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NCT Number	NCT01586624
EudraCT Number	2011-000627-33
Sponsor Protocol Number	CRUKD/11/001
Official Title	A Cancer Research UK Phase I dose escalation trial of the oral VEGFR and EGFR inhibitor, Vandetanib in combination with the oral MEK inhibitor, Selumetinib (VanSel-1) in solid tumours (dose escalation) and NSCLC (expansion cohort).
Documents, Version & Date	Protocol Version 13.0, dated 26 January 2018

CANCER RESEARCH UK | CENTRE FOR DRUG DEVELOPMENT

Cancer Research UK

Centre for Drug Development

A Cancer Research UK Phase I dose escalation trial of the oral VEGFR and EGFR inhibitor, Vandetanib in combination with the oral MEK inhibitor, Selumetinib (VanSel-1) in solid tumours (dose escalation) and NSCLC (expansion cohort).

Sponsor protocol number: CRUKD/11/001
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Sponsor: Cancer Research UK
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PARTICIPATING INVESTIGATORS AND CENTRES:

Contact details for participating investigators and centres can be found in the Trial Master File (TMF) contact list.

PROTOCOL VERSION HISTORY:

Version No.	Issue Date	Reason for update
1.0	15August2011	Initial version submitted for ethics and regulatory approval.
2.0	19December2011	Updated safety information regarding medications known to prolong QTc interval. Updated guidance regarding renal function assessment at elig bility. Administrative changes.
3.0	19May2012	Revised interval between treatment of patients 1 and 2 at each dose level. Time windows for PK sampling time points. Inclusion of measurement of CPK levels throughout study.
4.0	18October2012	Revision of DLT criteria regarding hypertension. Clarification of expansion cohort patient group (inclusion criteria). Clarification of exclusion criteria.
5.0	06March2013 Non substantial amendment	Clarification of additional Cohort 4.
6.0	02April2013	Addition of additional ophthalmological eye monitoring and associated dose modification. Revised medically important SAE reporting to include eye changes.
7.0	17October2013	Investigation of alternative vandetanib doses. Clarification of inclusion criteria INR value). Patient evaluability for dose escalation. Increase in patient numbers recruited to dose escalation phase. Non substantial amendments
8.0	30May2014	Update information relating to: Selumetinib exposure and patients of Asian ethnicity. Vitamin E exposure. LVEF guidelines. Dose modifications. Plus Non substantial amendments.
9.0	12November2014	Investigation of an increased maximum dose of vandetanib and alternative dosing schedules. Non substantial amendments.
10.0	07July2015	Addition of new site. Revision to total patient numbers. Revision to exclusion criteria. Update to precautions for treatment. Non substantial amendments.
11.0	18November2015	Change to inclusion criteria (previous treatments) Non substantial amendments.
12.0	10May2016	Exclusion criteria revision re: previous EGFR inh bitor treatment. Dose modification update relating to suspected ILD. Precautions for treatment update relating to ILD. Non substantial amendment relating to RECIST update to v1.1.
13.0	26January2018	Selumetinib capsules colour change. Clarification regarding study reporting schedule.

To note: NCI CTCAE version used throughout this protocol is version 4.02.

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LIST OF ABBREVIATIONS

A	ABPI	Association of the British Pharmaceutical Industry
	AE	adverse event
	AKT	serine/threonine protein kinase
	ALP	alkaline phosphatase
	ALT	alanine aminotransferase
	ANC	absolute neutrophil count
	aPTT	Activated partial thromboplastin time
	AST	aspartate aminotransferase
	AUC	area under the curve
B	BAD	biologically active dose
	BD	Bis die (twice daily)
	BP	blood pressure
	bpm	beats per minute
	BDBRAF	v-Raf murine sarcoma viral oncogene
	BSA	body surface area
C	^{0}C	degrees Celsius
	CDD	Centre for Drug Development
	CDM	Clinical Data Manager
	cfDNA	Circulating free DNA
	CI	Chief Investigator (formerly Co-ordinating Investigator)
	CLT	total body clearance
	C_{max}	maximum observed plasma concentration
	CNS	Central nervous system
	CPK	Creatine phosphokinase
	CR	complete response
	CRA	Clinical Research Associate
	eCRF	electronic case report form
	CR-UK	Cancer Research UK
	CSM	Clinical Study Manager
	CSR	Clinical Study Report
	CT	computerised tomography
	CTA	clinical trial authorisation
	CTCAE	Common Terminology Criteria for Adverse Events
D	Day	calendar day
	DCE - MRI	Dynamic contrast enhanced magnetic resonance imaging
	DCF	data clarification form
	DCR	disease control rate
	DLT	dose limiting toxicity
	DNA	Deoxyribonucleic acid
	DWI	Diffusion weighted imaging
E	ECG	electrocardiogram
	ECHO	echocardiogram
	EDC	electronic data capture
	EDTA	ethylene diamine tetra-acetic acid
	EGFR	Epidermal growth factor receptor
	EMA	European Medicines Agency
	EORTC	European Organisation for Research and Treatment of Cancer
	EPD	early progressive disease
	ERK	extracellular signal regulated kinases
F	FDA	Food and Drug Administration
	FDG	fluorodeoxyglucose

	FU	Formulation Unit
G	GCP	Good Clinical Practice
	g/dL	gram(s) per decilitre
	GFR	Glomerular filtration rate
	GLDH	Glutamate dehydrogenase
	GMP	Good Manufacturing Practice
	GTAC	Gene Therapy Advisory Committee
H	Hb	haemoglobin
	HCG	human chorionic gonadotropin
	HDPE	High-density polyethylene
	HIV	human immunodeficiency virus
	HPMC	hydroxypropylmethylcellulose
I	IAUC 60	Initial area under curve taken up to 60 seconds
	IB	Investigator Brochure
	IC50	half maximal inhibitory concentration
	ICH GCP	International Conference on Harmonisation of Good Clinical Practice
	ILD	interstitial lung disease
	IMP	investigational medicinal product
	INR	International normalised ratio
	ITF	Investigator Trial File
	IUD	Intrauterine device
K	KRAS	Kirsten rat sarcoma oncogene
	Ktrans	Volume transfer across a capillary wall
L	LVEF	left ventricular ejection fraction
M	MAD	maximum administered dose
	MAP	Mitogen activated protein kinase
	MEK	Mitogen-activated Protein/Extracellular Signal-regulated Kinase Kinase
	mg/m^2	milligram per square metre
	MHRA	Medicines and Healthcare products Regulations Agency
	MRI	magnetic resonance imaging
	msec	millisecond
	MTD	maximum tolerated dose
	MUGA	Multi gated acquisition scan
N	NCI	National Cancer Institute
	NSCLC	Non Small Cell Lung Cancer
O	OD	Omne in die (once daily)
	OCT	Optical coherence tomography
P	PD	progressive disease
	PDF	Portable document format
	PFS	Progression Free Survival
	PO	Per os (by mouth)
	PET	Positron emission tomography
	PI	Principal Investigator
	PK	pharmacokinetic
	PR	partial response
	PSRB	Protocol, Safety and Review Board
	PV	Pharmacovigilance
Q	QC	quality control
	QP	Qualified Person
	QT	measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
	QTc	QT interval corrected for heart rate

R	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumours
	RET	'rearranged in transformation' (kinase)
	RPM	revolutions per minute
	RP2D	Recommended Phase II dose
	RT	radiotherapy
S	SAE	serious adverse event
	SD	stable disease
	SGDCF	site generated data clarification form
	SDV	source data verification
	SOP	standard operating procedure
	SPC	Summary of Product Characteristics
	SUSAR	suspected unexpected serious adverse (drug) reaction
	SUV	Standardised uptake value
T	$T_{1/2}$	terminal elimination half-life
	T_{max}	time to reach C_{max}
	TPGS	alpha-tocopheryl succinate esterified to polyethylene glycol 1000 [PEG 1000]
U	ULN	upper limit of normal
	USM	urgent safety measure
	UV	ultra violet
V	V_{SS}	steady state volume of distribution
	ve	Extracellular, extravascular volume
	VEGF-A	Vascular endothelial growth factor -A
	VEGFR	Vascular endothelial growth factor receptor
	VOI	Volume of interest
	vp	Blood plasma volume
W	WFI	Water for Injection
	WBC	white blood cell
	WHO	World Health Organisation

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki (Appendix 2), the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: _____

Signature: _____

Date: _____

Sponsor Signature:

ON BEHALF OF SPONSOR, CENTRE FOR DRUG DEVELOPMENT OF CANCER RESEARCH UK:

NAME: _____

DIRECTOR OF CENTRE FOR DRUG DEVELOPMENT

SIGNATURE: _____

DATE: _____

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

1 PROTOCOL SUMMARY

1.1 Full title

A Cancer Research UK Phase I dose escalation trial of oral VEGFR and EGFR inhibitor, Vandetanib in combination with the oral MEK inhibitor, Selumetinib (VanSel-1) in solid tumours (dose escalation) and NSCLC (expansion cohort).

Short title: VanSel-1: A Phase I trial of Vandetanib (ZD6474) and Selumetinib (AZD6244).

1.2 Clinical trial objectives and endpoints

Primary objectives and endpoints

Primary objectives	Endpoints
Assessing the safety and toxicity profile of the combination of vandetanib and selumetinib.	Determining causality of each adverse event to vandetanib or selumetinib and grading severity according to NCI CTCAE Version 4.02
To propose a recommended dose and schedule for Phase II evaluation of the combination of vandetanib and selumetinib.	Determining the MTD of the combination of vandetanib and selumetinib as proposed by the protocol. OR the single agent recommended Phase II dose (RP2D) of vandetanib in combination with the single agent RP2D of selumetinib.

Secondary objectives and endpoints

Secondary objectives	Endpoint
Determine the plasma pharmacokinetic (PK) profiles of vandetanib and selumetinib and their metabolites	PK parameters during Cycle 1 including Cmax and AUC pre and post treatment with vandetanib alone and following the combination of vandetanib and selumetinib. Parameters to be measured include: • vandetanib • selumetinib and N-desmethyl metabolite. (other metabolites may be measured as determined during the study).
Expansion cohort To evaluate progression free survival (PFS) of patients with NSCLC after treatment with the combination of vandetanib and selumetinib.	Determine PFS at 12 weeks (measured from date of first dose of vandetanib) by RECIST (Response Evaluation Criteria In Solid Tumors) criteria.
Expansion cohort To evaluate the survival rate of patients with NSCLC after treatment with the combination of vandetanib and selumetinib.	Determine the one year survival rate.
Expansion cohort To assess the tumour metabolism in patients with NSCLC.	Measurement of tumour metabolism using CT FDG-PET imaging during Cycle 1 pre and post treatment with vandetanib alone and following the combination of vandetanib and selumetinib.

Tertiary objectives and endpoints

Tertiary objectives	Endpoint
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

1.3 Design

This is a Phase I, multi-centre, dose escalation study with an expansion cohort.

The dose escalation phase (using a rolling six trial design, Sklonik *et al*, 2008) will enrol between approximately 42-50 patients with any primary solid tumour and will determine the recommended dose and schedule for Phase II evaluation of the combination of selumetinib and vandetanib. The final number of patients (and cohorts) will depend on the number of dose escalations required to reach MTD. The safety and toxicity profile of the combination therapy will also be assessed.

The expansion cohort (using the RP2D defined in the dose escalation phase) will enrol approximately 30 patients with NSCLC and will aim to further investigate the safety and tolerability of the combination therapy. The anti tumour activity of the combination of selumetinib and vandetanib will be investigated by determining the PFS at 12 weeks and the one year survival rate.

[redacted]

[redacted]

1.4 Administration schedule

1.4.1 Vandetanib administration

Vandetanib is administered orally as a tablet formulation.

Vandetanib will be given at 300 mg once daily (od) for four days (to rapidly reach the approximate steady state dose of 100 mg od) followed by 10 days at 100 mg od. Dose loading of vandetanib will only occur once at the beginning of the study treatment (Cycle 1). Following the dose loading phase, the steady state dose will be maintained through subsequent cycles.

Based on emerging data from the study, the vandetanib loading dose and steady state dose may also be increased. Once or twice daily dosing will be considered.

1.4.2 Selumetinib administration

Selumetinib is administered orally as a capsule (hyd sulfate) formulation.

Selumetinib will be administered once (od) or twice a day (bd). Administration will start (on Day 15) following completion of 14 days of treatment with vandetanib as a single agent (Cycle 1 only).

For subsequent cycles, patients will receive 100 mg od vandetanib from Day 1 in combination with selumetinib for 28 days. The starting dose will be 25 mg bd.

Cohorts of up to 6 patients will receive escalating doses of selumetinib (25, 50 and 75 mg bd).

Based on emerging data from the study, once daily selumetinib dosing may be considered if twice daily dosing results in unacceptable toxicity.

Once the RP2D and schedule of the combination of vandetanib and selumetinib has been determined, approximately 30 NSCLC patients will be treated at this dose in the expansion cohort.

1.4.3 Treatment period – Cycle length

Cycle 1 will consist of 42 days. This includes the 14 days of vandetanib alone plus the 28 days of combination treatment.

Subsequent cycles will be of 28 days in length and consist of continuous combination treatment with vandetanib and selumetinib at steady state from Day 1. There is no planned interval between cycles. Patients may continue to receive the combination therapy in the absence of disease progression or unacceptable toxicity.

1.4.4 Treatment group

Approximately 42-50 patients with any solid primary tumour will be entered into the dose escalation phase of the study. Approximately 30 patients with NSCLC will be entered into the expansion cohort.

1.4.5 Expected accrual

It is expected that approximately 42-50 patients will be required to complete the dose escalation phase and approximately 30 patients will be required to complete the expansion cohort. However additional patients may be required if any patients fall into the categories listed in Section 5.7 ‘Replacement of patients’.

2 INTRODUCTION

2.1 Background

Lung cancer is the second most common cancer in the UK (Cancer Research UK, Cancer Stats 2011) and is increasing in incidence globally (International Agency for Research on Cancer, Globocan, 2008). More than 38,000 new cases are diagnosed each year in the UK resulting in lung cancer being the cause of more than one in five cancer deaths (Cancer Research UK, Cancer Stats 2011). Thus the disease has a major impact on mortality and morbidity on a global scale.

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of new cases of lung cancer (Cancer Research UK, Cancer Stats 2011). A minority of patients present with early stage disease amenable for surgery which is the only treatment that offers a realistic chance of cure. For patients with metastatic disease the first-line treatment option is usually systemic therapy and symptom management including radiotherapy. The choice of first line therapy depends on performance status, histology and predictive molecular markers. Despite advances made in earlier diagnosis, staging and treatment option, patients with advanced NSCLC still have a poor prognosis, with a median survival time of 8 to 11 months and a 1 year survival rate of 30% (Cancer Research UK, Cancer Stats 2011). Consequently, there is an urgent requirement to identify and develop new, effective treatment options for this disease.

Advances have been made in the design and development of agents directed against novel molecular targets in NSCLC, including the epidermal growth factor receptor (EGFR) tyrosine kinase activity (Mok et al 2009), vascular endothelial growth factor (VEGF) signalling (Sandler et al 2006), anaplastic lymphoma kinase (ALK) gene re-arrangements and extracellular regulated kinases (ERK) that have the potential for improving clinical outcome. Agents that target EGFR and VEGF signalling have demonstrated some benefit in the treatment of NSCLC but are limited by development of tumour resistance mechanisms that utilise alternative growth stimulatory pathways. As validated techniques for detailed analysis of the activity of signal transduction pathways are applied to the investigation of targeted agents it is possible to investigate new combination strategies in order to maximise the therapeutic potential of novel targeted agents. We present here the rationale for combined targeting of EGFR, VEGF and MEK. We will describe how the safety of this approach will be evaluated and the strategy for testing the hypothesis, at the molecular level, that such an approach is effective in NSCLC.

2.2 Investigational medicinal product

Structure of Vandetanib and Selumetinib

Details of the physical and chemical characteristics of vandetanib and selumetinib, the two investigational medicinal products (IMPs), are provided in the two investigator brochures. Please refer to Section 6.0 for further details on both IMPs.

2.2.1 Vandetanib

2.2.1.1 Drug class

Vandetanib is an inhibitor of EGFR tyrosine kinase, a receptor tyrosine kinase that is activated by binding of a range of structurally related ligands (i.e., EGF and transforming growth factor α [TGFα]). Over-expression of EGFR by tumour cells has been found to correlate with poor prognosis in a range of malignancies (e.g., bladder, breast, colorectal, gastric, head and neck, lung, ovarian and renal cancers), and some tumour cells produce large amounts of EGFR ligands (e.g., TGFα), which induce autocrine-stimulated tumour proliferation. In addition Vandetanib is a potent inhibitor of VEGFR-2 tyrosine kinase that is expected to inhibit VEGF-driven angiogenesis and, as a consequence, constrain solid tumour growth. Since angiogenesis is necessary for the growth and metastasis of all solid tumours, and VEGF is believed to have a pivotal role in this process, vandetanib treatment may have broad-spectrum clinical use. Vandetanib also has activity against oncogenic RET kinases, which are activated in certain cancers, e.g. medullary thyroid cancer.

2.2.1.2 Preclinical Experience

An extensive non-clinical package exists for vandetanib. A summary of the main toxicology studies are presented in Section 4.3 of the current version of the vandetanib IB. In summary, vandetanib had an IC50 of 0.4 μM in the hERG assay. In canine Purkinje fibre studies, vandetanib caused a concentration-dependent increase in action potential duration at concentrations of 1 μM and greater. Vandetanib also elevated systolic and diastolic blood pressure in rats and dogs. In studies of the pharmacokinetics of vandetanib, absolute bioavailability following oral solution dosing to rats and dogs was approximately 90% and 30% respectively. Absorption was slow with Cmax occurring 3 to 8 hours post-dose. Vandetanib showed high clearance and high volume of distribution in both species. Toxicokinetics were dose proportional at low doses with a less than proportion increase in exposure observed at higher doses. Vandetanib was shown to bind to both human serum albumin and AAG. Following dosing with [14C]vandetanib to the rat, radioactivity was rapidly and extensively distributed with the highest concentrations in the gastrointestinal tract, liver, spleen, adrenal glands and other glandular tissues; radioactivity penetrated into the CNS. Vandetanib was shown to be a weak inhibitor of P450 2D6 and 2C8 and a moderate inducer of P450 1A2, 2C9 and 3A4. Faecal excretion was the predominant route of elimination after oral dosing (50 to 60% in the rat and 80% in the dog); evidence of enterohepatic recirculation was also observed.

Extensive toxicology studies have been performed using vandetanib; these include multiple-dose studies of up to 6 months in rats and 9 months in dogs, genetic toxicology studies and reproductive toxicology studies. In rat studies the muzzle region showed dose-related acute folliculitis and epidermal micro-abscess formation at higher doses; this was considered to be a consequence of EGF receptor inhibition. Elevated plasma ALT, AST and GLDH activities, hepatocellular necrosis and acute cholangitis were seen at the higher doses of vandetanib. Histopathological and ultrastructural changes, consistent with the induction of phospholipidosis, were also recorded. Similar changes were not seen in the 1 month or 9 month dog studies where gastrointestinal tract toxicity was the dose-limiting finding. In 1

month rat and dog toxicity studies dose-related dysplasia was observed in the epiphyseal growth plates of the femorotibial joint in rats and in the femur of dogs. These effects on intestinal function and bone formation were considered to be a consequence of on target VEGFR and EGFR inhibition. Vandetanib demonstrated significant effects on all stages of female reproduction but no effects on male fertility in rats.

2.2.1.3 Clinical Experience

Vandetanib has been extensively investigated in the clinic. As of 26 May 2010, more than 4000 patients have been exposed to vandetanib including 8 Phase I, 12 Phase II and 5 Phase III patient studies (current version of the vandetanib IB). Studies have evaluated both vandetanib as a monotherapy and in combination with a range of other cancer therapeutics. The majority of patients in the vandetanib studies to date have had NSCLC. Refer to the vandetanib Investigators Brochure for detailed summaries. Vandetanib has not been given in combination with selumetinib before.

2.2.1.4 Clinical Pharmacokinetics

The PK of vandetanib is linear. The steady state exposure is reached at day 28 with a once-daily dosing. The absorption is slow with a median time to maximum plasma concentration (tmax) of 4 to 10 hours. The slow clearance (total plasma clearance after an oral dose (CL/f) of 11 L/h) and the large volume of distribution (3000 L) give a long terminal half-life (t1/2) of about 10 to 19 days. Vandetanib is eliminated both in the faeces and in urine. Therefore, in patients with mild and moderate renal impairment the exposure is increased by about 1.5-fold and by 2-fold in patients with severe renal impairment. Hepatic impairment or food has no effect on exposure. In healthy volunteers, the CYP3A4 inhibitor, itraconazole did not modify the exposure to vandetanib but the CYP3A4 inducer rifampicin significantly reduced by about 40% the exposure to vandetanib.

2.2.1.5 Safety

The CRUKD/11/001 study will explore a maximum total dose of 300mg with the option of increasing this up to 600mg (300mg bd during the loading phase only) should the safety profile of the combination with selumetinib be acceptable at the lower doses.

Vandetanib has been explored at several doses up to 1200mg od (healthy volunteers) with minimal symptoms. In cancer patients, chronic dosing of 600mg od has resulted in diarrhoea and other AEs.

Vandetanib has a very long half-life for a small molecule meaning that several weeks dosing are required to reach the 300mg od steady state plasma levels. In the CRUKD/11/001 study, a total dose of up to 600mg (as 300mg bd) can be administered at the start of the loading dose phase (Days 1 and 2) before reverting back to a maximum of 300mg od. This two day 600mg “dose loading” should allow plasma levels approximating the 300mg od steady state level to be reached within a few days thereby reducing the period during which the patient has sub pharmacodynamic plasma levels of Vandetanib. Given the extended half life of vandetanib (10-19 days), it is unlikely that two days of 600 mg administration would

result in the severity of toxicity seen in the chronic dosing setting and therefore have any safety impact on patients.

Vandetanib has an acceptable safety profile at a daily dose of 300 mg once a day (od) as demonstrated in previous studies (see current vandetanib IB). The most common adverse events (AEs) have been related to the skin (e.g., rash, acne, pruritis), the gastrointestinal tract (e.g., nausea, diarrhoea) and nervous system (e.g., fatigue). Cardiac AEs have also been observed including QTc prolongation in approximately <2% of patients treated with 100 mg vandetanib in combination with chemotherapy, and in approximately 5% to 10% of patients treated with 300 mg vandetanib depending on the study. The QTc prolongation was managed by dose interruption followed by dose reduction. It is estimated that Torsades de Pointes occurs in approximately 0.1-1% of patients receiving 300 mg vandetanib. These events were dose-dependent, and can be managed with appropriate monitoring and management. From a randomised, placebo controlled Phase III study administering 300mg vandetanib (D4200C00058), in patients with medullary thyroid cancer (MTC), other adverse events included headache, dysgeusia, gastrointestinal disorders (including diarrhoea, nausea, vomiting, abdominal pain), rash, hypertension, weight decreased, decreased appetite, anorexia, corneal micro-opacities which rarely affected vision that were noticed in some patients after a few months of treatment with vandetanib; refer to the vandetanib IB for detailed summaries of AEs.

2.2.1.6 Efficacy

Thirteen Phase II studies investigated the efficacy of vandetanib in patients with advanced or metastatic solid tumours or patients who had failed therapy (medullary thyroid cancer [MTC] (2), prostate cancer (1), colorectal cancer (2), breast cancer (3), NSCLC (4), small cell lung cancer (1)).

In Phase II NSCLC studies, there was an increase in progression-free survival (PFS) for patients treated with vandetanib compared to gefitinib (median PFS 11 weeks vs. 8.1) [6474IL/0003] (Natale *et al* 2009), patients treated with vandetanib plus docetaxel compared to docetaxel alone (approx 18 weeks vs 12) [6474IL/0006] (Heymach *et al* 2007). However, in a study comparing patients treated with vandetanib in addition to paclitaxel plus carboplatin with paclitaxel plus carboplatin alone, the median PFS was similar in both groups (24.0 weeks vs. 23.1) [6474IL/0007]. In a randomized double-blind dose-finding study, the objective response rate was 17.6% in the 100-mg group, 5.6% in the 200-mg group and 16.7% in the 300-mg group [D4200C00039].

In Phase III NSCLC studies (see current version of the vandetanib IB), there was a statistically significant advantage in PFS and time to deterioration of disease-related symptoms (TDS) for the addition of vandetanib to docetaxel compared with docetaxel alone (D4200C00032) (Herbst *et al* 2009). There was a trend for PFS in favour of vandetanib in combination with pemetrexed compared with pemetrexed alone, although this did not reach statistical significance (D4200C00036) (De Boer *et al* 2009), but the combination showed a statistically significant advantage in the disease control rate (DCR). Neither study showed a significant advantage in overall survival (OS) as a consequence of adding vandetanib to

standard chemotherapy. In a comparison with erlotinib, PFS and OS were similar for vandetanib (D4200C00057). There was a statistically significant improvement for vandetanib over placebo (both in combination with best supportive care [BSC]) for PFS and DCR; however, OS was similar for vandetanib and placebo (D4200C00044). In a Phase III study in patients with unresectable locally advanced or metastatic MTC for whom no standard therapeutic option was available. (D4200C00058), there was a statistically significant improvement in PFS for vandetanib compared with placebo. The AVAiL study which combined bevacizumab with carboplatin/paclitaxel also did not show an increase in overall survival but did show an increase in PFS (Reck *et al* 2009).

2.2.2 Selumetinib

Drug class

Selumetinib is an orally bioavailable, selective, non-competitive MEK inhibitor. MEK is a critical kinase in the mitogen-activated protein (MAP) kinase signal transduction pathway for many growth factor receptors including EGFR. Cell signalling through growth factor receptors and protein kinases plays an essential role in cell survival, proliferation and differentiation. One of the most important and best understood MAP kinase pathways is the RAS/RAF kinase pathway. In proliferative diseases dysregulation of the growth factor receptor-RAS/RAF MAP kinase pathway leads to uncontrolled cell proliferation and, eventually, tumour formation. It is anticipated that inhibition of MEK activity should inhibit transduction of the mitogenic signals from multiple pathways, resulting in an effect on tumour proliferation, differentiation and survival (Adjei *et al* 2008).

2.2.2.1 Preclinical Experience

An extensive non-clinical package exists for selumetinib. A summary of the main toxicology studies are presented in Section 4.3 of the current version of the selumetinib IB. In summary, selumetinib has been investigated non-clinically as free base and as Hyd-Sulfate salt. No significant safety pharmacology findings were reported in minipig cardiovascular studies or in rat behavioural, pulmonary and gastrointestinal function/tolerability studies. Absorption of selumetinib free base was moderate to high at low doses in rat, dog and monkey. Following dosing of the free base, there was evidence of dose-limiting absorption in mouse, rat, monkey and minipig. However, exposure from selumetinib Hyd-Sulfate salt increased approximately in proportion with dose in mouse and monkey and allowed higher exposures to be achieved in monkey than the free-base. In mouse toxicity studies a pharmacologically active metabolite, *N*-desmethyl selumetinib, was detected at plasma concentrations greater than 10% parent in some dose groups and is approximately 3 to 5 times more potent than the parent compound. Selumetinib was a weak direct inhibitor of CYP2C9 and a weak inducer of CYPs 3A, 1A and 2C9. CYP1A2 was the enzyme primarily responsible for the formation of the N-desmethyl metabolite although selumetinib was also a substrate for 2C19 and 3A4. In rat, monkey and mouse excretion was predominantly via the faeces.

2.2.2.2 Clinical Experience

Seven Phase I or II studies have evaluated selumetinib monotherapy both as a free base suspension (5 studies) or as Hyd-Sulfate capsule formulation (2 studies). Three Phase I or II studies have investigated the selumetinib Hyd-Sulfate capsule formulation in combination with a wide range of other cancer therapeutics. Refer to the selumetinib Investigators Brochure for detailed summaries. The MTD of selumetinib Hyd-Sulfate salt capsule was 75 mg bd. Selumetinib has not been given in combination with vandetanib before.

2.2.2.3 Clinical Pharmacokinetics

The pharmacokinetics of selumetinib were approximately dose proportional for both formulations. Selumetinib had a tmax of 1.5 hours, and t1/2 of 5 to 7 hours. Clearance (CL/F) and steady-state volume of distribution (Vss/F) remained largely consistent across the dose range studied. *N*-desmethyl selumetinib PK profile was largely similar to selumetinib, but exposures were much lower. The plasma pharmacokinetic parameters for selumetinib and selumetinib *N*-desmethyl were similar after single and multiple dosing, suggesting minimal accumulation over time. A food effect study involving administration of selumetinib to patients with advanced solid malignancies under fasting conditions and with a high-fat meal indicated a statistically significant effect of food on the exposure of selumetinib. Geometric least squares mean (Glsmean), Cmax and area under the plasma concentration-time curve (AUC) were reduced by 62% and 19%, respectively, under fed conditions. Therefore selumetinib should be taken with water on an empty stomach for 2 hours prior to dosing and 1 hour after dosing.

2.2.2.3.1 Exposure in subjects of Asian ethnicity

The pharmacokinetics of selumetinib were investigated in study D1532C00086, conducted in the UK involving healthy volunteers of Asian ethnicity (defined as being born in an Asian country, and expatriate for not longer than 5 years, and with maternal and paternal grandparents of Asian ethnicity). The subjects who received Selumetinib in Study D1532C00086 were of the following ethnicities: Japanese, Chinese, Filipino, Malay, Malaysian, Maldivian, Singaporean, Thai, Indian and Vietnamese, and it is not known in these groups whether Selumetinib exposure will be similar to Western subjects or to subjects of the specific Asian ethnicities included in Study D1532C00086.

The pharmacokinetic findings from study D1532C00086 do not support excluding subjects of Asian ethnicity from studies of Selumetinib. However, as it is possible that Asian subjects may experience higher Selumetinib plasma exposure (than would be expected in Western subjects receiving the same dose of selumetinib), there could be a potential for a higher risk of adverse events.

The number of Asian patients with advanced cancer who have received treatment with selumetinib is very low. Emerging information from ongoing study D1532C00067 of Japanese patients receiving selumetinib + docetaxel for second-line treatment of NSCLC suggests that febrile neutropenia may occur more commonly in Japanese patients (3 of 8 patients treated, although comparative data in Japanese patients receiving docetaxel

monotherapy is not available) than might be predicted from studies conducted in Western subjects.

Patients of Asian ethnicity are not excluded from studies evaluating selumetinib. However, when considering enrolling an individual of Asian ethnicity to a selumetinib clinical study, investigators should make a clinical judgment as to whether the potential risk of experiencing higher selumetinib plasma levels outweighs the potential benefit of treatment with selumetinib. The Patient Information and Consent form for studies of selumetinib includes information on the possibility of higher selumetinib plasma levels and occurrence of adverse events in Asian subjects than in subjects who are not of Asian origin. Investigators should be aware of the potentially higher risk of adverse events when monitoring patients of Asian ethnicity receiving treatment in clinical studies of selumetinib.

2.2.2.4 Safety

The maximum tolerated dose (MTD) of selumetinib was 100 mg bd as a free-base suspension and 75 mg bd as a Hyd-Sulfate salt capsule. Safety data have been evaluated from four Phase I studies and four Phase II monotherapy studies. The most frequently reported AEs in Phase II monotherapy studies with the free-base suspension formulation and Phase I monotherapy studies of both formulations were fatigue, dermatitis acneiform, nausea, diarrhoea, vomiting and peripheral oedema. Small mean increases in systolic and diastolic blood pressure have been observed in patients on selumetinib. No clinically significant trends were observed for pulse rate in any study. Review of ECG) parameters demonstrated no evidence of QTc prolongation. A trend towards elevated liver transaminases has been observed in patients who received bd dosing of selumetinib. The majority of transaminase elevations reported either remained within normal limits or increased by no more than a single Common Terminology Criteria (Version 3) for Adverse Events (CTCAE) grade. There was a trend towards a small mean decrease in albumin and in some patients an increase in serum phosphate that was observed after initiation of selumetinib. Refer to the current version of the selumetinib IB for detailed summaries of AEs.

2.2.2.5 Efficacy

There were no significant differences in the primary endpoints of four Phase II monotherapy studies (see current version of the selumetinib IB) comparing selumetinib free-base suspension formulation with standard chemotherapy regimes in melanoma, pancreatic cancer, colorectal cancer, or NSCLC [D1532C00003, D1532C00008, D1532C00011 and D1532C00016].

However, objective responses were seen in both the melanoma and NSCLC studies. In the Phase II melanoma study (D1532C00003) (Dummer *et al* 2008) 6 partial responses were noted in patients treated with selumetinib (out of 104 patients enrolled), 5 of which were in patients with the *BRAF* mutation. In the Phase II NSCLC study (D1532C00016), 2 patients treated with selumetinib (out of 40 enrolled) had a partial response (mutation status unknown).

One patient in the Phase I Study D1532C00005 treated with selumetinib capsule formulation (75 mg bd) had a complete response (out of 31 patients enrolled). This patient had a BRAF+ melanoma. In another Phase I study with selumetinib capsule formulation assessing the effect of food on the dosing with selumetinib (D1532C00020), 2 patients with melanoma had a partial response (out of 28 patients enrolled).

2.3 Rationale for the proposed trial

2.3.1 Proposed Combination Hypothesis for Vandetanib and Selumetinib

The proposed combination hypothesis is that combined inhibition of VEGF, EGF and MEK signalling in an unselected NSCLC patient population (refractory to first-line therapy) may deliver greater benefit than inhibition of any of these targets alone.

The primary aim of the expansion cohort is to demonstrate the effective targeting of EGFR, VEGF and MEK signal transduction through pharmacodynamic end points. The study is not powered sufficiently to deliver definitive clinical efficacy data and thus it is not essential to enrol a homogenous patient population. However, it would be important to have imaging and biomarker evidence to test the rationale of multiple pathway inhibition. Inclusion of patients, for example, who have had previous EGFR targeted therapy (and would normally be resistant to EGFR Tyrosine Kinase Inhibitors (TKIs)) and those who are EGFR TKI naïve and properly informed would be helpful. Having a less restrictive inclusion criteria would also significantly enhance the recruitment rate.

Inhibition of EGFR signalling has been shown to benefit NSCLC patients with activating mutations in the EGFR tyrosine kinase domain or those with high EGFR gene copy number (Mok *et al*.; 2009). There is mounting evidence that NSCLC patients with mutant *KRAS* are less likely to respond to EGFR signalling inhibition (Roberts *et al*.; 2010). The correlation is even more clear-cut in metastatic colorectal cancer where patient tumours containing *KRAS* mutations clearly do not respond to treatment with the anti-EGFR monoclonal antibodies cetuximab or panitumumab. This resistance is presumed to be due to the activation of pathways downstream of RAS such as MEK/ERK being driven by the mutant *KRAS* rather than the EGFR. Conversely, preclinical data indicates that tumour cell lines and human tumour xenografts with *BRAF* or *KRAS* gene mutations tend to be sensitised to MEK inhibition, because of their constitutive activation and dependency on ERK pathway signalling. However, some tumour cell lines have been identified (head and neck squamous cell carcinoma and colorectal carcinoma cells) that lack *BRAF* or *KRAS* gene mutation yet retain sensitivity to MEK inhibition, and these also tend to be sensitive to EGFR tyrosine kinase inhibitors.

VEGF signalling is believed to be a pivotal angiogenic factor that can induce the growth, survival and permeability of tumour blood vessels, required to support the progression of solid tumour disease. The monoclonal antibody bevacizumab that specifically sequesters VEGF-A, has been shown to improve survival in NSCLC patients when combined with standard paclitaxel and carboplatin chemotherapy (Sandler *et al*.; 2006). Clinical data from patients with metastatic colorectal cancer suggest that the response to VEGF inhibition is not influenced by *KRAS* gene status.

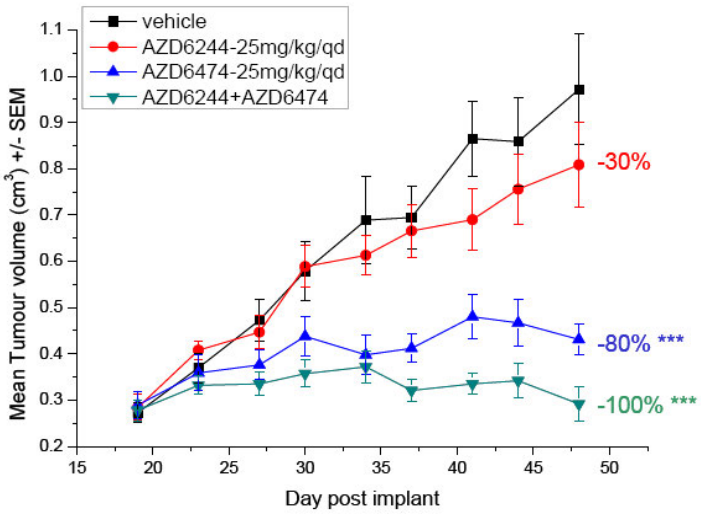
Consequently, combined inhibition of VEGF signalling, EGFR signalling and MEK signalling may deliver benefit in NSCLC patients.

2.3.2 Combination Non-Clinical Anti-Tumour Activity

The addition of MEK inhibition to inhibition of either EGFR or VEGFR signalling was initially studied by examining selumetinib in combination with gefitinib (a selective EGFR tyrosine kinase inhibitor) or cediranib (a potent VEGFR tyrosine kinase inhibitor without activity against EGFR). A combination efficacy study of selumetinib and gefitinib was performed *in vivo* using an A549 human NSCLC model (*KRAS* mutant). The A549 tumour cell line is comparatively insensitive to monotherapy treatment with selumetinib or gefitinib alone, and when grown as a human tumour xenograft, demonstrates only modest sensitivity to treatment with either agent. However, a combination of selumetinib and gefitinib demonstrates a greater anti-tumour effect in this tumour xenograft model than either agent alone. A combination efficacy study of selumetinib and cediranib was performed in a Calu-6 human NSCLC model (*KRAS* mutant). This tumour line is sensitive to monotherapy treatment with selumetinib but not to treatment with an EGFR tyrosine kinase inhibitor (gefitinib), both *in vitro* and *in vivo*. Calu-6 tumour xenografts are also sensitive to treatment with a VEGFR tyrosine kinase inhibitor, such as cediranib, *in vivo*. When selumetinib and cediranib were dosed concomitantly in this model, the combination demonstrated a greater anti-tumour effect than either agent alone. Similar results have also been reported with this combination in orthotopic lung cancer models using NCI-H441 and NCI-H460 cells (both *KRAS* mutant) (Takahashi *et al*, 2011, Poster 629, AACR). However, in none of these studies was a direct statistical comparison of either monotherapy versus the combination performed and it is unclear if the combination efficacy was additive or synergistic relative to the two monotherapies.

Taken together the above three studies suggest that inhibition of MEK in combination with inhibition of either EGFR or VEGFR signalling and may give enhanced efficacy over either agent as a monotherapy. A similar or greater antitumour effect could therefore be expected for the combination of selumetinib with the dual EGFR and VEGFR inhibitor vandetanib. The efficacy of this combination was therefore examined in the A549 human NSCLC model (*KRAS* mutant). Although this tumour model is comparatively insensitive to selumetinib or gefitinib monotherapy, it does respond significantly to vandetanib – which can be attributed to inhibition of VEGF signalling. Dose groups were vehicle control selumetinib alone (25 mg/kg, PO once daily), vandetanib alone (25 mg/kg, PO once-daily), and a combination of selumetinib (25 mg/kg, PO once daily) plus vandetanib (25 mg/kg, PO once-daily). Growth inhibition was calculated from the start of treatment by comparison of the mean change in tumour volume for control and treated groups. The addition of selumetinib to vandetanib was found to induce a 35% increased anti-tumour effect versus vandetanib alone (Figure 1.) The tumour growth inhibition in the combination group was significantly greater ($p<0.005$; two-tailed t-test) than that in the vandetanib group.

Figure 1. **Effect of administration of selumetinib (AZD6244; 25 mg/kg; orally once-daily), vandetanib (AZD6474; 25 mg/kg; orally once-daily), or a combination of the two, in on tumour size in A549 human NSCLC tumour xenografts.**



***P<0.0005 relative to vehicle control. To remove any size-dependency prior to statistical evaluation, data was log-transformed prior to statistical evaluation using a one-tailed two-sample t test.; one-tailed t-test

When body weights were examined, treatment with selumetinib did not induce weight loss relative to the control group and weight loss in animals receiving a combination of selumetinib and vandetanib was comparable to the weight loss observed with vandetanib alone. Two out of ten animals in the combination group were sacrificed early due to bloated abdomens and subsequently found to have fluid within their peritoneal cavity at autopsy. Such an effect has been observed as a consequence of amyloidosis at a low level in untreated athymic mice and the two cases in the combination arm of this study may be an exacerbation of this condition. Further studies investigating the toxicology of vandetanib and selumetinib in combination have not been conducted due to the late stage patient population in the trial. This is in accordance with the Note for guidance on non-clinical evaluation for anti-cancer pharmaceuticals (EMEA/CHMP/ICH/646107/2008; 2008).

2.3.3 Clinical experience of Vandetanib and Selumetinib Combination

Vandetanib and selumetinib have not been given in combination to patients.

2.3.4 Possible toxicities based on single agent studies

AEs related to the skin, gastrointestinal system, cardiovascular systems and fatigue are commonly observed with both agents.

Clinical administration of both agents has been associated with skin toxicities with dermatitis acneiform and photosensitivity reaching CTCAE (version 3.0) Grade ≥3 in vandetanib and the former also being the most common AE in selumetinib trials. The co-administration of vandetanib and selumetinib may result in a higher frequency or intensity of these dermatological adverse events, especially dermatitis acneiform and rash. Similarly, administration of both agents has been associated with gastrointestinal adverse events and

the co-administration of vandetanib and selumetinib may result in a higher frequency or intensity of these gastrointestinal adverse events, especially nausea and vomiting.

Cardiovascular adverse events in Phase III trials of vandetanib include hypertension, deep venous thrombosis, pulmonary thrombosis, pulmonary haemorrhage, peripheral ischaemia and cerebrovascular events. Hypertension is considered to be a class effect for VEGF pathway inhibitors. Prolongation of the QTc interval, using Bazett's correction, was seen in Phase II studies. Two cases of torsade de pointes (both reversible and non-fatal) have been reported out of more than 4000 patients who have received vandetanib. No significant changes in heart rate were observed. Hypertension has also been observed in clinical studies of selumetinib. Some patients receiving selumetinib have been observed to develop asymptomatic decreases in left ventricular ejection fraction (LVEF) in the absence of obvious confounding comorbidities. Patients receiving selumetinib frequently report the development or worsening of oedema, particularly at peripheral sites or the face. The underlying aetiology of the oedema and fluid accumulation adverse events is unclear at present. There is currently no evidence to suggest that the oedema is due to congestive cardiac failure. The co administration of vandetanib and selumetinib may result in a higher frequency or intensity of these cardiovascular adverse events, especially hypertension.

In addition studies of vandetanib monotherapy occurrences of dyspnoea, pneumonia and interstitial lung disease were reported in some cases CTCAE (version 3.0) Grade $\geq$3. There is also data from a pharmacoethnicity study suggesting that interstitial lung disease may occur more often in patients from Japan than in patients from elsewhere. Dyspnoea and interstitial lung disease have been reported in patients receiving selumetinib, although the majority of these events have occurred in patients with lung/pleural disease due to their underlying malignancy. The combination of two agents with this finding may result in a higher frequency or intensity of these adverse events.

The gastrointestinal AE's observed with both agents does raise the possibility of an interaction of the combination on the absorption one or both agents. Additionally both vandetanib and selumetinib have been shown to induce CYP3A4 and selumetinib is a substrate of CYP3A4 raising the possibility of metabolic interaction. Pharmacokinetics of both agents and the two most abundant metabolites of each will be performed during the study to detect any such interactions.

2.3.5 Supportive combination class data

Preliminary clinical data are available for a combination study of selumetinib with the EGFR inhibitor erlotinib. A total of 48 patients received treatment with selumetinib in combination with erlotinib 100 mg once daily (Study D1532C00004). Doses of 50 mg bd and 75 mg bd selumetinib were explored in combination with erlotinib however the combination of selumetinib 50 mg bd and erlotinib to be non-tolerated (due to Grade 3 rash and diarrhoea). The tolerability of once daily dosing of selumetinib 50, 100 or 150 mg was subsequently explored in combination with erlotinib. All patients who received chronic administration of selumetinib 150 mg bd and erlotinib experienced either Grade 2 or 3 adverse events of rash and/or diarrhoea and/or mucositis, which required dose interruptions and reductions in some patients; therefore, this dose combination was not recommended for use in clinical trials.

The most common AE across all selumetinib doses were diarrhoea and rash. There was no evidence of a PK interaction between selumetinib and erlotinib.

A preliminary review of the available safety data indicated that the adverse event profile for the combination of selumetinib with erlotinib is consistent with the individual monotherapy profiles for these agents. Selumetinib 100 mg once daily is the recommended dose for combination with erlotinib 100 mg once daily.

2.3.6 Marketing Experience

Selumetinib had not received marketing approval in any country or region (at the time of development of this protocol). In 2015, the FDA granted Orphan Drug Designation for selumetinib, for the treatment of uveal melanoma.

Regulatory submissions for vandetanib in combination with chemotherapy in patients with advanced NSCLC were submitted to the FDA and the EMA in June 2009 and withdrawn in October 2009.

The FDA and the EMA accepted regulatory submissions for review of vandetanib in the treatment of patients with advanced medullary thyroid cancer (MTC) in September 2010. Vandetanib has recently received FDA marketing approval (100 mg and 300 mg tablets) for treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

3 TRIAL DESIGN

This is a Phase I, multi-centre, dose escalation study (any solid tumour) with an expansion cohort (NSCLC). The expansion cohort will include functional imaging and assess tumour and blood biomarkers of both vandetanib and selumetinib.

3.1 Clinical trial objectives and endpoints

Primary objectives and endpoints

Primary objectives	Endpoints
Assessing the safety and toxicity profile of the combination of vandetanib and selumetinib.	Determining causality of each adverse event to vandetanib or selumetinib and grading severity according to NCI CTCAE Version 4.02
To propose a recommended dose and schedule for Phase II evaluation of the combination of vandetanib and selumetinib.	Determining the MTD of the combination of vandetanib and selumetinib as proposed by the protocol. OR the single agent recommended Phase II dose (RP2D) of vandetanib in combination with the single agent RP2D of selumetinib.

Secondary objectives and endpoints

Secondary objectives	Endpoint
Determine the plasma PK profiles of vandetanib and selumetinib and their metabolites	PK parameters during Cycle 1 including Cmax and AUC pre and post treatment with vandetanib alone and following the combination of vandetanib and selumetinib. Parameters to be measured include: • vandetanib • selumetinib and N-desmethyl metabolite. (other metabolites may be measured as determined during the study).
Expansion cohort To evaluate progression free survival (PFS) of patients with NSCLC after treatment with the combination of vandetanib and selumetinib.	Determine PFS at 12 weeks (from date of first dose of vandetanib) by RECIST (Response Evaluation Criteria In Solid Tumors) criteria.
Expansion cohort To evaluate the survival rate of patients with NSCLC after treatment with the combination of vandetanib and selumetinib.	Determine the one year survival rate.
Expansion cohort To assess the tumour metabolism in patients with NSCLC.	Measurement of tumour metabolism using CT FDG-PET imaging during Cycle 1 pre and post treatment with vandetanib alone and following the combination of vandetanib and selumetinib.

Tertiary objectives and endpoints

Tertiary objectives	Endpoint
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.1.1 Definition of dose limiting toxicity

The dose limiting toxicity (DLT) and maximum tolerated dose (MTD) are defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.

During the dose escalation phase, DLTs identified in Cycle 1 of combination treatment will inform the decisions to dose escalate through the increasing dose levels. DLTs will be defined throughout the treatment period during dose escalation and in the expansion cohort and will be considered in determining the RP2D. The criteria by which DLTs will be assessed against during Cycle 1 for dose escalation decisions are as follows:

A DLT is defined as an adverse event considered highly probable or probably **related to** vandetanib or selumetinib, that occurs during the first cycle of combination period:

- Death
- Neutropenia Grade 4 for ≥5 days duration (absolute neutrophil count (ANC) <0.5 x 10^9/L) *

- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) with Grade 3 or 4 neutropenia (absolute neutrophil count [ANC] <1.0 x 10^9/L and fever ≥38.5°C);
- Infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L)
- Thrombocytopenia Grade 4: a) for ≥5 days *See footnote, or b) associated with active bleeding, or c) requiring platelet transfusion.
- Grade 3 or 4 toxicity to organs other than the bone marrow including Grade 3 and Grade 4 biochemical AEs.
- Grade 4 diarrhoea
- Any drug related toxicity that causes a treatment interruption for > 2 weeks (14 successive days). If a patient is deemed fit to restart treatment on Day 15 then this is not a DLT.
- QTc prolongation >500 msec
- Grade 4 hypertension.
- Persistent hypertension (defined as blood pressure >160/100 mmHg) sustained for >1 week despite optimal therapy.

EXCLUDING:

- Grade 3 nausea
- Grade 3 or 4 vomiting in patients (who have not received optimal treatment with anti-emetics)
- Grade 3 skin toxicity (and patients are receiving supportive measures to manage toxicity)
- Grade 3 diarrhoea in patients (who have not received optimal treatment with anti diarrhoeals)
- Alopecia (any grade)

*** Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed within 5 days of the onset of the event to determine if a DLT has occurred. Continue to monitor the patient closely until resolution to Grade 3 or less.**

Should any change be made to the grade or causality of an AE during the trial that may alter its DLT status, the Centre for Drug Development (CDD) must be informed immediately as this may affect dose escalation decisions.

3.1.2 Definition of maximum tolerated dose

The MTD will be determined as the dose level below that at which two of up to six patients at the same dose level experience DLT in the first cycle of treatment (as defined in Section 3.1.1).

The maximum administered dose (MAD) could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level due to the expectation that higher dose levels would be too toxic to administer to patients. The recommended dose for the expansion cohort evaluation will be determined following discussion of all the relevant toxicity data between the Sponsor (to include review by the

Protocol Safety and Review Board) and the Study Team, including the Chief Investigator and participating investigators.

3.1.3 Patient evaluability

Dose escalation:

All patients who meet the eligibility criteria and receive at least one dose of the combination treatment (vandetanib and selumetinib) will be evaluable for safety assessment.

Patients who receive fewer than 21 of 28 daily doses of the combination treatment in Cycle 1 (for reasons other than toxicity) will not be evaluable for dose escalation decisions.

Expansion cohort:

All patients who meet the eligibility criteria and receive at least one dose of the combination treatment (vandetanib and selumetinib) will be evaluable for safety assessment.

All patients who meet the eligibility criteria receive at least one cycle* of vandetanib and selumetinib and have a baseline assessment of disease will be evaluable for response. To be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurements must be confirmed by repeat measurements performed no less than four weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the combination treatment is given.

*To be evaluable for response, a patient must receive a minimum 21/28 daily doses of the combination treatment in Cycle 1.

3.2 Design of the clinical trial

This is a Phase I, multi-centre, dose escalation study (any solid tumour) with an expansion cohort (NSCLC).

3.2.1 Dose escalation

The final number of patients recruited to this phase will depend on the number of dose escalations required to reach the RP2D.

In the dose escalation stage of the study, the Sponsor reserves the right to investigate alternative doses of vandetanib and selumetinib in response to emerging safety data. Recruitment into cohorts will follow a “rolling-six” design. Dose assignment for each cohort will be carried out, using all available data, by the Sponsor in conjunction with the CI and PI(s). Cohorts of three to six patientswill be entered at each dose level.

If one out of three patients experience a DLT (as defined in Section 3.1.1, up to six patients will be treated at that dose.

If one out of up to six patients experience a DLT, dose escalation will continue.

If two out of up to six (i.e. between two and six) patients experience a DLT dose escalation will stop and this dose will be defined as the maximum administered dose (MAD). At least three more patients will be treated at a dose below the MAD to define the MTD.

Each of the cohorts will assess vandetanib in combination with selumetinib. Selumetinib will initially be administered at three dose levels, 25, 50 and 75 mg (oral, twice daily).

The first three cohorts will initially investigate combining vandetanib (100mg, once daily) with increasing doses of selumetinib as follows:

Study cohort	Vandetanib	Selumetinib
Cohort 1	100 mg po od	25 mg po bd
Cohort 2	100 mg po od	50 mg po bd
Cohort 3	100 mg po od	75 mg po bd

Should MTD not be achieved on completion of Cohort 3, recruitment will continue into additional cohorts investigating alternative doses of selumetinib and vandetanib in combination.

The dosing regimen for each new cohort will be communicated and confirmed to clinical sites following the dose review meetings on completion of each cohort.

Cycle 1 will consist of 42 days. This includes the 14 days of vandetanib alone plus the 28 days of combination treatment.

Subsequent cycles will be of 28 days in length and consist of continuous treatment with vandetanib and selumetinib at steady state. There is no planned interval between cycles. Patients may continue to receive the combination therapy in the absence of disease progression or unacceptable toxicity (please see Section 5.6).

Pharmacokinetic parameters will also be measured pre and post treatment with single agent vandetanib and following combination treatment with selumetinib.

At the end of the dose escalation phase, safety data including a listing of all AEs will be collated and reviewed against the study objectives and endpoints. The decision to proceed to the expansion cohort will be made by the Sponsor following review of the data by the Sponsor (to include review by the Protocol and Safety Review Board), Chief Investigator and Principal Investigators. This decision will be communicated to all investigator sites by the Sponsor.

3.2.2 Expansion cohort

Once the RP2D of the combination has been determined, a further 30 NSCLC patients will be treated at this dose level.

All patients will continue to be assessed for safety and tolerability of the combination treatment. All patients will be imaged and will also be asked to consider additional consent to

an optional biopsy sampling schedule. It is expected that a minimum of 20 patients will complete the full imaging schedule and a minimum of 10 patients will consent to be biopsied. Patients who undergo the additional biopsies may also complete the full imaging schedule if further evaluable lesions are identified.

Imaging will be performed to measure tumour vascularisation and metabolism using FDG-PET [redacted] These functional imaging assessments will take place pre and post treatment with single agent vandetanib and following combination treatment with selumetinib. [redacted]

Progression free survival will be assessed at 12 weeks and one-year survival will also be recorded.

3.2.3 Study duration

Following completion of recruitment to the dose escalation phase, the data will undergo review and assessment by the Sponsor. The Sponsor will confirm the decision to proceed to the expansion cohort.

The recruitment period of the dose escalation phase could increase pending the addition of further cohorts to investigate alternate doses of the study drug combination.

Patients can continue on study treatment on observation of SD, PR or CR therefore time on study for patients cannot be defined. Patients may continue to receive the combination therapy in the absence of disease progression or unacceptable toxicity. If the patient has not progressed after 6 cycles, they may be treated for further cycles after a formal written request has been made to and written approval received from the Sponsor.

4 PATIENT SELECTION

4.1 Eligibility criteria

The patient must fulfil the eligibility criteria (listed in Sections 4.1.1 and 4.1.2).

4.1.1 Inclusion criteria

1. **(Dose escalation cohorts)** Histologically or cytologically proven solid tumour for which no conventional therapy exists or is declined by the patient
2. **(Expansion cohort only)** Histologically or cytologically confirmed NSCLC patients only, for which no conventional therapy exists or is declined by the patient.
   - If only cytologically confirmed, baseline biopsy is mandatory for a patient to be eligible.
   - For NSCLC patients to be eligible for the expansion cohort they must have received:
     - One prior line of chemotherapy and/or
     - Previous platinum based chemotherapy and/or
     - At least one previous EGFR inhibitor
3. **(Expansion cohort only)** Measurable disease according to RECIST criteria Version 1.1
4. Life expectancy of at least 12 weeks
5. World Health Organisation (WHO) performance status of 0-1 (Appendix 1)
6. Baseline LVEF ≥ 50%
7. Haematological and biochemical indices within the ranges shown below. These measurements must be performed within one week (Day -7 to Day -1) before the patient goes on study.

Laboratory Test	Value required
Haemoglobin (Hb)	≥9.0 g/dL
Absolute neutrophil count	≥1.5 x 10^9/L
Platelet count	≥100 x 10^9/L
Normal serum calcium (adjusted)*	2.15-2.55 mmol/L
Normal serum magnesium*	0.60-1.0 mmol/L
Normal serum potassium	≥4.0 mmol/L
Either: Serum bilirubin	≤1.5 x upper limit of normal (ULN) This does not apply to patients with Gilbert's disease.
Or: Alanine amino-transferase (ALT) or aspartate amino-transferase (AST) and alkaline phosphatase (ALP)	≤ 2.5 x ULN unless raised due to liver metastases in which case up to 5 x ULN is permissible
Either: Calculated creatinine clearance (using the Wright or C&G formula)	> 50 mL/min
Or: Isotope clearance measurement**	≥ 50 mL/min (uncorrected)
INR or aPTT***	< 1.5 x ULN

*or normal range according to the local laboratory
** Isotope clearance result to be used to confirm eligibility if calculated C&G/Wright method results in GFR of = 50 mL/min.
*** Therapeutic INR values (2.0-3.0) are acceptable to confirm eligibility for patients who are taking concomitant warfarin.

8. 18 years or over

9. Ability to swallow and retain oral medications.

10. Written (signed and dated) informed consent and be capable of co-operating with treatment, and follow-up

4.1.2 Exclusion criteria:

1. Radiotherapy (except for palliative reasons), endocrine therapy, immunotherapy or chemotherapy during the previous 4 weeks (6 weeks for investigational medicinal products) before treatment.

2. Patients who have been withdrawn from treatment with agents that target EGFR because of unacceptable toxicity (prior treatment with these agents is allowed) and those patients who have had an EGFR dose reduction by 50% or more (dose modifications as per standard clinical practice is allowable and is not considered a reduction e.g. afatinib administration).

3. Expansion cohort only: Prior treatment with any agent that targets MEK or VEGFR or VEGF

4. Any prior exposure to RAS or RAF inhibitors

5. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or certain Grade 2 toxicities, which in the opinion of the Investigator and the Centre for Drug Development (CDD) should not exclude the patient.

6. Symptomatic brain metastases (patients must be stable for >3 months post RT treatment) or spinal cord compression.
7. Patients with interstitial lung disease.
8. Pregnant or lactating women are excluded. Female patients with the ability to become pregnant who have a negative serum or urine pregnancy test before enrolment and agree to use two of the following three highly effective forms of combined contraception (oral, injected or implanted hormonal contraception and condom, have a intra-uterine device and condom, diaphragm with spermicidal gel and condom) for four weeks before entering the trial, during the trial and for six months afterwards are considered eligible.

9. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using one form of highly effective contraception [condom plus spermicide] during the trial and for six months afterwards). Men with pregnant or lactating partners should be advised to use barrier method contraception (e.g. condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

10. Major surgery from which the patient has not yet recovered.

11. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.

12. Known to be serologically positive for Hepatitis B, Hepatitis C or Human Immunodeficiency Virus (HIV).

13. Cardiac conditions as follows:
    - Clinically significant cardiovascular event within 3 months prior to entry to include:
        - Myocardial infarction
        - Angina requiring use of nitrates more than once weekly
        - Superior vena cava syndrome

  - Class II/III/IV cardiac disease (New York Heart Association [NYHA]) (Appendix 4)
  - Presence of cardiac disease that in the opinion of the Investigator increases the risk of ventricular arrhythmia.
- History of arrhythmia which is symptomatic or requires treatment (CTCAE 4.02), symptomatic or uncontrolled atrial fibrillation despite treatment or asymptomatic sustained ventricular tachycardia. Patients with atrial fibrillation controlled by medication are permitted.
- Uncontrolled hypertension (BP > 160/100 despite optimal therapy)
- Prior or current cardiomyopathy
- Atrial fibrillation with heart rate >100 bpm
- QTcB (Bazett's formula) > 450 msec on screening ECG (Note: If a patient has a QTcB interval ≥ 450 msec on screening ECG, the screen ECG may be repeated twice [at least 24 hours apart]. The average QTcB from the three screening ECGs must be < 450 msec in order for the subject to be eligible for the study.)
- History of congenital long QT syndrome
- History of Torsade de Pointes (or any concurrent medication with a known risk of inducing Torsades de Pointes. See Appendix 16.8)

14. Concomitant medications that are potent inducers of CYP3A4 function i.e. rifampicin, rifabutin, phenytoin, carbamazepine, Phenobarbital and St John's Wort.
15. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial (e.g. evidence of severe or uncontrolled systemic disease or concurrent condition or that may affect ability to absorb oral agents).
16. Current malignancies of other types, with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin. Cancer survivors, who have undergone potentially curative therapy for a prior malignancy, have no evidence of that disease for five years or more and are deemed at negligible risk for recurrence, are eligible for the trial.
17. If a participant plans to participate in another interventional clinical study, whilst taking part in this Phase I study. Participation in an observational study would be acceptable.
18. Ophthalmological conditions as follows:
    a. Current or past history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR) or retinal vein occlusion.
    b. Intraocular pressure (IOP) > 21 mmHg or uncontrolled glaucoma (irrespective of IOP).

[redacted]

4.2 Patient enrolment

All patients who provide informed consent must be registered in the electronic data capture (EDC) system including any screen failures. The screening number will be automatically allocated during the process.

Before enrolling the patient in the trial, the Investigator or designated representative must determine the eligibility of the patient. Please ensure that CDD are notified of any eligibility concerns at least four working days before treatment is planned.

Eligible patients must be enrolled in the EDC system before they start treatment with vandetanib. If the patient is eligible the patient number will be automatically allocated during the enrolment process.

Dose level allocation will be confirmed to the Investigator (and team as applicable) by the CDD following patient enrolment.

5 TREATMENT

5.1 Selection of the Phase I starting dose and schedule

5.1.1 Selection of Vandetanib dose

Initially vandetanib will be dose loaded at 300 mg od for four days (to rapidly reach the approximate steady state dose of 100 mg od) followed by 10 days at 100 mg od. The dose loading will achieve the steady state plasma concentration at a faster rate than would be possible using 100 mg od tablets. The steady state plasma concentration will then be maintained by dosing once daily with 100 mg.

Dose loading the vandetanib for the first four days of the study is a novel approach which has not been performed in clinical trials using vandetanib before.

In vandetanib monotherapy trials, it was observed that 28 days of 100 mg od administration was required before a steady state of vandetanib was achieved. The length of time to achieve steady state is a concern, especially in the expansion cohort which will recruit NSCLC patients. Disease progression in this group of patients can be rapid. To reduce the time between starting vandetanib and achieving steady state a novel administration schedule has been proposed to reach the steady state of vandetanib within 14 days and allow administration of the combination treatment. The loading dose of 300 mg od vandetanib has been explored in monotherapy trials and has been found to be tolerable to patients (please see current version of vandetanib IB).

The vandetanib dose at steady state is based on the experience of previous clinical trials (refer to the vandetanib IB for detailed summaries of previous trials), which showed acceptable tolerability and safety profile at the selected dose level.

Steady state doses of 200 or 300mg od vandetanib will be considered based on emerging data during the study.

Should the steady state dose of 300mg od be explored, an increased ‘loading phase’ total dose of vandetanib may be considered i.e. 600mg (300md bd) for two days before reverting back to 300mg od. This two day 600mg “dose loading” should allow for plasma levels approximating the expected 300mg od steady state level to be reached within a few days thereby reducing the period during which the patient has sub pharmacodynamic plasma levels of Vandetanib. Steady state will therefore be reached within 14 days as in previous cohorts. Pharmacokinetic modelling of the proposed regimens using a 200 or 300 mg dose of vandetanib has been performed and the appropriate loading phase of vandetanib has been established for both doses should a decision be made to increase the vandetanib dose.

5.1.2 Selection of Selumetinib dose

The starting dose of selumetinib has been selected as 25 mg bd. The starting dose of 25 mg bd is two dose levels below the highest dose of the Hyd-sulfate capsule form explored in previous clinical trials (refer to the selumetinib Investigator Brochure (IB) for detailed summaries of previous trials), 75 mg bd, which showed an acceptable tolerability and safety profile.

This is the first time the combination of vandetanib and selumetinib will be used in humans. Therefore a reduced starting dose of selumetinib has been selected followed by dose escalation to 50 mg bd and then 75 mg bd. Selumetinib 100 mg od is the recommended dose in combination with erlotinib (EGFR inhibitor) (Study D1532C00004, see current selumetinib IB) therefore once daily administration of selumetinib may be considered on observation of unacceptable toxicity under twice daily administration (see Section 3.2).

5.2 Dosing schedule/treatment schedule

Vandetanib is an orally administered tablet. The vandetanib dose is to be taken once or twice a day.

Selumetinib is an orally administered capsule. The selumetinib dose is to be taken once or twice a day.

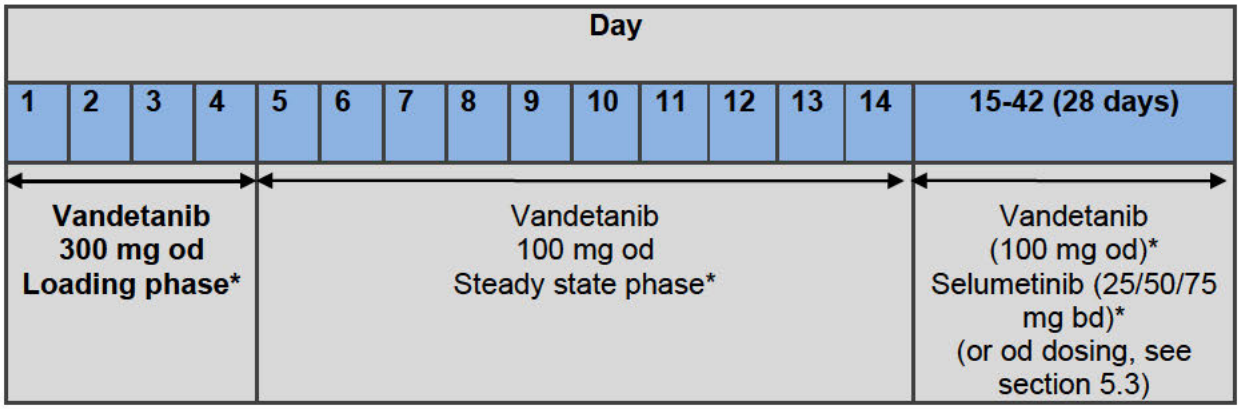
Patients should take the correct number of vandetanib tablets and selumetinib capsules at the same time every day. Tablets and capsules are to be taken whole and not split. The vandetanib tablets and selumetinib capsules must be swallowed whole (with water) and not chewed, crushed, dissolved or divided.

Selumetinib should be taken on an empty stomach - no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing. There is no restriction on dosing with food for vandetanib therefore vandetanib and selumetinib should be taken at the same time adhering to those restrictions associated with selumetinib.

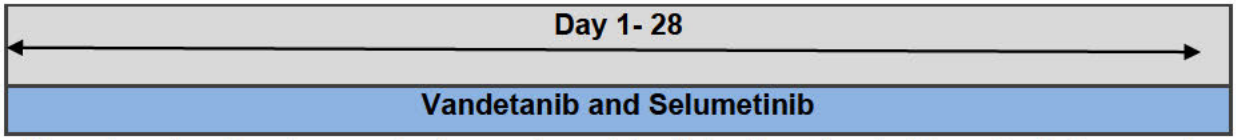
5.2.1 Dose escalation phase.

Cohorts 1-3: Vandetanib is being dose loaded for the first four days at 300 mg once daily (od) and then be maintained by dosing once daily with 100 mg. Dose loading of vandetanib will only occur once at the start of Cycle 1, at the beginning of the study treatment. Selumetinib will be administered twice a day (bd). Administration will start after on Day 15 following 14 days of treatment with vandetanib alone. The starting dose will be 25 mg bd administered orally. Cohorts of up to 6 patients will receive escalating doses of selumetinib (25, 50 and 75 mg bd).

Cohorts 1-3: Cycle 1 of treatment (loading dose plus single agent plus combination i.e. Days 1- 42) is as follows:



Cycle 2 of treatment onwards will consist of combination treatment only as follows:



There is no loading dose or single agent vandetanib treatment period from Cycle 2 onwards.

For cohorts post Cohort 3: following review of PK and clinical data by the Sponsor and Investigators, the Sponsor will confirm:

- Vandetanib loading and single agent dose and schedule (Cycle 1 only)
- Vandetanib dose and schedule in combination with selumetinib
- Selumetinib dose and schedule

On commencing combination therapy, one cycle will consist of continuous daily dosing for 28 days. There will be no planned interval between cycles.

Patients may continue to receive the combination therapy in the absence of disease progression or unacceptable toxicity. If the patient has not progressed after 6 cycles, they may be treated for further cycles after a formal written request has been made to and written approval received from the Sponsor.

5.2.2 Expansion cohort.

All patients will be dosed according to the RP2D of the combination of vandetanib and selumetinib as established in the dose escalation phase.

Patients may continue to receive the combination therapy in the absence of disease progression or unacceptable toxicity. If the patient has not progressed after 6 cycles, they may be treated for further cycles after a formal written request has been made to the Sponsor and written approval received.

5.3 Dose escalation schedule

In the dose escalation stage of the study, the Sponsor reserves the right to investigate alternative doses of vandetanib and selumetinib in response to emerging safety data. Recruitment into cohorts will follow a “rolling-six” design. Dose assignment for each cohort will be carried out, using all available data, by the Sponsor in conjunction with the CI and PI(s).

If MTD is not reached by the third cohort (100 mg vandetanib and 75 mg selumetinib) , based on emerging data from the study,

- Vandetanib loading dose and steady state dose may be increased. Once or twice daily dosing will be considered.
- Once daily selumetinib dosing may be considered if twice daily dosing results in unacceptable toxicity.

Treatment will be continuous for up to 28 days for safety assessment and dose escalation purposes. Up to six patients will be studied at each dose level. Dose delay and reductions will be mandated according to protocol-defined criteria.

Treatment of subsequent patients at each dose level should not begin until the first patient has completed 14 days of single agent vandetanib. Their start of treatment date may be staggered by the Sponsor dependent upon emerging data.

A rolling six design (Sklonik *et al*, 2008) will be used to recruit patients. Three to six evaluable patients will be entered at each dose level for the determination of MTD.

The dose level of selumetinib and vandetanib will be assigned according to the number of patients currently enrolled at the current dose level, the number of DLTs (and any other drug related adverse events) observed at the current dose level and the number of patients enrolled who are at risk of developing a DLT. When sufficient data, as deemed by the Sponsor and (Chief Investigator) CI, are available to assess these, the selumetinib and vandetanib dose level will be assigned according to the following:

If the data is available from a minimum of three patients who have been treated in a cohort and no DLTs have been observed at that dose level for the complete duration of their first cycle, then dose escalation can be considered.

If one DLT has been observed at the current dose level in the first cycle, the dose will remain the same.

If two patients experience a DLT at any dose level during the first cycle, the dose will be de-escalated and the previous dose level will be expanded to include up to 6 patients.

If not all data are available from at least three patients in order to take a decision on dose escalation but an eligible patient is ready to begin treatment, the dose level will remain the same. Up to 6 patients may be enrolled at that dose level.

In the event of two patients experiencing a DLT at the first dose level, the dose level may be de-escalated following discussion of all the relevant toxicity data between the Sponsor and the Study Team, including the Chief Investigator.

Dose escalation meetings will be held to determine if it is safe to escalate the dose to the next level. These reviews will be triggered when sufficient patients have had the opportunity to complete the first cycle of combination treatment.

The safety data including a list of DLTs and all AEs will be reviewed along with all other available data by the Sponsor, CI and PI(s). The decision to dose escalate or expand a cohort will be communicated to all investigator sites by the Sponsor.

It is not anticipated that smaller dose escalations or de-escalations will be employed but would need to be considered if there is a large difference in the number of DLTs in two adjacent dose levels.

Following completion of the dose escalation phase, a review of the data will be performed by the Sponsor (to include review by the Protocol, Safety and Review Board (PSRB) before approval is granted by the Sponsor that the expansion cohort can be opened.

Once the MTD of the combination has been determined the expansion cohort will commence. The MTD determined in this cohort will be the dose level of the combination recommended for Phase II trials.

Expansion cohort.

Up to 30 patients with NSCLC will be enrolled to the expansion cohort. All patients will be treated with the combination of vandetanib and selumetinib. The dose of vandetanib and selumetinib will be the RP2D which will be determined in the dose escalation stage of the study.

5.3.1 Intra-patient dose escalations

No intra-patient dose escalation is allowed.

5.3.2 Expansion of dose level(s)

If one out of three patients experience a DLT (as defined in Section 3.1.1, up to six patients will be treated at that dose. If one out of up to six patients experience a DLT, dose escalation will continue. If two out of up to six (i.e. between two and six) patients experience a DLT dose escalation will stop and this dose will be defined as the maximum administered dose (MAD). At least three more patients will be treated at a dose below the MAD to define the MTD.

The MAD could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level, due to the expectation that higher dose levels would be too toxic to administer to patients.

5.4 Dose modifications

5.4.1 Dose interruptions

In the event of drug related toxicity, drug administration must be withheld (except for skin, fatigue, nausea, myalgia or arthralgia, unless these specific toxicities do not respond to supportive measures) until Grade 1 or below or until the patient meets the eligibility criteria parameters.

- On observation of a Grade 2 cardiac toxicity (any causality), both vandetanib and selumetinib should be stopped until resolution.
- On observation of G3 diarrhoea, if this does not resolve within 48 hours, both vandetanib and selumetinib should be stopped until resolution (i.e. until Grade 0 or 1 or until the patient meets the eligibility criteria parameters).
- On observation of non-specific respiratory signs and symptoms, where infectious, neoplastic, and other causes are unlikely or have been excluded and a diagnosis of interstitial lung disease (ILD) is likely or confirmed, both IMPs should be interrupted.

Patients must meet eligibility criteria parameters prior to each cycle and following a treatment interruption if the intention is to re-treat.

The maximum unscheduled dose interruption period is two weeks. Patients failing to recover to NCI CTCAE Grade 1 or less after two weeks will be withdrawn from the study.

There are over lapping toxicities associated with both vandetanib and selumetinib. Therefore it may not be clear which agent is responsible for any observed toxicity. If this is the case then administration of both drugs must be stopped at the same time until resolution to the above criteria.

Vandetanib administration should not be interrupted if possible; the aim is to maintain vandetanib to reduce the requirement to repeat the ‘loading’ phase of vandetanib administration. Therefore on observation of a Grade 2 drug related toxicity, selumetinib alone can be stopped (vandetanib can continue as a single agent administration). The patient should be closely monitored (whilst on vandetanib alone) to ensure the toxicity resolves to Grade 1 or less within 24 hours. If toxicity continues at same grade or increases within 24 hours then vandetanib should also be stopped.

To note: selumetinib should not be given as a single agent.

5.4.1.1 Management of vandetanib and selumetinib toxicity

Vandetanib and selumetinib have overlapping toxicity profiles. As this is the first time they have been used in combination, there is the risk that the frequency and severity of common toxicities could increase.

5.1.1.1.1 Gastrointestinal toxicities

Initially, no prophylactic anti emetics or anti diarrhoeals will be prescribed however there will be ongoing review of emerging toxicity data throughout the study. If the data shows unacceptable GI toxicity then a change on policy will be implemented for the prescription of prophylactic medications.

On observation of gastrointestinal toxicities, these are to be managed as per hospital guidelines.

5.1.1.1.2 Ocular toxicities

If any grade of toxicity affecting the macula and/or affecting patient's vision is observed then study treatment must be stopped and intensified monitoring should be implemented as per site ophthalmologist recommendation. Restarting treatment will be considered on discussion with the PI, ophthalmologist and Sponsor.

If Grade 1 ocular toxicity is observed which does not affect the macula or patient's vision, then continue study treatment and intensify monitoring as per site ophthalmologist recommendation.

If Grade 2 or above ocular toxicity is observed, not affecting the macula or patient's vision, treatment must be stopped and intensified monitoring should be implemented as per site ophthalmologist recommendation. Restarting treatment will be considered on discussion with the PI, ophthalmologist and Sponsor.

5.1.1.1.3 Guidelines for management of other toxicities

Guidelines for the management of other toxicity observed during the study can be found in the following appendices:

- Skin toxicity (Appendix 5)
- QTc prolongation (Appendix 6). Please also see Appendix 8 for medications known to prolong QTc.

  Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and to prevent an increased risk of QTc prolongation.

  Please also see Appendix 8 for medications with high risk of causing Torsade de Pointes (TdP). This appendix also notes guidance for wash out periods and guidelines for acceptable concomitant medications that may be associated with TdP.

- LVEF drop (Appendix 7). This appendix describes suggested investigation and management of asymptomatic decreases in LVEF).

- Hypertension Should be managed according to local trust policy.

Anticipated vandetanib and selumetinib toxicity

Please see the current versions of the vandetanib and selumetinib IBs and the vandetanib and selumetinib IB supplement for anticipated toxicities and toxicities that have been observed in previous clinical trials.

5.4.2 Dose reductions

This section is applicable to both the dose escalation phase and also the expansion cohort.

The dose of the combination treatment will be reduced to the previous dose level for any patient who experiences a DLT. If a patient has a dose reduction, their dose should not be re-escalated. NCI CTCAE Version 4.02 is applicable for Section 5.4.2.

5.4.2.1 Vandetanib and Selumetinib dose reduction

During single agent (vandetanib) phase

If vandetanib administration is interrupted during the single agent phase at the start of Cycle 1 (first 14 days):

- If the interruption was unrelated to vandetanib, administration can recommence as per protocol with no dose reduction.

- If the interruption was related to vandetanib,
  - If toxicity ≤G2, administration can continue as per protocol with no dose reduction on return to Grade 1 or baseline.
  - If toxicity is Grade 3 or above the patient must permanently discontinue study treatment.

During combination phase

If combination treatment is interrupted for **<10 days** during the combination treatment, on re-starting treatment:

- If the interruption was **unrelated to vandetanib or selumetinib**, both drugs can be administered together in combination following the interruption with no dose reduction.

- If the interruption was **related to vandetanib,** on return to Grade 1 or below, vandetanib should be dose reduced to the next lowest dose level od*. A dose reduction to selumetinib is not mandated.
  *If single agent dose is 100mg then administration of vandetanib given every other day can be considered however selumetinib must also be administered in combination (selumetinib is not to be administered as a single agent).

- If the interruption was **related to selumetinib,** on return to Grade 1 or below, selumetinib should be dose reduced to next lowest dose level. A dose reduction to vandetanib is not mandated.

If combination treatment is interrupted for **10-14 days**, on re-starting treatment:

- If the interruption was **unrelated to vandetanib or selumetinib**, vandetanib should be administered as a single agent (no dose reduction) for 10 days at steady state dose level (dependant on cohort) before re-introducing selumetinib (no dose reduction).

- If the interruption was **related to vandetanib**, vandetanib should be administered as a single agent for 10 days at the next lowest dose level od* before re-introducing selumetinib. A dose reduction to selumetinib is not mandated.
  *If single agent dose is 100mg then administration of vandetanib given every other day can be considered however following re-loading, selumetinib must also be administered in combination with vandetanib every other day (selumetinib is not to be administered as a single agent).

- If the interruption was **related to selumetinib**, vandetanib should be administered as a single agent for 10 days at the same dose level od (no dose reduction) before re-introducing selumetinib at the next lowest dose level.

Administration of vandetanib given every other day can be considered following a dose interruption however selumetinib must also be administered in combination.

Selumetinib must not be administered as a single agent.

5.4.2.2 Selumetinib dose reduction

Modification	Selumetinib original dose (at time of dose modification)	Selumetinib reduced dose
1	Original dose (twice daily)	Original dose (once daily) or Reduce by one dose level (twice daily)
2	Original dose (once daily)	Reduce by one dose level (twice daily)
3	Reduced dose level (twice daily)	Reduced dose level (once daily)

Following a dose reduction, the dose will not be escalated again for that patient.

a) Following an initial dose reduction, if a patient experiences an occurrence of a **new toxicity** requiring treatment interruption, selumetinib should again be withheld until the toxicity improves to CTCAE (version 4.02) Grade 1 or baseline, except for rash where CTCAE Grade 2 rash is acceptable. Upon recovery, treatment may resume as follows:

- The current dose can be reduced to either a once daily administration or
- The dose administered can be at the previous dose level (as investigated in the dose escalation phase) and be administered twice daily (if dose reduction to once daily administration has already taken place).

b) If a patient experiences a recurrence of the same toxicity as that causing a previous dose interruption and/or dose reduction, selumetinib should be withheld until the toxicity improves to CTCAE (version 4.02) Grade 1 or baseline, except for rash where CTCAE Grade 2 rash is acceptable. Upon recovery, treatment should resume at a permanently reduced or adjusted dose:

1) Once daily: if no dose reduction has yet occurred
2) Reduced dose, twice daily: (if dose reduction to once daily has already occurred)
3) Reduced dose, once daily: if steps (1) and (2) have already occurred.

If a patient experiences recurrence of any toxicity requiring dose interruption whilst receiving the lowest dosing schedule for this study, the patient must discontinue study treatment.

If a patient receiving the lowest dosing schedule experiences a novel toxicity that cannot be adequately managed by dose interruption and medical interventions then the patient must discontinue study treatment, as no further dose reductions/adjustments are permitted.

5.5 Missed doses

Patients should take the correct number of vandetanib tablets and selumetinib capsules at the same time every day (Section 5.2).

Should a patient miss a scheduled dose (e.g. forgetting to take the drugs) then the patient should wait until the next scheduled dose and continue as per normal drug administration.

Should a patient miss a scheduled dose due to vomiting, the patient should not re-take the dose, either for vandetanib or selumetinib but should wait until their next scheduled dose for both drugs.

5.6 Duration of treatment

Patients will continue on study treatment unless a) the patient asks to be withdrawn b) there is evidence of disease progression or c) the patient is experiencing unacceptable toxicity or for any of the reasons listed in Section 11.

If a patient is benefiting from treatment with vandetanib and selumetinib (i.e. has stable or responding disease as measured by RECIST 1.1) and the patient is not experiencing any Grade 3 or greater drug-related AEs after 6 cycles of combination treatment, then the Chief/Principal Investigator can ask the Sponsor if the patient can continue with treatment. The Sponsor will request a full toxicity profile of that patient when considering the request. The patient may be treated for further cycles after a formal written request has been made to and written approval has been received from the Sponsor. If the Sponsor decides not to allow the patient to continue treatment, based on the information provided or on other information received, then the Sponsor's decision is final.

Patients will be followed up for 28 calendar days after the last administration of the study drug. If there are adverse events that occurred while the patient was on study which are attributed (including possibly drug-related AEs) to the study drug and are still present 28 calendar days after the last administration of study drug or occur in the 28 calendar days

post study drug administration; the patient will be followed up monthly afterwards until resolution or stabilisation of these events, unless the patient starts another anti-cancer treatment.

Although the Investigator will make every reasonable effort to keep each patient on study until the patient progresses or receives the maximum number of cycles, the patient may be removed from the study for other reasons. (Refer to Section 11).

5.7 Replacement of patients

Dose escalation:

Patients will be replaced in this phase if they fulfil at least one of the following criteria:

- If a patient withdraws from treatment prior to the end of Cycle1, for reasons other than drug related toxicity.
- Patients who receive fewer than 21 of 28 daily doses of the combination treatment of either drug, in Cycle 1 (for reasons other than drug related toxicity) will be replaced by another patient at the same dose level.

Expansion cohort:

Patients will be replaced in the expansion cohort if they fulfil at least one of the following criteria:

- If a patient withdraws from treatment prior to the end of Cycle1, for any reason
- Patients who receive fewer than 21 of 28 daily doses of the combination treatment of either drug, in Cycle 1 (for any reason) will be replaced by another patient at the same dose level.

5.8 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. Details (including doses, frequency, route and start and stop dates) of the concomitant medication given must be recorded in the patient's medical records and the electronic case report form (eCRF).

Radiotherapy may be given concomitantly for the control of bone pain; however these irradiated lesions will not be evaluable for response.

The patient must not receive other anti-cancer therapy or investigational drugs while on the trial.

5.9 Precautions for treatment

a) Electrolytes to include serum magnesium and potassium must be maintained within normal limits (potassium MUST be maintained at > 4.0mmol/L).

Monitoring to occur weekly for Cycles 1 and 2 then prior to Day 1 of subsequent cycles.

b) Patients should avoid excessive sun exposure and use adequate sun screen protection (SPF 50) if sun exposure is anticipated.

c) Patients should be informed to notify their study doctor or nurse if they experience any visual disturbances or ocular pain.

d) Selumetinib capsules contain D-α- Tocopheryl polyethylene glycol 1000 succinate (TPGS, a water-soluble form of vitamin E) as an excipient. The maximum daily dose of vitamin E that a study patient may receive from selumetinib is approximately 261.6mg/day. Therefore:

Patients should not take vitamin E supplements or multivitamin supplements which provide a total daily dose in excess of 100% of the recommended daily allowance for vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.

e) Interstitial lung disease (ILD) or pneumonitis has been observed with vandetanib, and deaths have been reported. Cases of ILD have also been observed with selumetinib when administered in combination with other agents, including docetaxel. A diagnosis of ILD should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnoea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations.

f) Selumetinib should be administered with caution in patients who are also receiving concomitant coumarin anticoagulant medications e.g. warfarin. These patients should have their INR monitored/anticoagulant assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

g) Patients should avoid medications that are known to either induce or inhibit the activity of hepatic microsomal isoenzymes CYP1A2, CYP2C19 and CYP3A4, as this may interfere with the metabolism of selumetinib.Please see link to Flockhart list which provides a complete list of inhibitors/inducers http://medicine.iupui.edu/clinpharm/ddis/).

h) The administration of vandetanib with anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, sotalol, dofetilide) and other drugs that may prolong the QT interval (including but not limited to chloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide) should be avoided (see Appendix 8 for list of drugs that may cause QTc prolongation).

i) Interactions between vandetanib and metformin, and vandetanib and digoxin are described in the Vandetanib IB. Patients receiving concomitant metformin and vandetanib or concomitant digoxin and vandetanib should be monitored as clinically

appropriate. Patients receiving concomitant metformin may require a lower dose of metformin.

j) Study treatment is contraindicated in patients with GFR <50 mls/min.

k) During the study, patients should avoid consuming large amounts of grapefruits, Seville oranges, or any other products that may contain these fruits, e.g., grapefruit juice, as these may affect selumetinib metabolism.

6 PHARMACEUTICAL INFORMATION

6.1 Supply of Vandetanib and Selumetinib

A complete certificate of analysis and a Qualified Person (QP) certification must be supplied with each shipment of vandetanib and selumetinib (IMPs) and be retained in the Pharmacy File.

For information on vandetanib and selumetinib and re-ordering of supplies, contact the Clinical Research Associate (CRA)/Clinical Study Manager (CSM) responsible for the trial who will arrange further supplies. Initial supplies will be ordered for each site following the site initiation visit and confirmation from the Sponsor that the site is open to recruitment.

Vandetanib and selumetinib will be supplied by:

Fisher Clinical Services (UK) Limited
Langhurstwood Road
Horsham,
West Sussex
RH12 4QD
Telephone number: 01403 212700
Email address: info@fisherclinicalservices.com

For the reordering of supplies, the Sponsor will send a copy of the drug shipment form to Fisher Clinical Services (UK) Limited. Fisher Clinical Services (UK) Limited must send confirmation of shipment to the CSM/CRA once the IMP has been despatched to the clinical trial site.

The primary and secondary packaging for the IMP will be labelled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP). An example of the label can be found in the Pharmacy File.

6.2 Pharmaceutical data

6.2.1 Formulation of Vandetanib and Selumetinib

Vandetanib will be supplied as a 100 mg tablet. The tablets are round, plain, biconvex, white film coated with a diameter = 8.5mm containing vandetanib 100 mg w/w, calcium hydrogen phosphate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate, with a film coating containing hypromellose, polyethylene glycol 300 and titanium dioxide. Vandetanib tablets are supplied in white high density polyethylene (HDPE) bottles with foil-lined, induction-sealed, child-resistant closures.

Selumetinib will be supplied as 25 mg capsules. The size 4 HPMC white (batches expiring latest June 2018) or blue (new batches) capsules (hyd sulfate formulation) contain 25 mg w/w of selumetinib (expressed as free base) D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS; a water-soluble form of vitamin E). Selumetinib capsules are supplied in white HDPE bottles with foil-lined, induction-sealed, child-resistant closures. The container includes a desiccant canister.

6.2.2 Storage conditions

All supplies must be stored in a secure, limited access storage area. Both vandetanib and selumetinib must be stored at room temperature (specifically below 30°C).

6.2.3 Stability of Vandetanib and Selumetinib

Please refer to the label on the primary package for the expiry date of the IMP.

6.2.4 Dispensing of Vandetanib and Selumetinib

Sufficient tablets of vandetanib and capsules of selumetinib must be dispensed on each occasion to cover the prescribed dose, (as described in Section 5.3 and 5.4), over the period to the next scheduled dispensing.

Dispensing of each drug will generally cover one cycle (28 days) of both drugs in combination. The only exception to this will be at the start of Cycle 1 where the patient will be dispensed vandetanib alone to cover the two weeks of the single drug administration. They will then be seen on Day 15 to begin their combination treatment and prescribed one cycles worth of vandetanib and selumetinib. Pharmacy will supply original packs of IMP to patients. Packs will not be split for dispensing.

6.2.5 Vandetanib and Selumetinib administration

For drug administration details please see section 5.2.

For guidance on dose modifications please see section 5.4.

For details on precautions of treatment and prohibited concomitant medications, please see section 5.6.

6.2.6 Vandetanib and Selumetinib Accountability

Accurate records of all IMPs (vandetanib and selumetinib) shipments received, tablets and capsules dispensed, and all IMP returned must be maintained. This inventory record must be available for inspection at any time by CRAs or CSMs of the Centre for Drug Development (CDD). IMP supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

Patients will be given the appropriate number of tablets and capsules to take with them for one cycle of combination treatment from Cycle 2 onwards. For the loading phase of vandetanib and Cycle 1 of combination, patients will be provided with the appropriate number of additional vandetanib tablets. They should be asked to complete a patient diary card to document drug administration and to return the bottle and any remaining tablets/capsules at each visit. Remaining tablets/capsules will be returned to pharmacy for IMP reconciliation. The Investigator should make every effort to ensure patients' compliance to treatment.

The Investigator undertakes not to destroy any unused IMP unless directed to by CDD. Any unused IMP must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record. During the

course of the trial the CRA will check the numbers of bottles of tablets of vandetanib and bottles of capsules of selumetinib shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

7 INVESTIGATIONS SCHEDULE

In cases where a patient has investigations at a different hospital, for example weekly blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the results. The results must be recorded on the eCRF and the reports from the other hospitals must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

7.1 Pre-treatment evaluations

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records so that the eCRF can be checked against the source data.

Please also refer to the tabulated Schedule of Assessments in Section 7.5.

7.1.1 Obtaining written informed consent

Written informed consent must be obtained from the patient before any protocol-specific procedures are carried out and within four weeks before the patient's first dose of vandetanib. The patient must be given adequate time to think about their commitment to the study.

Only the PI and those Sub-Investigator(s) delegated responsibility by the PI, and have signed the Delegation Log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). The date of the signatures of both the patient and the PI/Sub-Investigator must be the same.

The PI or the Sub-Investigator must inform the patient about the background to, and present knowledge of the normal management of their disease and the IMPs (vandetanib and selumetinib) and must also ensure that the patient is aware of the following points.

- The known toxicity of the IMPs and the possibility of experiencing side-effects.
- That combining vandetanib and selumetinib is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception. (refer to Section 9.6).
- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.
- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the informed consent form and patient information sheet must be given to the patient to keep and the original informed consent form and patient information sheet, must

be filed in the Investigator Trial File (ITF) (unless otherwise agreed that the original consent form will be filed in the medical records and the copies kept in the ITF).

7.1.2 Evaluations within four weeks (28 days)

The following must be performed/obtained **within the four weeks before** the patient receives the first dose.

- Written informed consent (as detailed in Section 7.1.1)
- Demographic details
- Medical history including prior diagnosis, prior treatment, concomitant diseases and concomitant treatment
- Radiological Disease Assessments every 2 cycles
    - To include thoracic CT in expansion cohort
    - Radiological measurements using the most appropriate imaging for each patient using computerised tomography (CT) scan or magnetic resonance imaging (MRI) –must be performed **within four weeks before** the patient receives the first dose
- Bone scan (optional as clinically indicated)
- Ophthalmological exam (including slit lamp, visual acuity, visual fields, colour vision, optical coherence tomography (OCT) and intraocular pressure)
    - Adverse events relating to visual function have been reported in all studies with selumetinib to include blurred vision (please see IB supplement for further details of visual function toxicity). Therefore eye exams have been built into the schedule of events to allow for continuous assessment throughout study treatment.

Note that all adverse events (AEs), including serious adverse events (SAEs), must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure (see Section 9 for further details).

7.1.3 Evaluations within two weeks (14 days)

The following must be performed **within the two weeks before** the patient receives the first dose of vandetanib:

- Serum or urine human chorionic gonadotropin (HCG) test to rule out pregnancy at trial entry; results must be obtained and reviewed before the first dose of the IMP is administered, if applicable (i.e. women of child bearing potential).

7.1.4 Evaluations within one week (seven days)

<u>Dose escalation and expansion cohort</u>

The following must be performed **within one week before** the patient receives the first dose:

- Complete physical examination;
- Height, weight, WHO performance status, temperature, blood pressure (BP sitting) and pulse rate;
- Electrocardiogram (ECG): Three to be performed within 5-10 minutes of one another;
- Echocardiogram (ECHO) / Multi gated acquisition scan (MUGA) (maintain one method at each site);

- Laboratory tests (blood/ urine samples) to confirm eligibility.
    - Haematology – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils and lymphocytes), reticulocytes and platelets
    - Biochemistry – sodium, potassium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), alanine aminotransferase (ALT),aspartate aminotransferase (AST), serum magnesium, creatine phosphokinase (CPK)
    - Urinalysis –glucose, protein and blood
    - Blood clotting measurements – INR or aPTT
- GFR assessment (calculated) using Wright or Cockcroft and Gault formula to be performed.
    - Isotope clearance result to be used to confirm eligibility if calculated C&G/Wright method results in GFR which equals 50 mL/min. Confirmatory Isotope clearance result in these cases must be ≥ 50 mL/min.
    - GFR assessments as clinically indicated throughout study period (calculated C&G/Wright formula and/or Isotope clearance measurement as applicable).

Expansion cohort (Cycle 1) only:

7.2 Evaluations during the trial

This section describes the evaluations that must be undertaken during the trial.

The following assessments should be performed throughout the trial period.

Adverse events and concomitant treatments: At each visit, before each IMP administration, an assessment of any AE experienced since the previous visit must be made by the Investigator or Research Nurse and the start and stop dates of the AE together with

the relationship of the event to treatment with vandetanib or selumetinib must be recorded in the medical records. All AEs must be graded according to NCI-CTCAE Version 4.02. Any concomitant treatment must also be recorded in the medical records and eCRF. (See Section 9 for further details regarding AE reporting requirements.)

Radiological assessment of disease (to include thoracic CT in expansion cohort): Following the baseline assessment (Section 7.1.2), radiological assessment must be performed every two cycles. If a patient comes off study for reasons other than progressive disease, this should also be repeated at the off study visit, 28 days after the last drug administration, unless such assessment has been performed within the previous four weeks.

7.2.1 Evaluations during Cycle 1

This section describes the evaluations to be undertaken during the first cycle of study treatment. The first cycle is defined as administration of single agent vandetanib (14 days to include the loading phase) and administration of vandetanib and selumetinib in combination for 28 days (therefore a total of 42 days). For cycle definitions please see Section 1.4.3.

Therefore in Section 7.2.1, evaluations will be described between Days 1 and 42.

7.2.1.1 Evaluations during Day 1 (Prior to first dose of vandetanib)

Required for dose escalation and expansion cohorts

- Physical examination: symptom-directed physical examination.
- WHO performance status, temperature, pulse rate, BP (sitting).
- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;

Expansion cohort (Cycle 1) ONLY

- [redacted]

7.2.1.2 Evaluations during Day 5 (+/- 1 day)

Required for dose escalation and expansion cohorts

- Physical examination: symptom-directed physical examination.
- WHO performance status, temperature, pulse rate and BP (sitting).
- ECG
- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;

Dose escalation cohort (Cycle 1) ONLY – DAY 4

- **Pharmacokinetics (blood sampling)**: (see Section 8.3 for specific time points)

7.2.1.3 Evaluations during Day 12 (+/- 2 days)

Expansion cohort (Cycle 1) ONLY

- [redacted]

7.2.1.4 Evaluations on Day 15 (prior to first dose of vandetanib and selumetinib in combination)

Required for dose escalation and expansion cohorts

- Physical examination: symptom-directed physical examination.
- WHO performance status, temperature, pulse rate and BP (sitting).
- ECG
- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;
- Urinalysis –glucose, protein and blood

Dose escalation cohort (Cycle 1) ONLY

- **Pharmacokinetics (blood sampling)**: (see Section 8.3 for specific time points)

7.2.1.5 Evaluations on Day 22

Required for dose escalation and expansion cohorts (Cycle 1 and 2 only)

- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;
- Ophthalmological exam: detailed in Section 7.1.2 (+/- 2 days)

7.2.1.6 Evaluations at Day 29

Required for dose escalation and expansion cohorts (Cycle 1 and 2 only)

- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;
- ECG

Dose escalation cohort (Cycle 1) ONLY

- **Pharmacokinetics (blood sampling)**: (see Section 8.3 for specific time points)

7.2.1.7 Evaluations on Day 36

Required for dose escalation and expansion cohorts (Cycle 1 and 2 only)

- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;

7.2.1.8 Evaluations on Day 42 (+/- 5 days)

Expansion cohort (Cycle 1) ONLY

- **Pharmacodynamics (optional tumour biopsies)** (See Section 8.4.1 for specific time points).
  - Three endobronchial samples from tumour tissue will be collected.

[redacted]

7.2.2 Evaluations during Cycle 2

Combination of vandetanib and selumetinib from Cycle 2 Day 1

Required for dose escalation and expansion cohorts

On the first day of Cycle 2, prior to dosing

- ECGs to be performed as clinically indicated but not less than pre C2 D1 of combination and pre Day 1 of every cycle.
- ECHO/MUGA scan (within 7 days prior to Cycle 2 Day 1 is acceptable)
- Ophthalmological exam (as per 7.1.2) (within 7 days prior to Cycle 2 Day 1 is acceptable).
- Physical examination: symptom-directed physical examination.
- WHO performance status, temperature, pulse rate and BP (sitting) and weight.

- **Weekly** laboratory tests
  - Haematology tests: detailed in Section 7.1.4;
  - Biochemistry tests: detailed in Section 7.1.4;

7.2.3 Evaluations for Cycle 3 onwards

Required for dose escalation and expansion cohorts

- **Cycle 3 Day 1**: Ophthalmological exam (as per 7.1.2) (within 7 days prior to Cycle 3 Day 1 is acceptable).

On the first day of each cycle (-3 days allowable), prior to dosing

- Physical examination: symptom-directed physical examination.
- WHO performance status, temperature, pulse rate and BP (sitting) and weight.
- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;
- Ophthalmological exam (as per 7.1.2) (for patients experiencing visual disturbances), as clinically indicated.ECG

7.2.4 Evaluations (radiological) at Week 10

- The first radiological assessment of disease (to include thoracic CT in expansion cohort) should be performed following completion of Cycle 2 of combination treatment i.e. Week 10. Radiological assessment to be performed every two cycles thereafter.

Expansion cohort (Cycle 1) ONLY

- [redacted]

7.3 Evaluations at 'off-study' visit

Evaluations at the 'off-study' visit must be performed 28 days after the last dose of vandetanib and selumetinib. The following investigations must be done:

- Physical examination (symptom directed)
- WHO performance status, temperature, pulse rate, BP (sitting) and body weight.
- Haematology tests: detailed in Section 7.1.4;
- Biochemistry tests: detailed in Section 7.1.4;
- Urinalysis: detailed in Section 7.1.4;
- ECG
- Radiological assessment of tumour disease, unless assessment has been performed within the previous four weeks (28 days);
- Assessment of AEs and
- Assessment of concomitant treatments.

Expansion cohort (Cycle 1) ONLY

- [redacted]

7.4 Follow-up

Patients will be followed up for 28 days after the last administration of vandetanib and selumetinib. If any AEs and SAEs are:

- considered to have a highly probable, probable or possible causal relationship to vandetanib and selumetinib, and:
- occurred while the patient was on study and are still present 28 days after the last administration of both IMPs or
- occur in the 28 days post vandetanib and selumetinib administration;

Then the patient will be followed up monthly afterwards until resolution, to baseline or stabilisation of these events, unless the patient withdraws their consent or starts another anti-cancer treatment.

All patients will be followed up for survival at one year (to be calculated from Cycle 1 Day 1 of dosing)

7.5 Schedule of events (1) Loading phase of vandetanib and Cycle 1 of combination (vandetanib and selumetinib) only

Observation/Investigation	Baseline/Pre-study		Standard evaluation for loading phase Single agent Vandetanib (Days 1-14 only)													Standard evaluation for Cycle 1 of combination					Follow up and off study requirements as per Cycle 2 onwards (k)
			Day																		
	Within 4 weeks (Day -28 to Day 1)	Within 1 week (Day -7 to Day 1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	22	29	36	42	
Written informed consent	X																					
Demographics	X																					
Medical history	X																					
Adverse event evaluation	From date of informed consent		Continually review																			
Concomitant treatments	X		Continually review																			
Radiological disease assessment (a)	X																	X				
Ophthalmological exam (b)	X		Repeat if clinically indicated															X				
Pregnancy test (c)	Within 2 weeks (Day -14 to Day 0)																					
Clinical disease assessment (if applicable)		X (if applicable)																				
Physical examination		X	X			(Day 5 +/- 1d)											X					
Temperature, BP and pulse		X	X			(Day 5 +/- 1d)											X					
Height		X																				
Weight		X																				
WHO performance status		X	X			(Day 5 +/- 1d)											X					
Laboratory tests: haematology and biochemistry (d)		X (to confirm elig bility)	X			(Day 5 +/- 1d)											X	X	X	X		
Urinalysis		X															X					
GFR assessment		X (C&G/Wright and if applicable Isotope clearance)	As clinically indicated (calculated C&G/Wright and if applicable Isotope clearance measurement)																			
Electrocardiogram (ECG) (e)		X				(Day 5 +/- 1d)											X		X			
ECHO/MUGA		X	To be performed as clinically indicated																			
Vandetan b administration (l)			Continuous daily dosing – Doses and schedule of each IMP to be confirmed by the Sponsor																			
Selumetinib administration (l)			Not applicable														See above					
Blood for pharmacokinetic assays (f)						X											X		X			

[redacted]

(a) Radiological (CT, MRI, X-ray) disease assessment (to include thoracic CT in the expansion cohort). Bone scan to be performed as clinically indicated.

(b) To include slit lamp assessment, visual acuity, visual fields, colour vision, optical coherence tomography and intraocular pressure. C1D22 assessment, +/- 2 days allowable.

(c) Pregnancy test (serum or urine HCG) .If the patient is a woman of child bearing potential.

(d) In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.

(e) Three ECGs to be performed within 5-10 mins of one another prior to dosing.

(f) **Dose escalation phase only:**
PK time points: Days 4, 15 and 29. Allowable time windows for time points are noted in Section 8.3.

[redacted]

(k) Monthly follow-up required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) that are present at time that patient comes off the trial. Monthly follow-up to continue until resolution, to baseline, stabilisation or patient starts another anti-cancer treatment.

(l) Alternate doses may be investigated – the Sponsor will confirm doses and schedule of each study drug for each new cohort. Please see section 3.2.

7.6 Schedule of events (2) Cycle 2 of combination (vandetanib and selumetinib) onwards

Observation/Investigation	Standard Evaluations for each cycle 1 cycle = 28 days (vandetanib and selumetinib treatment)						Off study and Follow-up	
	Day 1	Day 8	Day 15	Day 22	10 weeks* (Post end Cycle 2)	12 weeks	Off study: 28 days after last dose of IMP	Follow-up: monthly(s)
Adverse event evaluation	Continually review						X	Until resolution
Concomitant treatments	Continually review						X	
Radiological (CT, MRI, X-ray) disease assessment (to include thoracic CT) (m)	To be performed every two cycles				X		X (unless performed within previous 4 wks)	
Ophthalmological exam (n)	C2D1, C3D1 and as clinically indicated throughout study treatment for patients experiencing visual disturbances							
Clinical disease assessment (if applicable)	As clinically indicated						As clinically indicated	
Physical examination	On the first day of each cycle: symptom-directed physical examination						Symptom-directed physical examination	
Temperature, blood pressure and pulse	On the first day of each cycle						X	
Weight	On the first day of each cycle						X	
WHO performance status	On the first day of each cycle						X	
Laboratory tests: haematology and biochemistry (o)	X	X	X	X			X	To resolution of drug-related lab AEs
GFR assessment	As clinically indicated (calculated C&G/Wright and if applicable Isotope clearance measurement)							
Urinalysis	As clinically indicated						X	
Electrocardiogram (ECG) (p)	Prior to Day 1 of every cycle						X	
ECHO/MUGA (q)	C2D1 and then every 12 weeks (or more often as clinically indicated)							
Vandetan b administration (t)	Continuous daily dosing – Doses and schedule of each IMP to be confirmed by the Sponsor							
Selumetinib administration (t)	Continuous daily dosing – Doses and schedule of each IMP to be confirmed by the Sponsor							
Expansion cohort only (NSCLC patients)								

[redacted]

(m) Bone scan to be performed as clinically indicated.

(n) To include slit lamp assessment, visual acuity, visual fields, colour vision, optical coherence tomography and intraocular pressure. Examinations must be performed prior to Cycle 2 Day 1 and Cycle 3 Day 1 (within 7 days prior to C2D1 and C3D1 is acceptable). Additional eye examinations can then be performed as clinically indicated.

(o) Haematology and biochemistry to be assessed weekly during Cycle 1 and 2 and then prior to Day 1(-3 days time window) of subsequent cycles.

In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.

(p) More frequent ECGs required in patients with symptoms symptomatic of cardiac impairment.

(q) MUGA/ECHO to be performed prior to Cycle 2 Day 1 (within 7 days prior to C2D1 is acceptable) then ECHOs and MUGAS to be performed every 12 weeks or more often as clinically indicated

[redacted]

(s) Monthly follow-up required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) that are present at time that patient comes off the trial. Monthly follow-up to continue until resolution, to baseline, stabilisation or patient starts another anti-cancer treatment

(t) Alternate doses may be investigated – the Sponsor will confirm doses and schedule of each study drug for each new cohort. Please see section 3.2

***To note: First radiological assessment to be performed at the end of Cycle 2. Thereafter radiological assessment to be performed every two cycles.**

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

8.1 Sampling summary

Name of assay	Purpose of assay	Type of sample	Vials used	Total volume per patient per cycle	Timings*	Storage conditions	How to ship/ transport	Person/place responsible for analysis	Frequency of analysis****
PRIMARY ASSAYS									
There are no primary assays performed for this study									
SECONDARY ASSAYS									
Blood PK (vandetanib) Cycle 1 only)	To determine PK parameters including Cmax and AUC and metabolites	Plasma	Lithium heparin vacutainers	0 hrs (pre dose) 0.5 hrs 2 hrs 4 hrs 6 hrs 10 hrs (Days 15 & 29 only) 24 hrs Day 4 6 x 2 mL = 12 mL/day Days 15 & 29 7 x 2 mL = 14 mL/day **= 40 mL total**	• Day 4 • Day 15 (pre-selumetinib dose) • Day 29 (two weeks post D1 of combination)	-20^{0}C	Contact CRA to arrange courier to CRO.	AZ sub contractor	Batched (by patient for first two patients) Thereafter analysis will be performed following completion of each cohort.
Blood PK (selumetinib) (Cycle 1 only)	To determine PK parameters including Cmax and AUC and metabolites	Plasma	EDTA vacutainers	0 hrs (pre dose) 0.5 hrs 2 hrs 4 hrs 6 hrs 10 hrs 24 hrs 7 x 3 mL = 21 mL/day **= 42 mL total**	• Day 15 (pre-selumetinib dose) • Day 29 (two weeks post D1 of combination)	-80^{0}C	Contact CRA to arrange courier to CRO.	AZ sub contractor	Batched (by patient for first two patients) Thereafter analysis will be performed following completion of each cohort.

Name of assay	Purpose of assay	Type of sample	Vials used	Total volume per patient per cycle	Timings*	Storage conditions	How to ship/ transport	Person/place responsible for analysis	Frequency of analysis****
[redacted]									
				[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
					[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Name of assay	Purpose of assay	Type of sample	Vials used	Total volume per patient per cycle	Timings*	Storage conditions	How to ship/ transport	Person/place responsible for analysis	Frequency of analysis****
	[redacted]			[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

8.2 Primary assays

There are no primary assays associated with this protocol.

8.3 Secondary assays (dose escalation cohort only)

8.3.1 Pharmacokinetic analysis - Cycle 1 only

Vandetanib and selumetinib will be measured in plasma according to agreed standard operating procedures and validated methods. Validated high-performance liquid chromatography-mass spectrometry assays following liquid-liquid or protein precipitation extraction will be employed to measure plasma vandetanib and selumetinib and its metabolite, N-desmethyl metabolite.

Vandetanib PK

Parameters to be measured include plasma vandetanib and other metabolites may be measured as determined during the study.

A two mL blood sample will be collected into lithium heparin vacutainers at detailed below.

Day 4, Day 15 (pre first dose selumetinib) and Day 29 (two weeks following Day 1 of combination) at the following time points:

- 0 hrs (pre dose)
- 0.5 hrs (+/- 5 min)
- 2 hrs (+/- 10 min)
- 4 hrs (+/- 30 min)
- 6 hrs (+/- 30 min)
- 10 hrs **(Not to be measured on Cycle 1, Day 4. Sampling at 10 hrs is required on Cycle 1 Days 15 and 29 only).**
- 24 hrs (+/- 1 hr)

Selumetinib PK

Parameters to be measured include plasma selumetinib and N-desmethyl metabolite. If warranted, other metabolites may be measured as determined during the study.

A three mL blood sample will be collected into EDTA vacutainers at detailed below.

To note, PK sampling time points for selumetinib will start prior to and following administration of the first dose (morning dose).

Day 15 (pre first dose selumetinib) and Day 29 (two weeks following Day 1 of combination) at the following time points:

- 0 hrs (pre dose)
- 0.5 hrs (+/- 5 min)
- 2 hrs (+/- 10 min)
- 4 hrs (+/- 30 min)

- 6 hrs (+/- 30 min)
- 10 hrs (+/- 1 hr)
- 24 hrs (+/- 1 hr)

The approximate maximum volume of blood withdrawn for analysis of vandetanib and selumetinib concentrations from each patient is of 82 mL.

Analysis will be performed by Astra Zeneca sub contractors. For the first two patients entered onto the study, all PK samples for both vandetanib and selumetinib will be sent to each subcontractor (following processing of the Day 29 sample of each patient at the clinical site). Thereafter samples will be analysed after each cohort (or as requested by CR-UK) and data may be included in dose escalation decisions.

Handling, storage and shipment details of PK samples are described in the study laboratory manual.

8.4 [redacted]

8.4.1 [redacted]

[redacted]

8.4.2 [redacted]

[redacted]

8.4.2.1 [redacted]

[redacted]

8.4.2.2 [redacted]

[redacted]

8.4.2.3 [redacted]

8.4.2.4 [redacted]

8.5 Imaging assessments (Expansion cohort (Cycle 1 only)

Name of Imaging Technique	Purpose	Total per patient	Timing	Frequency of review
Secondary objective (Expansion cohort only)				
FDG-PET	Measurement of tumour metabolism	Max 3 scans	Baseline (x1) Between Day 12 (+/- 2 days) (x1) Day 42 (+/- 5 days) (4 weeks on combination) (x1)	Following scanning of 20 patients
Tertiary objectives (Expansion cohort only)				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.5.1 Timing and type of imaging assessments

A histological and radiological evaluation of malignancy, to confirm a diagnosis of disease, as judged appropriate by the Investigator, must be performed before the patient starts the trial. A radiological examination as per normal clinical practice must be performed within 4 weeks of vandetanib treatment to confirm disease state.

All FDG-PET[redacted] assessments performed during the trial will be according to agreed SOPs and validated methods.

All PET imaging data will be centrally reviewed by the Churchill Hospital. Image acquisition protocol for standard FDG-PET will be defined by the team at the Churchill Hospital.

[redacted]

Imaging protocols will be provided to all participating sites to ensure consistency between imaging techniques.

8.5.2 FDG – PET (Baseline imaging and during treatment evaluations)

One baseline FDG-PET scan must be performed within one week prior to the first dose of vandetanib. This baseline scan can be performed on one of the days on which one of the baseline DCE-MRI scans is acquired.

During treatment, a further FDG-PET scan will be performed on Day 12 (+/- 2d) (to acquire single agent vandetanib data) and then one further FDG-PET scan on Day 42 (+/- 5d) (to acquire vandetanib and selumetinib combination data).

8.5.3 [redacted]

9 ASSESSMENT OF SAFETY

9.1 Adverse event definitions

Adverse event

For screening failures, serious adverse events (SAEs) will be reported to the Pharmacovigilance (PV) Department, Centre for Drug Development CDD) from the date of consent until the date the patient is confirmed as ineligible.

For eligible patients, SAE and adverse event (AE) collection and monitoring commences from the time the patient gives their written consent to participate in the trial and continues for 28 days after the last administration of vandetanib and selumetinib (investigational medicinal products [IMPs]).

An AE is any untoward, undesired or unplanned occurrence in a patient administered an IMP, a comparator product or an approved drug. An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

Other reportable events that must be treated as SAEs are listed below.

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration, must be reported to the Pharmacovigilance Department in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Overdose with or without an AE.
- Inadvertent or accidental exposure to an IMP with or without an AE, including for example, spillage of the IMP that contaminates staff.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.

Serious adverse events (SAEs)

An SAE is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – see Section 9.2);
- results in persistent or significant incapacity or disability;

- is a congenital anomaly or birth defect;
- is any other medically important event.*

*A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above.

Medically important events

The following should be reported to the PV department of the CDD as Medically Important SAEs regardless of causality to the IMP.

- Skin toxicity, CTCAE Grade 3 or above.
- Diarrhoea, CTCAE Grade 3 or above.
- Eye disorders involving the retina, CTCAE Grade 1 or above (e.g. retinal detachment, retinal tear, retinal vascular disorder, retinopathy).
- All other eye disorders, CTCAE Grade 2 or above.

(NCI CTCAE version 4.02)

If during the course of the study, other medically important events are identified and there is a requirement to report specific events outside of the standard criteria, this will be communicated to site and the protocol will be updated to reflect this.

Determining adverse event causality

The relationship of an AE to the IMP is determined as follows.

Highly probable Starts within a time related to the IMP administration and No obvious alternative medical explanation.
Probable Starts within a time related to the IMP administration and Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible Starts within a time related to the IMP administration and A causal relationship between the IMP and the AE is at least a reasonable possibility.
Unlikely The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.
Not related The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely

causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

Expectedness

Assessment of expectedness will be made by the PV Department against the current version of the Investigator Brochures (IB) for vandetanib and selumetinib and the IB Supplement for this trial.

Suspected, unexpected, serious, adverse reactions (SUSARs)

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed by CDD for seriousness, causality and expectedness. The PV Department will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant Ethics Committee(s) within the timelines specified in legislation (SI 2004/1031 as amended).

9.2 Expedited reporting of serious adverse events

All SAEs, regardless of causality, must be reported to the PV Department in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be <u>faxed</u> to Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.

[redacted]

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4.02 must be used to Grade each SAE, and the worst Grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the PV Department on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added on the fax cover sheet when sending the SAE report form to the PV Department.

Should the Investigator become aware of any drug related SAEs after the patient goes ‘off study’, these must also be reported to the PV Department within the specified timelines above.

Events exempt from being reported as SAEs to the Pharmacovigilance Department

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the electronic case report form (eCRF).

Elective admissions – Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting. Hospitalisation for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE.

Prolongation of hospitalisation without an associated adverse event - (for example, prolonged hospitalisation while appropriate social care is set up for elderly patients)"

Death due to disease progression - Cases of death due to disease progression do not require SAE reporting, unless considered related to the IMP.

9.3 Recording of adverse events and serious adverse events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The CDD Medical Advisor and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

9.4 Follow-up of adverse events

Follow-up will continue until all the necessary safety data for the event has been gathered and until the drug-related AE or SAE has either resolved, returned to baseline or stabilised. The PV Department will make requests for further information to the trial site at regular intervals. Requested follow-up information should be reported to the PV Department in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information should be reported to the PV Department as soon as possible.

9.5 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The Medicines and Healthcare products Regulations Agency (MHRA) and the main Research Ethics Committee (REC) must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- [redacted]

- [redacted]
- [redacted]

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

The Sponsor will then notify the MHRA and the main REC within three days of USM initiation. The pharmaceutical company (Astra Zeneca) will also be informed of USM initiation.

9.6 Pregnancy

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- oral contraceptives and condom; (oral, injected or implanted hormonal contraceptives should be used for four weeks before the patient joins the study)
- intra-uterine device (IUD) and condom;
- diaphragms with spermicidal gel and condom.

Contraceptives should be used throughout the trial and for six months after completing the trial.

It should be explained to the patient that if his partner is pregnant or breast-feeding when he enters the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to vandetanib or selumetinib.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of last IMP administration must be reported to the PV Department within 24 hours of the site staff becoming aware of it using a Pregnancy Notification Form. It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. The PV Department will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Outcome Form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to six months after the last IMP administration. It is the Investigator's responsibility to ensure the patient's partner is aware that consent is collected from them in order for CRUK CDD to collect follow up information for the

pregnancy including the outcome of the pregnancy and the baby's health following birth, on a Pregnancy Outcome Form. In case the partner of a patient becomes pregnant, a consent form should be provided to the patient's partner in order to obtain consent for collecting privacy data in accordance with the data protection act. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this.

10 ASSESSMENT OF EFFICACY

10.1 Measurement of disease

Disease must be measured according to the RECIST (version 1.1) criteria given in Appendix 3.

10.2 Timing and type of tumour assessments

A thorough clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the investigational medicinal product (IMP). The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments must be performed within four weeks before starting treatment. The interval between the last anti-cancer therapy and these measurements must be at least four weeks (28 days). All clinical measurements to assess response must be done within **one** week before the patient starting treatment.

All complete (CR) and partial responses (PR) must be confirmed by two consecutive observations not less than four weeks apart. All stable disease (SD) must be confirmed by two consecutive observations not less than six weeks apart.

Copies of the scans must be available for external independent review if requested by the Centre for Drug Development (CDD).

Baseline evaluations

These must include radiological measurements as indicated *(*chest computerised tomography (CT) scan, abdominal CT scan, magnetic resonance imaging (MRI), bone scan) and/or clinical measurements as appropriate. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses. (See Section 1.2.1 of RECIST (version 1.1) criteria)

Evaluations during and at 'off-study'

Tumour assessments must be repeated every six weeks or more frequently, when clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients, who are removed from the trial for reasons other than progressive disease, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the Principal Investigator to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST criteria.

10.3 Tumour response

All patients who meet the eligibility criteria and receive at least one cycle of trial medication and have a baseline assessment of disease will be evaluable for response. To be assigned a status of CR or PR, changes in tumour measurements must be confirmed by repeat measurements performed no less than four weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the investigational medicinal product (IMP) is given.

Should rapid tumour progression occur before the completion of the first cycle of combination treatment (vandetanib and Selumetinib for 28 days) the patient will be classified as having early progression (EP).

Tumour response should be classified as “not evaluable” (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by CDD may undertake an independent review of all the Investigator’s assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the trial. In case of disagreement between the Investigator’s and the expert reviewers’ assessment, discussion will take place between the two parties in order to reach a consensus. However, if it is not forthcoming, the assessment of the expert reviewers will be retained in the clinical study report. The eCRF will reflect the Investigator’s opinion.

Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF, even though the criteria for determination of CR or PR by the protocol must be confirmed after two consecutive observations, no less than four weeks apart.

Other definitions of outcome

Toxic death: Any death to which drug toxicity is thought to have a major contribution.

Early death: Death during the first 4 weeks of combination treatment (that is not a toxic death).

11 PATIENT WITHDRAWAL BEFORE COMPLETION OF TREATMENT SCHEDULE

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial (i.e. until 28 days after last vandetanib and selumetinib administration). However, if the Investigator removes a patient from the trial or if the patient declines further participation, final 'off-study' assessments should be performed before initiating any new anti-cancer treatment.. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

Patients who are removed from the trial due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the serious adverse event (SAE) report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from trial.

- AE/SAE including unacceptable toxicity
- Withdrawal of consent
- Serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance)
- Sponsor's decision to terminate the trial
- Withdrawal by the Investigator for clinical reasons not related to the IMP (vandetanib or selumetinib) including symptomatic deterioration
- Evidence of disease progression
- Pregnancy

12 DEFINING THE END OF TRIAL

The ‘end of trial’ is defined as the date when the last patient has completed the ‘off-study’ visit or the final follow-up visit (whichever is the latter).

It is the responsibility of the CDD to inform the Medicines and Healthcare products Regulations Agency (MHRA) and the Main Research Ethics Committee (REC) within 90 days of the ‘end of the trial’ that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the Main REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given. The pharmaceutical company (Astra Zeneca) will also be informed of early termination/halt.

The entire trial will be stopped when:

- The drugs are considered too toxic to continue treatment before the required number of patients being recruited.
- The stated number of patients to be recruited is reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, CDD and the Investigators must ensure that adequate consideration is given to the protection of the patient’s interest.

13 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The final analysis will be conducted after one of the following conditions is met.

- The trial is terminated early (for example, due to toxicity).
- All patients have completed their 'off-study' visit (i.e. 28 days after the last dose of vandetanib and selumetinib) and have been followed up for survival for one year from the first dose of IMP (Cycle 1 Day 1).

A clinical data cut-off date will be established to allow for primary analysis clinical study report (CSR) reporting once all recruited patients have been followed up for survival for a minimum of one year after the date of first IMP administration (Cycle 1 Day 1). The primary analysis CSR will include data from all treated patient visits/assessments up to and including the clinical cut-off date.

Any patients who continue to receive the combination therapy in the absence of disease progression or unacceptable toxicity after the clinical cut-off date will be included in an addendum to the final CSR. Only long-term safety data will be included in an addendum to the CSR.

PFS rate at 12 weeks will also be analysed for expansion cohort patients, according to the RECIST criteria. Assuming that the PFS rate in vandetanib alone is 9%, to test the hypotheses that the combination will increase the PFS rate to 23% under identical conditions, recruiting a total of 30 patients with NSCLC in a single arm design will give 82% power and 10% 1-side significant level.

The survival rate of NSCLC patients will also be analysed at one year. In addition to reporting the proportion of patients alive at 12 months, a Kaplan Meier curve will be plotted with 95% CI together with median survival provided.

13.1 Presentation of data

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the trial conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol violations, IMP accountability and other data that impact on the general conduct of the trial.

Baseline characteristics will be summarised (number and frequency) for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

13.2 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by number and frequency as data listings. Laboratory variables will be

described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.

Adverse events (AEs) will be reported for each dose level and presented as tables of frequency of AEs by body system and by worse severity grade observed. Tables should indicate related and unrelated events. Laboratory data will be presented by patient and reviewed alongside the AE listings.

13.3 Pharmacokinetics

The plasma concentration/time data will be analysed using non-compartmental methods. The PK parameters to be determined for vandetanib, selumetinib and other metabolites include the maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the plasma concentration time curve (AUC).

13.4 Pharmacodynamics

The following biomarkers will be measured in tumour tissue and blood pre and post treatment with the combination of vandetanib and selumetinib.

[redacted]

Imaging

FDG- PET scan

PET-CT scanning will be performed according to SOPs. The order of events for further imaging sessions will be a duplicate of the first dose and imaging. Full technical details of the imaging protocols will be found within the Imaging Manual.

The PET-CT images will be reported independently by two nuclear medicine trained radiologists. If there is discrepancy between the radiologists a third nuclear medicine

radiologist will be used as an arbiter. Semi-quantitative analysis will be performed expressing the uptake of tracer within tumour deposit as a standardized uptake value (SUV). Both maximum and mean values will be recorded.

SUV will be measured by drawing volumes of interest (VOI) using a minimum threshold value method for delineation of the tumour using Advantage Workstation 4.4 software (GE Healthcare) and calculating uptake according to a standardized formula incorporating body weight, timing and injected dose.

[redacted]

13.5 Anti-tumour activity

Documenting anti-tumour activity is a secondary objective of this trial. Patients must receive at least one cycle of the trial medication to be evaluable for response. Objective responses and the best tumour response achieved by each patient while on trial will be presented in the data listings.

Progression free survival and overall survival will be described for all patients and presented in data listings.

14 ADMINISTRATION

This trial is conducted under a clinical trial authorisation (CTA) and approval from the Medicines and Healthcare products Regulations Agency (MHRA) and the relevant Research Ethics Committee(s) will be obtained before the start of this trial. This trial is sponsored and monitored by the Cancer Research UK, Centre for Drug Development Office (CDD). Applicable regulatory requirements are described in this section.

14.1 Protocol deviations and amendments

Do not deviate from the protocol unless approval has been obtained from the CDD. The CDD has a no waiver policy with regard to inclusion and exclusion criteria. All proposed deviations from the protocol must be discussed and approved by the Sponsor.

Amendments to the protocol may only be made with the approval of the CDD. A protocol amendment may be subject to review by Cancer Research UK's Protocol Safety & Review Board (PSRB) and the assigned Ethics Committee. Depending on the type of protocol amendment, MHRA approval may also be required. Written documentation of the Ethics Committee (and if appropriate the MHRA) 'favourable opinion' (i.e. approval) must be received before the amendment can be implemented and incorporated into the protocol if necessary.

14.2 Completion of the electronic case report form (eCRF)

Electronic CRFs approved by the CDD will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Delegation Log provided by the CDD and have been authorised by the Investigator should enter or change data in the eCRFs. Authorised users will be included on a Master User List in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

Data will be entered directly into electronic screens by authorised site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorised personnel must answer the queries by making relevant amendments to data or providing a response. Answered queries will be closed or reissued as appropriate.

Once the patient is 'off study' and the eCRF has been fully completed, the Investigator must provide an electronic signature to authorise the complete subject casebook.

At the end of the trial all eCRFs are retained and archived by the CDD and a portable document format (PDF) copy provided to the Investigator who is responsible for archiving at site.

14.3 Trial performance and monitoring

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. CDD must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the CDD Clinical Research Associate (CRA) is responsible for monitoring data quality in accordance with CDD's standard operating procedures (SOPs) and all data pertaining to a patients participation in a trial must be available to the CRA. Before the trial start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review trial records and compare them with source documents;
- check pharmacokinetic and pharmacodynamic samples and storage;
- discuss the conduct of the trial and the emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

The Investigator undertakes not to destroy any unused IMP unless directed to by CDD. Any unused IMP must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record. During the course of the trial the CRA will check the numbers of bottles of tablets of Vandetanib and bottles of capsules of Selumetinib shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

It is the responsibility of the Sponsor to inform the Main REC within 90 days of the 'end of the trial' that the trial has closed. (See definition in Section 12).

14.4 Source document verification

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be recorded in the eCRF, documented on the source data verification (SDV) form and the monitoring report.

Some source data may exist only electronically and be entered, or loaded directly into the eCRF.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the CDD appointed to audit the trial, and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

14.5 Clinical study report

At appropriate intervals, interim data listings will be prepared to give the Investigator the possibility to review the data and check the completeness of information collected. All clinical data will be presented at the end of the trial on final data listings. CDD will prepare a clinical study report based on the final data listings. The report will be submitted to the Investigator(s) for review and confirmation it accurately represents the data collected during the course of the trial. A summary of the final clinical report must be provided by the CDD to the MHRA and to the Research Ethics Committee within one year of submission of the 'end of trial' notification to the MHRA.

14.6 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and serious adverse event (SAE) report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation or for longer if needed by CDD. Records must not be destroyed without prior written approval from CDD.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

14.7 Ethical considerations

Before starting the trial, the protocol, patient information sheet and consent form must go through the CDD's external review process, undergo review by the PSRB and the appropriate Ethics Committee.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The

Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and Chief/Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the Declaration of Helsinki (Appendix 2).

14.8 Indemnity

This trial is being carried out under the auspices of Cancer Research UK and therefore injury to a patient caused by the compounds under trial will not carry with it the right to seek compensation from the pharmaceutical industry. Cancer Research UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

14.9 Publication policy and press releases

Results of this trial must be submitted for publication. The CDD must be involved in reviewing all drafts of the manuscripts, abstracts, press releases and any other publications. Manuscripts must be submitted to CDD at least 35 days in advance of being submitted for publication to allow time for CDD to schedule a review and resolve any outstanding issues. Abstracts and press releases must be submitted to CDD at least 20 days in advance of being released. The Chief Investigator should be the principal author and any Investigator recruiting ≥ 10% of patients should be listed as an author. Imaging experts performing central review of imaging should also be listed as authors as applicable. Authors must acknowledge that the trial was sponsored by and performed with the support of CDD.

The contribution of CDD must be recognised by a member of staff being included as an author on the publication.

15 REFERENCES

Note for Guidance on Good Clinical Practice. ICH Topic E6. CSMP/ICH/135/95. EMEA, May 1996, updated September 1997 with post Step 4 errata included

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities L121/34-44*

Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. **October 2005***. ENTR/F2/BL D(2003) CT 1 (Revision 2)*

Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use. **February 2006.** *ENTR/CT 2 (Revision 1)*

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. **April 2006.** *ENTR/CT 3 (Revision 2)*

The **Medicines** for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 1031)

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. *Official Journal of the European Union L 91/13*

The Medicines for Human use (Clinical Trials) Amendment Regulations 2006 (Statutory Instrument 2006/1928).

1. Adjei, A.A., Cohen, R.B., Franklin, W., Morris, C., Wilson, D., Molina, J.R., Hanson, L.J., Gore, L., Chow, L., Leong, S., Maloney, L., Gordon, G., Simmons, H., Marlow, A., Litwiler, K., Brown, S., Poch, G., Kane, K., Haney, J., Eckhardt, S.G. (2008) Phase I Pharmacokinetic and Pharmacodynamic Study of the Oral, Small-Molecule Mitogen-Activated Protein Kinase Kinase 1/2 Inhibitor AZD6244 (ARRY-142886) in Patients With Advanced Cancers. *J Clin Onc*, **26**(13), 2139-2146.

2. Buonaccorsi, G. A., O'Connor, J. P., Caunce, A., Roberts, C., Cheung, S., Watson, Y., Davies, K., Hope, L., Jackson, A., Jayson, G. C., Parker, G. J. (2007) Tracer kinetic model–driven registration for dynamic contrast-enhanced MRI time-series data. *Magn. Reson. Med*, **58**(5): 1010-1019

3. de Boer, R., Humblet, Y., Wolf, J., Nogova, L., Ruffert, K., Milenkova, T., Smith, R., Godwood, A., Vansteenkiste, J. (2009) An open-label study of vandetanib with pemetrexed in patients with previously treated non-small-cell lung cancer. *Ann Oncol*, **20**(3), 486-491.

4. Cancer Research UK, Cancer Stats, Lung Cancer Report accessed 2011.

5. Dummer, R., Robert, C., Chapman, P., Sosman, J., Middleton, M., Bastholt, L. (2008) AZD6244 (ARRY-142886) vs temozolomide in patients with advanced melanoma: An open-label, randomized, multicentre, phase II study. *J Clin Onc*, **26**, suppl abstr 9033.

6. Herbst, R.S., Sun, Y., Eberhardt, W.E.E., Germonpre, P., Saijo, N., Zhou, C., Wang, J., Longyun, L., Kabbinavar, F., Ichinose, Y., Qin, S., Zhang, L., Biesma, B., Heymach, J.V., Langmuir, P., Kennedy, S.J., Tada, H., Johnson, B.E. (2010) Vandetanib plus docetaxel versus docetaxel as second line treatment for patients with advanced non small cell lung cancer (Zodiac): a double blind randomised Phase III trial. *Lancet Onc*, **11**(7), 619-626.

7. Heymach, J.V., Johnson, B.E., Prager, D., Csada, E., Roubec, J., Pesek, M., Spasova, I., Belani, C.P., Bodrogi, I., Gadgeel, S., Kennedy, S.J., Hou, J., Herbst, R.S. (2007) Randomized, Placebo-Controlled Phase II Study of Vandetanib Plus Docetaxel in Previously Treated Non–Small-Cell Lung Cancer. *J Clin Onc*, **25**(27), 4270-4277.

8. International Agency for Research on Cancer, Globocan 2008 website accessed 15 August 2011.

9. Investigator brochure selumetinib (AZD6244) version 10 dated 18April2011.

10. Investigator brochure vandetanib (ZD6474) version 11 dated 26May2010.

11. Kety, SS. (1951). The theory and application of the exchange of inert gas at the lungs and tissues. *Pharmacol Rev* **3**, 1−41.

12. Mok, T., Wu, Y.L. ,Zhang, L. (2009). A small step towards personalized medicine for non-small cell lung cancer. *Discov Med*, **8**(43), 227-31.

13. Naish, J.H., Kershaw, L.E., Buckley, D.L., Jackson, A., Waterton, J.C., Parker, G.J. (2009) Modeling of contrast agent kinetics in the lung using T1-weighted dynamic contrast enhanced MRI. *Magn. Reson. Med*, **61**: 1507-1514

14. Naish, J. H., Parker, G.J., Beatty, P.C., Jackson, A., Young, S.S., Waterton, J.C., Taylor, C.J. (2005) Improved quantitative dynamic regional oxygen enhanced pulmonary imaging using image registration. *Magn. Reson. Med*, 54: 464-469

15. Natale, R.B., Bodkin, D., Govindan, R., Sleckman, B.G., Rizvi, N.A., Capo, A., Germonpre, P., Eberhardt, W.E.E., Stockman, P.K., Kennedy, S.J., Ranson, M. (2009) Vandetanib Versus Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer: Results From a Two-Part, Double-Blind, Randomized Phase II Study. *J Clin Onc*, **27**(15), 2523-2529.

16. Reck, M., von Pawel, J., Zatlukal, P., Ramlau, R., Gorbounova, V., Hirsh, V., Leighl, N., Mezger, J., Archer, V., Moore, N., Manegold, C. (2009) Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first line therapy for nonsquamous non-small cell lung cancer: AVAiL. *J Clin Onc*, **27** (8), 1227-1234.

17. Roberts, P.J., Stinchcombe, T.E., Der, C.J., Socinski, M.A. (2010) Personalised medicine in non-small cell lung cancer: is KRAS a useful marker in selecting patients for epidermal growth factor receptor-targeted therapy? *J Clin Onc*, **28**(31), 4769-4777.

18. Sandler, A., Gray, R., Perry, M.C., Brahmer, J., Schiller, J.H. *et al* (2006). Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*, **355**(24), 2542-50.

19. Sklonik, J.M., Barrett, J.S., Jayaraman, B., Patel, D. and Adamson, P. (2008). Shortening the timeline of pediatric Phase I trials: The rolling six design. *J Clin Onc*, **26**(2), 190-195.

20. Takahashi, O., Komaki, R., Smith, P.D., Jurgensmeier, J.M., Ryan, A.J., Bekele, B.N., Wistuba, I.I., Jacoby, J.J., Korshunova, M.V., Biernacka, A., Erez, B., Hosho, K., Herbst, R.S., O'Reilly, M.S. (2011) MEK inhibition by selumetinib (AZD6244) inhibits progression with a multicentric antiangiogenic effect and enhances the efficacy of cediranib in orthotopic human lung cancer models. Abstract No, 629. AACR 2011.

21. Talbot, D., von Pawel, J., Cattell, E., Yule, S.M., Johnston, C., Zandvliet, A.S., Huitema, A.D.R., Norbury, C.J., Ellis, P., Boosquee, L., Reck, M. (2007). A randomised Phase II pharmacokinetic and pharmacodynamic study of Indisulam as second line therapy in patients with advanced non small cell lung cancer. *Clin Cancer Research*, **13** (6), 1816-1822.

22. Talbot, D., Ranson, M., Davies, J., Lahn, M., Callies, S., Andre, V., Kadam, S., Burgess, M., Slapak, C., Olsen, A.L., McHugh, P.J., de Bono, J.S., Matthews, J., Saleem, A., Price, P. (2010) Tumour survivin is downregulated by the antisense oligonucleotide LY2181308: A proof-of-concept, first-in-human dose study. Clinical Cancer Research, **16** (24), 6150-6158.

23. Tofts, P.S., Brix, G., Buckley, D.L., Evelhoch, J.L., Henderson, E., Knopp, M.V., Larsson, H.B., Lee, T.Y., Mayr, N.A., Parker, G.J., Port, R.E., Taylor, J., Weisskoff, R.M. (1999) Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusible tracer: standardized quantities and symbols. *J Magn Reson Imaging* **10**, 223–232.

16 APPENDICES

16.1 WHO PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

16.2 DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

**Adopted by the 18th World Medical Assembly,
Helsinki, Finland, June 1964
amended by the 29th World Medical Assembly
Tokyo, Japan, October 1975,
and
the 35th World Medical Assembly,
Venice, Italy, October 1983
and
the 41st World Medical Assembly,
Hong-Kong, September 1989
and
the 48th General Assembly,
Somerset West, Republic of South Africa, October 1996**

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I - BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of

this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II - MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (1,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III - NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

16.3 MEASUREMENT OF DISEASE

New response evaluation criteria in solid tumours (RECIST criteria): Revised RECIST guideline (version 1.1)

E.A. Eisenhauer *et al*. (2009) *European Journal of Cancer* **45:** 228-247

Note that this is an abridged version of the RECIST criteria. Please refer to the above article for detailed appendices and if in doubt.

1. Measurability of tumour at baseline

1.1. Definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

1.1.1. Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable).
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with 10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

All measurements should be recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI:

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More

details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in the publication from Eisenhauer et al.

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy:

The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers:

Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response.

Cytology, histology:

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1).

2.2. Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the

article by Bogaerts *et al*. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. An example in Fig. 3 of the publication by Eisenhauer et al.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non- pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’ (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3. Response criteria

2.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2. Special notes on the assessment of target lesions

Lymph nodes.

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'.

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment:

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease.

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease.

This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. Should a response not be documented until after the end of therapy in this trial, post-treatment assessments may be considered in the determination of best overall response as long as no alternative anti-cancer therapy has been given. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1. Time point response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in this trial (in which confirmation of complete or partial response IS NOT required):

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable. A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Table 1 – Time point response: patients with target (+/–non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD(a) NE
Not all evaluated	No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.
(a) 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required

Overall response	Overall response	BEST overall response
First time point	Subsequent time point(s)	
CR	CR	CR
CR	PR	SD, PD or PR(a)
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
(a) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression

even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 to 3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

16.4 NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I – patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain)

Class II – patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain)

Class III – patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain)

Class IV – patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

16.5 MANAGEMENT OF SKIN TOXICITY

Dermatological toxicity is anticipated for both vandetanib and selumetinib therefore the following guidance is recommended for patients on study and also guidance once study treatment has been discontinued. It is strongly recommended that all patients follow a program of sun protective measures while receiving study therapy and for 3-4 weeks after discontinuing study therapy. The aim is to reduce the risk of development of skin rash, minimize the severity of skin rash, and to minimize the requirement for dose reduction of study therapy. If a patient develops a skin rash, the following actions are recommended for the management of this reaction:

- A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams, either topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams. Patients with severe skin rashes, e.g., Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, and toxic skin eruptions, should be treated with systemic glucocorticoids and should not continue treatment, even at a lower dose.

- The rash should be graded/assessed by a physician as soon as possible according to the NCI CTCAE (version 4.02) cutaneous toxicity criteria and documented accordingly

- If the rash is CTCAE Grade 1, consider starting with mild to moderate topical steroids (e.g., betamethasone), topical antibiotics such as clindamycin gel, systemic antibiotics or no treatment if the patient is asymptomatic.

- Please note: Use of topical steroid cream with higher potency may be considered early in patients with moderate rash on the face. Topical or systemic antihistamines, and occasionally retinoid creams can also be considered.

- If a rash of CTCAE Grade 2 or higher is detected, immediate symptomatic treatment should be provided e.g. topical steroid or pimecrolimus cream and consider adding an oral tetracycline or a similar agent.

- If a rash of CTCAE Grade 3 or higher is detected, study treatment must be withheld until recovery to Grade 1 or below (See Section 5.4). The addition of topical steroids is recommended.

Pruritus of any grade may be treated with an antihistamine, such as diphenhydramine or hydroxyzine hydrochloride.

Secondary infection may complicate or worsen skin toxicity. To reduce the likelihood of nasal infection, intranasal mupirocin may be considered. Infected rash may be treated with a short course of an oral tetracycline, such as doxycycline. Sun exposure should be avoided in patients receiving doxycycline or other tetracycline antibiotics.

If there is a clinical diagnosis of impetigo, or an infection with *Staphylococcus aureus* is confirmed, topical mupirocin might be used. Infected lesions suspected to be treatment-resistant should be cultured. If there is no improvement after two weeks of treatment, therapy for the rash should be considered ineffective and discontinued and study treatment should not re start.

Xerosis can be treated with classical emollients.

If severe cutaneous toxicity recurs at reduced dose of vandetanib and selumetinib, the patient will permanently discontinue study treatment.

16.6 MANAGEMENT OF QTc PROLONGATION

For a list of medications known to prolong QTc, please see Appendix 8.

The electrocardiogram (ECG) must be evaluated by the local cardiologist or Investigator or qualified personnel at site, for the presence of QTcB prolongation or other abnormalities, in particular any changes in the T Wave morphology that would suggest a higher likelihood for the development of any arrhythmia.

Any clinically significant abnormal findings of QTcB prolongations will be recorded as adverse events.

On study monitoring

For a single QTcB value >480ms, withhold vandetanib (and selumetinib if in combination phase).

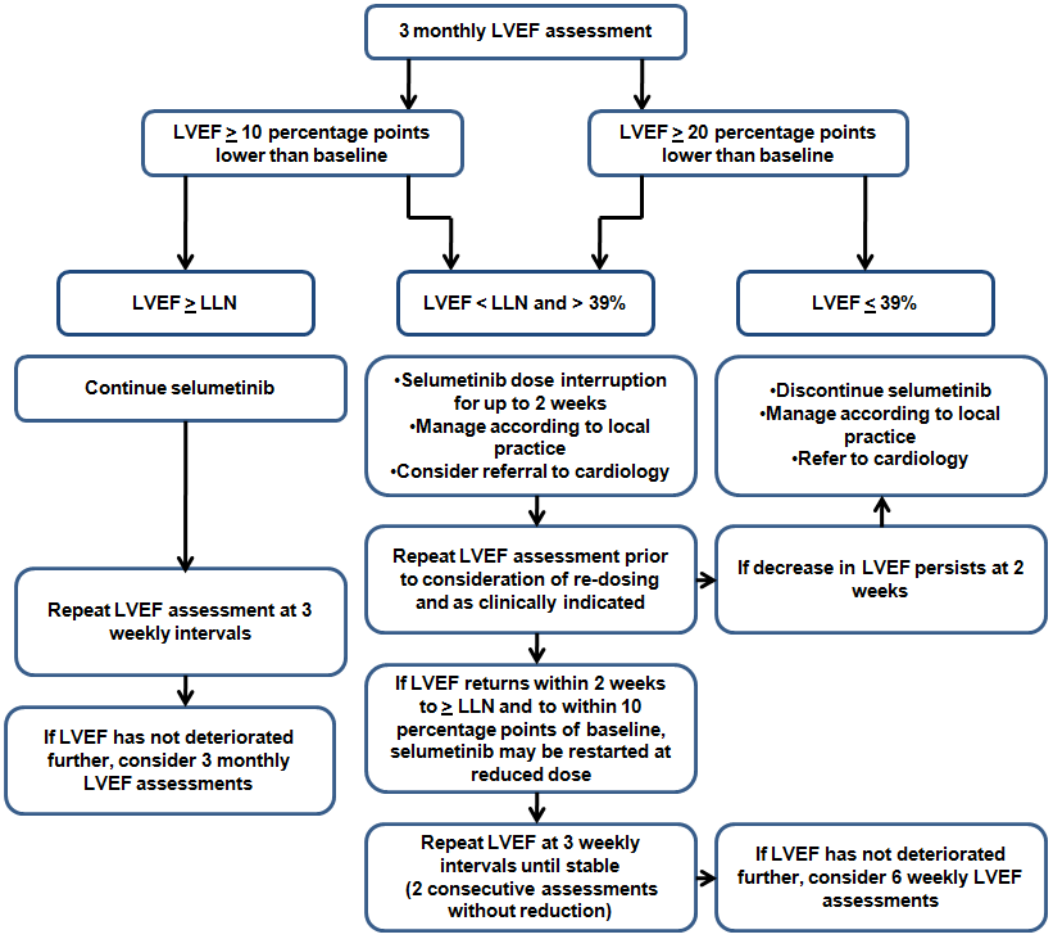
ECGs will be followed at least once a week (performed on the same day each week) along with electrolytes, until QTcB falls below 480ms. Vandetanib may then be resumed at a permanently lower dose (dosing every other day at same dose level), after the QTcB returns to <480ms.

If vandetanib is restarted after the QTcB prolongation has resolved, ECGs (along with electrolytes) should be performed two weeks following restarting study treatment and then prior to Day 1 of each cycle thereafter.

Serum potassium levels should be maintained at 4.0mmol/L or higher and serum magnesium and calcium should be kept within normal range to reduce the risk of QTc prolongation.

Vandetanib treatment may be resumed at a lower dose after the QTcB recovers to less than 480 ms.

16.7 INVESTIGATION OF ASYMPTOMATIC DECREASES IN LVEF.



16.8 MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES

Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (Table 1) are not allowed within 2 weeks of first dose or during study (at least 4 weeks for Levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment.

If after reviewing the list of drugs in Table 1, the investigator finds that any ongoing patient is now taking a Group 1 drug, the investigator is to manage the patient immediately as follows:

- The investigator should switch the patient to an alternative drug as soon as possible.
- If it is not possible to switch the patient to an alternative drug, the patient will have to stop study treatment.

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Amiodarone	Anti-arrhythmic / abnormal heart rhythm	TdP risk regarded as low
Arsenic trioxide	Anti-cancer / Leukemia	
Astemizole	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Bepridil	Anti-anginal / heart pain	
Chloroquine	Anti-malarial / malaria infection	
Chlorpromazine	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	GI stimulant / heartburn	Restricted availability
Clarithromycin	Antibiotic / bacterial infection	
Disopyramide	Anti-arrhythmic / abnormal heart rhythm	
Dofetilide	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Anti-nausea / nausea	Not available in the U.S.
Droperidol	Sedative; Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	Antibiotic; GI stimulant / bacterial infection; increase GI motility	
Halofantrine	Anti-malarial / malaria infection	
Haloperidol	Anti-psychotic / schizophrenia, agitation	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Anti-arrhythmic / abnormal heart rhythm	
Levomethadyl	Opiate agonist / pain control, narcotic dependence	

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Mesoridazine	Anti-psychotic / schizophrenia	
Methadone	Opiate agonist / pain control, narcotic dependence	
Moxifloxacin	Antibiotic / bacterial infection	
Pentamidine	Anti-infective / pneumocystis pneumonia	
Pimozide	Anti-psychotic / Tourette's tics	
Probucol	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Anti-arrhythmic / abnormal heart rhythm	
Sotalol	Anti-arrhythmic / abnormal heart rhythm	
Sparfloxacin	Antibiotic / bacterial infection	
Terfenadine	Antihistamine / Allergic rhinitis	No longer available in U.S.
Thioridazine	Anti-psychotic / schizophrenia	
Vandetanib (*Does not apply to this study)	Anti-cancer / Thyroid cancer	"Zactima®" is the proposed brand name

Table 2: Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes.

Co-administration of drugs that in some reports might be associated with TdP but at this time lack substantial evidence (Table 2) should be avoided within 2 weeks of first dose and during study. However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the subject must be closely monitored including regular checks of QTc and electrolytes. For patients who start on the drugs in this group while on the study treatment, the ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the patient remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no QTc prolongation has been noted during 4 weeks of co-administration of a drug from Table 2. The electrolytes should be maintained within the normal range using supplements if necessary.

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Alfuzosin	Alpha1-blocker / Benign prostatic hyperplasia	
Amantadine	Dopaminergic/Anti-viral / Anti-infective/ Parkinson's Disease	
Atazanavir	Protease inhibitor / HIV	
Azithromycin	Antibiotic / bacterial infection	
Chloral hydrate	Sedative / sedation/ insomnia	
Clozapine	Anti-psychotic / schizophrenia	
Dolasetron	Anti-nausea / nausea, vomiting	
Dronedarone	Anti-arrhythmic / Atrial Fibrillation	
Escitalopram	Anti-depressant / Major depression/ Anxiety disorders	
Famotidine	H2-receptor antagonist / Peptic ulcer/ GERD	
Felbamate	Anti-convulsant / seizure	
Flecainide	Anti-arrhythmic / abnormal heart rhythm	
Foscarnet	Anti-viral / HIV infection	
Fosphenytoin	Anti-convulsant / seizure	
Gatifloxacin	Antibiotic / bacterial infection	
Gemifloxacin	Antibiotic / bacterial infection	
Granisetron	Anti-nausea / nausea and vomiting	
Indapamide	Diuretic / stimulate urine & salt loss	
Isradipine	Anti-hypertensive / high blood pressure	
Lapatinib	Anti-cancer / breast cancer, metastatic	
Levofloxacin	Antibiotic / bacterial infection	
Lithium	Anti-mania / bipolar disorder	
Moexipril/HCTZ	Anti-hypertensive / high blood pressure	
Nicardipine	Anti-hypertensive / high blood pressure	
Nilotinib	Anti-cancer / Leukemia	
Octreotide	Endocrine / acromegaly, carcinoid diarrhea	
Ofloxacin	Antibiotic / bacterial infection	
Ondansetron	Anti-emetic / nausea and vomiting	
Oxytocin	Oxytocic / Labor stimulation	
Paliperidone	Antipsychotic, atypical / Schizophrenia	

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Perflutren lipid microspheres	Imaging contrast agent / Echocardiography	
Quetiapine	Anti-psychotic / schizophrenia	
Ranolazine	Anti-anginal / chronic angina	
Risperidone	Anti-psychotic / schizophrenia	
Roxithromycin*	Antibiotic / bacterial infection	*not available in the United States
Sertindole	Antipsychotic, atypical / Anxiety, Schizophrenia	
Sunitinib	Anti-cancer / RCC, GIST	
Tacrolimus	Immunosuppressant / Immune suppression	
Tamoxifen	Anti-cancer / breast cancer	
Telithromycin	Antibiotic / bacterial infection	
Tizanidine	Muscle relaxant /	
Vardenafil	phosphodiesterase inhibitor / vasodilator	
Venlafaxine	Anti-depressant / depression	
Voriconazole	Anti-fungal / anti-fungal	
Ziprasidone	Anti-psychotic (schizophrenia)	