT-IRT review for details).

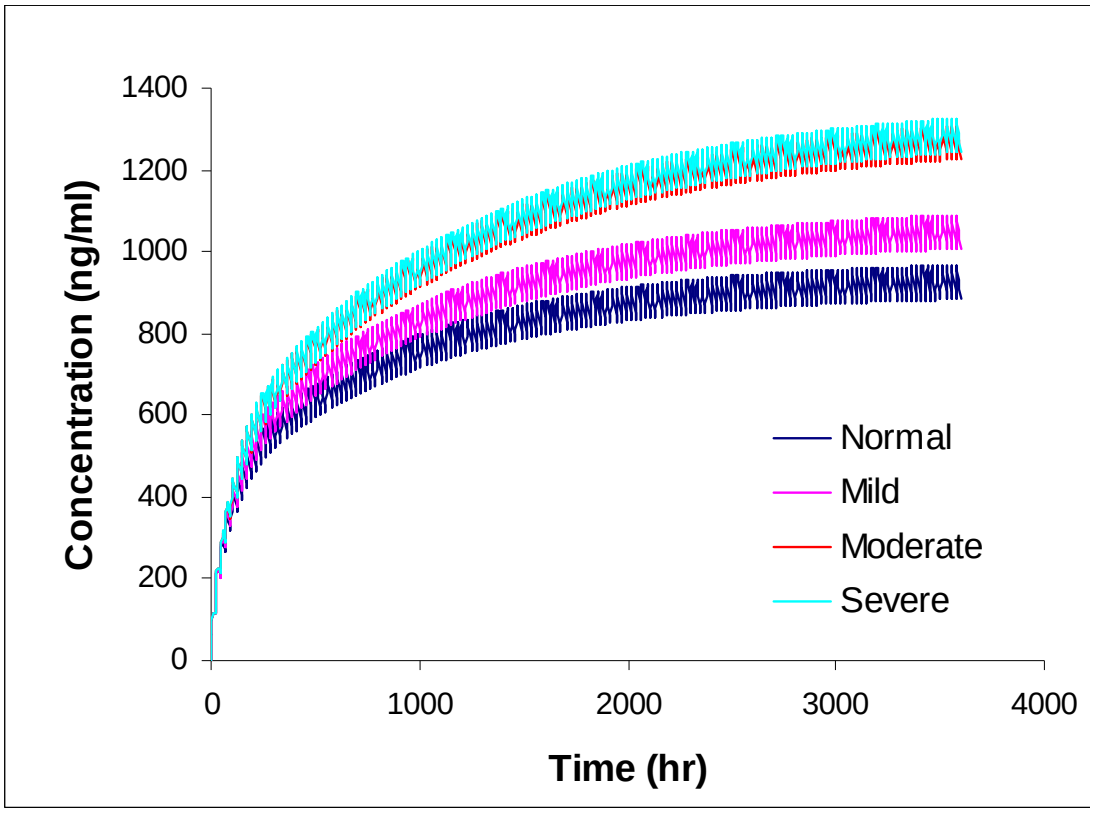


Figure 18: Concentration vs. time profiles for normal patients and patients with renal impairment

Table 7: Clearance parameters for simulation of steady-state concentrations by renal function group

Renal Function Group	CL/F utilized for simulation (L/h)	CL/F observed in dedicated renal impairment study (L/h)
Normal	13.2	11.7
Mild	11.6	10.3
Moderate	9.49	8.44
Severe	9.35	8.32

Table 8: Predicted steady-state concentrations for normal patients and patients with renal impairment

	$C_{max,ss}$ (ng/ml)	$C_{min,ss}$ (ng/ml)
Normal	960	884
Severe	1320	1244

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/s/

YOUNG J MOON
12/08/2010

PENGFEI SONG
12/08/2010

ANSHU MARATHE
12/08/2010

CHRISTINE E GARNETT
12/08/2010

BRIAN P BOOTH
12/09/2010

NAM ATIQUR RAHMAN
12/09/2010

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**22-405**
Submission Date:	7/7/2010, 10/15/2010
Brand Name:	Zictifa
Generic Name:	Vandetanib
Formulation:	Tablets
Strength:	100 and 300 mg
Applicant:	AstraZeneca
Reviewer:	John Duan, Ph.D.
Submission Type:	Initial NDA

Vandetanib is a new molecular entity that is a potent and selective inhibitor of the primary receptor of Vascular Endothelial Growth Factor (VEGF) with additional activity against Epidermal Growth Factor receptor (EGFR) tyrosine kinase and oncogenic RET kinase. Vandetanib is intended to confer clinical benefit in patients with unresectable locally advanced or metastatic medullary thyroid cancer.

COMMENTS

1. The following comments were conveyed to the applicant on September 15, 2010.

   Based on the submitted information, your proposed dissolution method and specification are not acceptable, for the following reasons:

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

4. Due to the deficiencies in the dissolution model, the (b) (4) finished product dissolution testing is not acceptable. The applicant decided to withdraw the dissolution model from the application with an expectation that the proposal would be submitted as a prior approval supplement.

RECOMMENDATION

The applicant has updated the relevant sections according to the changes of the dissolution method and acceptance criterion. The applicant also withdrew the dissolution model and end product dissolution test will be conducted. No further action is necessary from biopharmaceutics perspective at this time.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

cc: NDA 22405
Angelica Dorantes, Patrick Marroum, John Duan

APPENDIX. Submission Summary

I. INTRODUCTION

Vandetanib is a new molecular entity that is a potent and selective inhibitor of the primary receptor of Vascular Endothelial Growth Factor (VEGF) with additional activity against Epidermal Growth Factor receptor (EGFR) tyrosine kinase and oncogenic RET kinase. Vandetanib tablets consist of 2 tablet strengths containing 100 and 300 mg of vandetanib respectively. Both tablets are manufactured from a (b) (4) containing vandetanib at a level of (b) (4)

Vandetanib is intended to confer clinical benefit in patients with unresectable locally advanced or metastatic medullary thyroid cancer. The intended clinical dose for vandetanib is 300mg once daily. In the event of toxicity, the 300 mg daily dose can be reduced to 200 mg (two 100 mg tablets) and then to 100 mg if necessary.

The quantitative composition of vandetanib 100 and 300 mg tablets is presented in the following table.

Ingredients	100 mg Amount per tablet Amount (mg)	Amount (% of tablet core)	300 mg Amount per tablet Amount (mg)	Amount (% of tablet core)
Tablet core				
Vandetanib	100.0	(b) (4)	300.0	(b) (4)
Dibasic calcium phosphate dihydrate[a]	(b) (4)			
Microcrystalline cellulose				
Crospovidone				
Povidone				
Magnesium stearate				
(b) (4)				
Core tablet weight (mg)				
Tablet coating				
Hypromellose 2910[c, d]				
Polyethylene glycol 300[c, e]				
Titanium dioxide[c]				
(b) (4)				
Nominal coated tablet weight (mg)				

[a] An alternative name is calcium hydrogen phosphate dihydrate.
(b) (4)
[c] Coating constituents may be applied using a proprietary mixture, eg. (b) (4) Relative ratios will remain constant.
[d] An alternative name is hydroxypropyl methylcellulose.
[e] An alternative name is Macrogol.
[f] Total tablet weight gain after coating should be (b) (4) w/w.
NA Not applicable.

Physicochemical properties of vandetanib

The major physicochemical properties of vandetanib are listed in the following table.

(b) (4)

Under the Biopharmaceutical Classification System (BCS), vandetanib is a Class II compound.

Solubility experiments have assessed the maximum dose strength of 300 mg at 37°C (see the table below). Vandetanib is highly soluble up to and including pH 6.

(b) (4)

Vandetanib has been shown to exhibit high permeability through Caco-2 cell monolayers when compared to standards of known permeability as seen in the following table.

Conc (μM)	Papp (A to B) (x 10^{-6} cms^{-1})	Papp (B to A) (x 10^{-6} cms^{-1})	B to A :A to B Papp ratio	Absorption potential	Efflux
1	17.9±0.9	14.0±3.3	0.78	High	No
10	23.8±0.1	17.8±1.7	0.75	High	No
50	31.2±1.0	16.8±2.0	0.54	High	No

Vandetanib has been shown to be stable in human gastric fluid and human intestinal fluid for at least 90 and 180 minutes respectively.

II. THE DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

(b) (4)

16 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

V. SYNOPSIS OF THE BIOSTUDY

Study Title: A Randomized, Open-label, Incomplete Crossover, Phase I Study to Assess the Pharmacokinetic Exposure of Four Oral Tablet Variants of ZD6474 and an Oral Solution Formulation of ZD6474 in Healthy Subjects

Investigator: Lawrence Wyn Andrews, MD

Study center: This study was conducted at (b) (4)

Study dates: Phase of development First subject enrolled February 4, 2004; Last subject completed November 24, 2004.

Objectives:
The primary objective of this study was to characterize the plasma concentration time profile of an oral solution formulation of ZD6474 (Part I) and four tablet variants (Part II).

The secondary objectives of the study were:

1. To determine the pharmacokinetic (PK) parameters of a single-dose oral solution of ZD6474, by assessment of area under the curve from zero to infinity (AUC), AUC from zero to 840 hours (AUC0-840), AUC from zero to last quantifiable plasma concentration (AUC0-t), maximum plasma concentration (Cmax) and terminal half-life (t1/2); and of four tablet variants of ZD6474 by assessment of Cmax, AUC0-840, and t1/2.

2. To assess the safety of ZD6474 in all subjects by continuous real-time electrocardiogram (ECG) monitoring for 24 hours after dosing, clinical monitoring of adverse events (AEs), blood pressure (BP), heart rate (HR) measurements, and clinical chemistry, hematology, and urinalysis values.

Additionally, it was intended to investigate any potential in vitro-in vivo correlation (IVIVC) for ZD6474 using the data obtained from this study.

Study design:

This was an open-label study, consisting of 2 parts (Parts I and II) and designed to assess the PK exposure of an oral solution formulation of ZD6474 and four oral tablet variants of ZD6474 in healthy subjects.

Part I consisted of a single study day (Period 1) in which a single dose of ZD6474 300-mg oral solution was administered to each subject.

This solution was used to define the unit impulse response (UIR) for the purposes of deconvolution, which was to be performed on an individual basis, and therefore the

solution was required to be administered to all subjects. Due to the extremely long t1/2 of ZD6474, to ensure that the plasma concentration-time profile for the UIR was fully described, PK samples were obtained for 6 weeks after administration of the oral solution (Part I).

Subjects remained resident in the Clinical Pharmacology Unit (CPU) for 24 hours following administration of ZD6474. Safety and PK assessments were done for 6 weeks post-dose.

Part II was a randomized, open-label, incomplete block design consisting of 3 study days (Periods 2, 3, and 4). Each subject received single doses of three of the four tablet variants of ZD6474 300 mg, one on each of the 3 study days (Periods 2, 3, and 4). Subjects were randomly allocated to a treatment sequence group prior to the first dose in Part II. The treatment sequence groups were randomized so that each treatment occurred 4 times on each study day. Due to the long t1/2 of ZD6474, a minimum of 5 weeks had to elapse between each study day of Part II. Based on previous data, this should have ensured that at least 90% of the area under the curve (AUC) was captured and that the impact of any pre-dose concentrations on the subsequent plasma-concentration time profiles was negligible.

Subjects remained resident for a minimum of 24 hours following administration of each dose of ZD6474. Furthermore, subjects were required to remain in the CPU and monitored until resolution of QTc prolongation to less than 30 msec of baseline was documented. Safety and PK assessments were obtained for 5 weeks after each dose.

The duration of participation of each subject was expected to be up to approximately 27 weeks: up to 4 weeks during screening, 6 weeks in Period 1, 5 weeks in Period 2, 5 weeks in Period 3, 5 weeks in Period 4, and 2 weeks in follow-up until the termination visit.

Subject:

Twenty-three subjects were enrolled, received study drug in Period 1, and were randomized to a treatment sequence for Periods 2 – 4. A total of 12 (52%) subjects completed the study. Eleven subjects were terminated early; 6 after the first study period, 4 after the second study period, and 1 after the third study period.

The reasons for early termination were as follows: 5 subjects were unwilling to continue in the study, 3 subjects withdrew due to AEs, 1 subject developed study specific discontinuation criteria (positive urine drug screen), 1 was lost to follow-up, and 1 was withdrawn for “other” reasons (initially lost to follow-up but returned to clinic for off-study visit).

Test product:

This study used one single oral solution of ZD6474 300 mg (batch number: 14116B03) and four oral tablet variants of ZD6474 300 mg (batch numbers: 11296H03 [Tablet variant A], 11294C03 [Tablet variant B], 12858C03 [Tablet variant C] and 12856I03 [Tablet variant D]). All tablet variants were manufactured at a scale of (b) (4) using equipment of the same type as that proposed for use in the initial commercial manufacturing train. Subjects received a single dose of the oral solution of ZD6474 in Part I. In Part II, subjects received single doses of three of the four tablet variants of ZD6474 300 mg, one on each of the 3 study days (Periods 2, 3, and 4).

Variables

Pharmacokinetic

The primary outcome variable was the plasma concentration-time profile of ZD6474 following administration of the solution and four different tablet variants. Secondary outcome variables for ZD6474 in Part I were Cmax, AUC0–t, AUC, AUC0-840, and t1/2. The secondary outcome variables for ZD6474 in Part II were Cmax, AUC0–t, and t1/2.

Safety

The outcome variables used to assess safety were AEs, supine BP and HR, 12-lead ECG, and clinical chemistry, hematology, and urinalysis. In addition, patients were monitored for 24 hours after dosing by real-time ECG. Any clinically significant findings from the real-time ECG or 12-lead ECG were reported as AEs.

Statistical methods

No formal statistical analysis was performed. The PK endpoints within each period of the study were listed for individual subjects and summarized by oral solution/tablet variant.

Pharmacokinetic results:

AUC, Cmax, and t1/2 for the ZD6474 oral solution and each of the four ZD6474 tablet variants are summarized in the table below.

	AUC (ng h/mL)			Cmax (ng/mL)			t1/2 (hr)		
	N[a]	gmean	CV%	N[a]	gmean	CV%	N[a]	gmean	CV%
Oral solution	15	28700	28.3	15	169.9	26.67	15	231.5	24.47
Tablet variant A	10	34530	23.02	10	183.8	29.37	10	228.1	18.36
Tablet variant B	10	30330	22.62	10	163.1	32.87	10	221.7	30.71
Tablet variant C	11	30080	31.68	11	157.8	20.72	11	231	32.07
Tablet variant D	9	31010	28.25	9	159.4	45.3	9	226.3	15.44

a Analysis includes subjects who completed Period 1 of the study and had sufficient samples to characterize the PK profile of at least one of the tablet variants.

Following a single oral dose of 300-mg ZD6474 solution, Cmax was achieved at a median of 8 hours, ranging from 6 to 18 hours. The geometric mean (gmean) for AUC

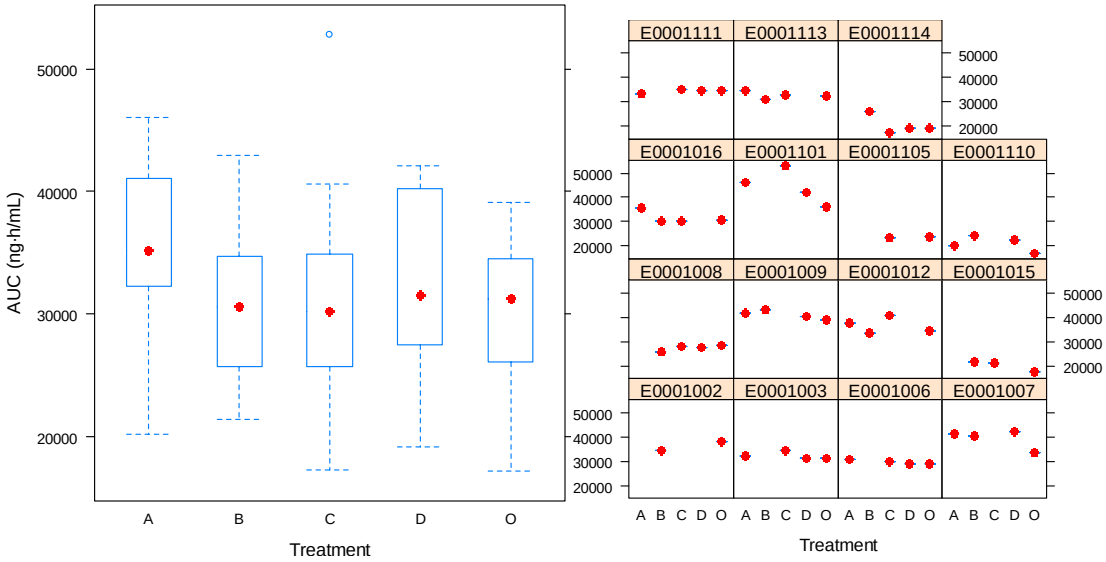
and Cmax for the ZD6474 oral solution was 28700 ng.h/mL and 169.9 ng/mL, respectively. Administration of the standard ZD6474 tablet (variant A) resulted in a greater exposure than obtained for the oral solution, in terms of both AUC and Cmax, with gmean of 34530 ng.h/mL and 183.8 ng/mL, respectively. Each of the three other tablet variants resulted in slightly lower exposure than that observed for the standard ZD6474 tablet, AUC and Cmax being approximately 85% to 90% of the standard tablet. These data show that exposure to ZD6474 does not appear to be affected by variations to the standard tablet composition or manufacturing process.

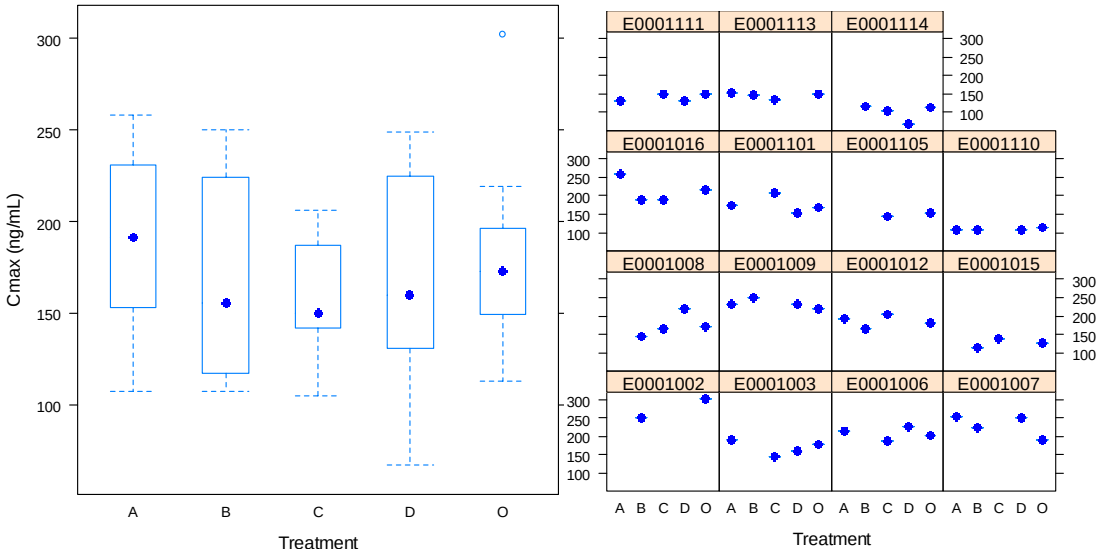
Safety results:

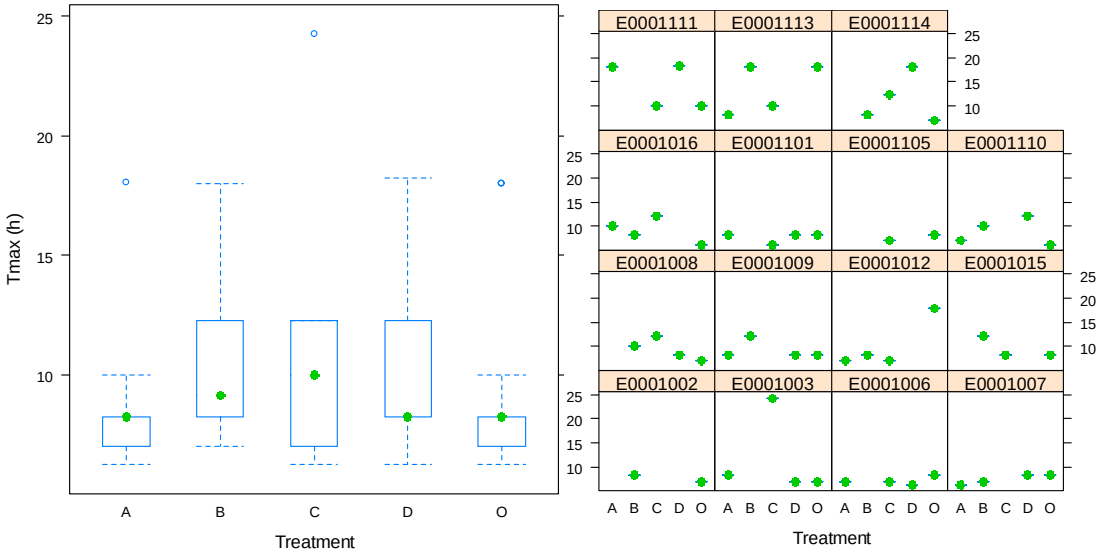
The most common AEs were pruritus (n=9, 39%), headache (n=6, 26%), fatigue (n=5, 22%), nausea (n=5, 22%), and vomiting (n=4, 17%). The proportion of subjects experiencing AEs was similar between treatments, with the exception of headache and pruritus, which were more commonly reported in subjects during treatment with the oral solution. There were no serious adverse events (SAEs).

Reviewer's Comments

These data show that the exposure to ZD6474 is similar for each of the tablet variants as shown in the following figures for comparisons of AUC, Cmax and Tmax among different variants. In the figures, O is the oral solution while A, B, C, and D are tablet variants. An informal BE analysis showed that all variants were bioequivalent.







The following table shows the 90% confidence intervals of the ratios of AUC to infinity, AUC to last time point and Cmax between different variants (B, C, and D) and the targeted formulation (A).

Parameter	Variants	Ratio	Upper Confidence limit	Lower Confidence limit
AUCinf	B	98.9648	109.570	89.3858
AUCinf	C	99.0101	109.186	89.7825
AUCinf	D	97.1482	107.468	87.8190
AUCt	B	97.6967	108.029	88.3529
AUCt	C	97.9526	107.888	88.9323
AUCt	D	96.3113	106.408	87.1724
Cmax	B	91.7803	105.765	79.6446
Cmax	C	95.4907	109.434	83.3239
Cmax	D	92.3278	106.271	80.2137

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN Z DUAN
12/08/2010

PATRICK J MARROUM
12/08/2010

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	22-405	**Brand Name**	ZICTIFA
DCP Division	5	**Generic Name**	Vandetanib
Medical Division	Oncology	**Drug Class**	Tyrosine kinase inhibitor
OCP Reviewer	Young Jin Moon	**Indication(s)**	Patients with unresectable locally advanced or metastatic medullary thyroid cancer
OCP Team Leader	Qi Liu	**Dosage Form**	100 mg and 300 mg tablets
Date of Submission	July 7, 2010	**Dosing Regimen**	One 300 mg tablet once daily
Due Date of OCP Review	December 17, 2010	**Route of Administration**	Oral
Priority PDUFA Due Date	January 7, 2011	**Sponsor**	AstraZeneca

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		
Isozyme characterization:	**X**	**3**		
Blood/plasma ratio:	**X**	**1**		
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**9**		
multiple dose:	**X**			
Patients-				
single dose:	**X**	**9**		
multiple dose:	**X**			
Dose proportionality -				
fasting / non-fasting single dose:	**x**	**4**		
fasting / non-fasting multiple dose:	**X**	**4**		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**		
In-vivo effects of primary drug:				
Cotherapy:	**X**	**3**		
In-vitro:	**X**	**10**		
Subpopulation studies -				
ethnicity:				
gender:				

geriatrics:				
renal impairment:	X	1		
hepatic impairment:	X	1		
pediatrics:				
PD:				
Phase 2:	X	2		
Phase 3:	X	1		
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	2		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:				
Data sparse:	X	3		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
QTC studies:	X	1		
In-Vitro Release BE				
(IVIVC):	X	1		
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies		37		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Formulation used in the pivotal trial and to-be-marketed formulation are same.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the	X			

	CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in			X	

	this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

The comments below have been conveyed to the sponsor.

Please refer to the section of 5.3.3.5 (regarding the population PK study reports) in your submission of NDA022405 (Sequence No. 0000) dated 09 July 2010. Submit the companion pharmacokinetic models and datasets including individual concentration vs. time and corresponding pharmacokinetic parameters by patient as SAS transport files. The following are the general expectations for submitting pharmacometric models and data:

- *All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.*
- *Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).*
- *A model development decision tree and/or table which gives an overview of modeling steps.*

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Young-Jin Moon

Reviewing Clinical Pharmacologist Date

Qi Liu

Team Leader/Supervisor Date

Cc: DDOP: CSO - **L Skarupa;** MTL - **V Maher**; **A Ibrahim** MO - **G Kim; K DeLorenzo**

DCP-5: Reviewer - **Y Moon, P Song, A Marathe;** TL - **Q Liu; C Garnett**
Deputy DD TL - **B Booth;** DD - **A Rahman**

Clinical Pharmacology - NDA Filing Memo

NDA: **22-405/000 Original Submission** **IND: 60,042**
Compound: **ZICTIFA (Vandetanib), one 300 mg tablet for oral administration**
Sponsor: **AstraZeneca**
Filing Date: **July 7, 2010**
Reviewer: **Young-Jin Moon, Ph.D.**

- NME
- MOA: tyrosine kinase inhibitor-selective for VEGFR2, EGFR, and RET
- Indicated for unresectable locally advanced or metastatic medullary thyroid cancer
- 100 mg and 300 mg tablets are available.
- History

ZACTIMA (b) (4)	ZICTIFA (July 7, 2010)
NSCLC	MTC
100 mg once daily with chemotherapy	300 mg once daily

- Efficacy
  - Pivotal (Study 58)
    - A randomized, double-blind, placebo-controlled phase 3
    - 1° endpoint: PFS

	N	Median PFS	HR[a]	95% CI	p-value
ZICTIFA 300 mg	73/231 (32%)	Not reached (predicted 30.5 months)	0.46	0.31, 0.69	0.0001
Placebo	51/100 (51%)	19.3 months			

(N: Number of events/number of randomized patients)

  - Supportive (Study 8 (300 mg) and 68 (100 mg))- single arm phase 2 in hereditary MTC
    - Proposed dose is based on Study 8 (N=30). 1° endpoint was response rate.
    - Study 68 (N=19) was conducted in parallel with the pivotal study to assess whether there is any efficacy of 100 mg dose. 1° endpoint was response rate. Both 100 and 300 mg were active, but a greater level of activity was seen in 300 mg.

Variable		Study 08	Study 68	Study 58	
		Vandetanib 300 mg (N=30)[a]	Vandetanib 100 mg (N=19)[a]	Vandetanib 300 mg (N=231)[a]	Placebo (N=100)[a]
PFS	Median, months	27.9	16.2[b]	30.5[b]	19.3
ORR	Number of responses	6 (20.0%)	3 (15.8%)	104 (45.0%)	13 (13.0%)[c]

- Adverse events
  - Warning: QT prolongation and Torsades des Points

- Most common (>25%): diarrhea, rash, nausea, hypertension and headache

Total 23 clinical studies contributing PK

- ADME: 800 mg
- Hepatic/Renal: 800 mg
- Food effect: 300 mg (highest dose used in phase 3)
- DDI: 300 mg
  - Rifampicin
  - Itraconazole (FDA agreed with this at the pre-NDA meeting on May 30, 2006 (SN# 358)
- Relative bioavailability in HV (N=23): Effect of 4 oral tablet variants and an oral solution on PK 300 mg single dose
- PK in HV: Single ascending dose phase 1 at 300 to 1200 mg
- PK in patients: Ascending dose phase 1 in Western (50 to 600 mg) and Japanese (100 to 400 mg) patients with solid tumors
- Sparse PK in phase 2 and phase 3 studies

Pharmacometrics

- QT study: Phase 1 in HV (N=28) vandetanib 700 mg single oral dose vs. Ondansetron 32 mg single IV
- Population PK

Study	Detail	Doses
Study 58	Pivotal study in MTC PopPK PK/PD for efficacy and AEs	300 mg once daily (N=231; 218 Caucasian, 8 Asian, 1 Black, 4 Others)
Study 8	Phase 2 in hereditary MTC PopPK PK/PD for QTc, AEs, TTP, CTN, CEA	300 mg once daily (N=30)
Study 68	Phase 2 in hereditary MTC PopPK PK/PD for QTc, AEs, TTP, CTN, CEA	100 mg once daily (N=19)
Studies 1, 2, 3, 6 in NSCLC patients Studies 12, 15, 21, 24 and 30 in HV	Investigation into absorption. *Previously submitted	100, 200, 300, 400, 700, 800, 1200 mg
Studies 3, 6 in NSCLC patients Studies 12, 15, 21 and 24 in HV	PK and PD in HV and patients-comparison of HV and P *Previously submitted	100, 200, 300, 400, 700, 800, 1200 mg

Genomics

- Effect of race on PK (not included in the labeling)
    - Pivotal (Study 58): Majority of the patients were Caucasians (95%), no conclusive difference between racial groups could be detected.
    - Study 1, 43, and 4 were used to compare PK between Western, Japanese, and Chinese patients groups. There was no difference in exposure between these groups.
- Study 2 and Study 39 provided exploratory data to support inhibition of VEGFR-2 and EGFR signaling, although these studies are not considered to provide compelling evidence for target inhibition in tumors.

Appendix. Studies which support clinical pharmacology

Study	Number randomized/treated and type of subjects	Design
Phase 1		
D4200C00001 6474IL/0001 (Study 01)	77/77 Western patients with solid tumor	Rising single dose followed by multiple dose: 50 mg, 100 mg, 200 mg, 300 mg, 500 mg,600 mg
D4200C00043 TVE-15-11 (Study 43)	0/18 Japanese patients with solid tumor	Rising single dose followed by multiple dose: 100 mg, 200 mg, 300 mg, 400 mg (single doses)
D4200L00004 (Chinese Study 04)	0/36 Chinese patients with solid tumor	Rising multiple dose: 100 mg every other day; 100 mg once daily and 300mg once daily
D4200C00012 6474IL/0012 (Study 12)	0/23 Healthy male subjects	300 mg, 400 mg, 800 mg, 1200 mg (single doses)
D4200C00015 6474IL/0015 (Study 015)	16/16 Healthy male subjects	DDI study ZD6474: 300 mg (single dose) Itraconazole (CYP3A4 inhibitor): 200 mg
D4200C00016 6474IL/0016 (Study 16)	0/30 Normal: 8, Child Pugh group A: 8, group B: 8, group C: 6	Hepatic impairment study 800 mg (single dose)
D4200C00021 6474IL/0021 (Study 21)	28/28 Healthy male subjects	Cardiac repolarization ZD6474: 700 mg (single oral dose) Ondansetron 32 mg (single IV dose)
D4200C00022 6474IL/0022 (Study 22)	0/32 10 normal, 6 mild, 6 moderate, 10 severe	Renal impairment study 800 mg (single dose)
D4200C00024 6474IL/0024 (Study 24)	16/16 Healthy subjects (15 male, 1 female)	Food effect study 300 mg (single dose)
D4200C00025 6474IL/0025 (Study 25)	0/4 Healthy male subjects	ADME study [14C]-ZD6474: 800 mg (single dose)
D4200C00026 6474IL/0026 (Study 26)	18/18 Healthy male volunteers	DDI study 300 mg (single dose) rifampicin (CYP3A4 inducer)
D4200C00030 6474IL/0030 (Study 30)	23/23 Healthy volunteers (21 male, 2 female)	Effect of 4 oral tablet variants and an oral solution on PK exposure 300 mg (single dose)
D4200C00050 6474IL/0050 (Study 50)	24/22 Patients with advanced colorectal cancer and liver metastases	Effect of vandetan b on vascular permeability 100 mg, 300 mg (once daily doses)
Other phase 1		
D4200C00038 6474IL/0038 (Study 38)	0/21 Patients with metastatic colorectal adenocarcinoma.	Effect of FOLFIRI on ZD6474 PK ZD6474: 100 mg, 300 mg (once daily doses) FOLFIRI: standard 14 day treatment cycles
D4200C00041 6474IL/0041 (Study 41)	0/21 Patients with locally-advanced or metastatic NSCLC.	Effect of pemetrexed on ZD6474 PK ZD6474: 100 mg, 300 mg (once daily doses) Pemetrexed: 500 mg/m^2
D4200C00039 6474IL/0039	53/53 Japanese patients with NSCLC	Dose finding study to assess efficacy (objective response) and safety

Study	Number randomized/treated and type of subjects	Design
Phase 1		
(Study 39)		ZD6474: 100, 200 and 300 mg (once daily doses) PK/PD including QTc
Phase 2 – Medullary Thyroid Cancer		
D4200C0008 6474IL/0008 (Study 8)	0/30 Patients with locally advanced or metastatic hereditary MTC	ZD6474: 300 mg (once daily doses)
D4200C00068 6474IL/0068 (Study 68)	0/19 Patients with locally advanced or metastatic hereditary MTC	ZD6474: 100 mg (once daily doses)
Phase 2 - NSCLC		
D4200C00003 6474IL/0003 (Study 03)	168/168 Patients with NSCLC	Comparison of the efficacy of ZD6474 with the efficacy of ZD1839 (IRESSA™) ZD6474: 300 mg (once daily doses) Iressa: 250 mg (once daily dose) PK/PD including QTc
D4200C00006 6474IL/0006 (Study 06)	127/144 Patients with NSCLC	Safety, tolerability and efficacy of ZD6474 in combination with docetaxel (TAXOTERE™) ZD6474: 100 mg, 300 mg (once daily doses) Docetaxel: 75 mg/m^2 DDI with docetaxel
Phase 2 – Other		
D4200C00002 6474IL/0002 (Study 02)	0/46 Female patients with metastatic breast cancer.	Efficacy of ZD6474 in patients with metastatic breast cancer based on the objective response rate ZD6474: 100 mg and 300 mg QTc
Phase 3 - MTC		
D4200C00058 6474IL/0058 (Study 58)	331/231 Patients with MTC	ZD6474: 300 mg (once daily oral)
D4200C00057 6474IL/0057 (Study 57)	1240/1237 Patients with NSCLC	Efficacy of ZD6474 versus erlotin b ZD6474: 300 mg (once daily oral) Erlotinib: 150 mg (once daily oral)

Signatures

Young-Jin Moon	Qi Liu, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **L Skarupa;** MTL - **V Maher**; **A Ibrahim** MO - **G Kim; K DeLorenzo**

DCP-5: Reviewer - **Y Moon, P Song, A Marathe;** TL - **Q Liu; C Garnett**
Deputy DD TL - **B Booth;** DD - **A Rahman**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22405	ORIG-1	IPR PHARMACEUTICALS INC	Zictifa (Vandetanib)

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/s/

YOUNG J MOON
08/19/2010

QI LIU
08/20/2010