Drug	**Vandetanib (ZACTIMA™; ZD6474)**
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Randomized Placebo-Controlled Pilot Study of ZD6474 as a Chemopreventive Agent for Premalignant Lesions of the Head and Neck

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PROTOCOL SYNOPSIS

Randomized Placebo-Controlled Phase II Study of ZD6474 as a Chemopreventive Agent for Premalignant Lesions of the Head and Neck

Study Centre(s) and Number of Subjects Planned
University of Chicago
University of Texas MD Anderson Cancer Center

Study period		Phase of development
Estimated date of first subject enrolled	October 2011	Phase 0
Estimated date of last subject completed	October 2013	

Objectives
To assess the change in microvessel density (MVD) from baseline to 3 months in preneoplastic lesions from patients treated with ZD6474 compared to placebo

Study Design
Randomized, double-blind, placebo controlled

Target Subject Population
Only subjects felt to be at high risk for oral squamous cell carcinoma (OSCC) will be enrolled to maximize risk/benefit ratio. Subjects will be required to have an area of dysplasia on prior biopsy or a history of OSCC.

Investigational Product, Dosage and Mode of Administration
ZD6474 (vandetanib), 100 mg, oral

Comparator, Dosage and Mode of Administration
Placebo

Duration of Treatment
6 months

Safety
Adverse events will be monitored and reported as detailed in the protocol. Data and Safety Monitoring meetings will be held weekly. Adherence will be monitored by pill counts and diaries. Toxicity and adherence will be reported as secondary endpoints.

Statistical Methods
The primary endpoint of this study is the comparison between treatment groups of the within-patient change in MVD score from baseline to 3-months following treatment initiation

(ΔMVD). The primary analysis upon which the sample size calculations are based is the comparison of ΔMVD between treatment arms using a two-sample *t*-test with unequal variances. A Wilcoxon ranksum test may be used if the normality assumption is not satisfied. Alternatively, ΔMVD may be transformed (e.g. log-transformation) to satisfy the normality assumption. Additional analyses of the primary endpoint will include linear regression models with treatment effect and other prognostic factors as covariates.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
OSCC	Oral Squamous Cell Carcinoma
VEGF(R)	Vascular Endothelial Growth Factor (Receptor)
EGFR	Epidermal Growth Factor Receptor
MVD	Microvessel Density

1. INTRODUCTION

Despite advances in diagnosis and treatment, improved long-term survival for oral squamous cell carcinoma (OSCC) patients has remained modest (1, 2). Several factors contribute to this relatively poor outcome. First, OSCC is often diagnosed at an advanced stage. Second, as a result of "field cancerization", the development of multiple primary tumors has a major impact on survival. For patients with early stage disease, second primary tumors are their most common cause of treatment failure and death (1, 2). Therefore, to improve outcomes, a comprehensive treatment plan must include effective chemoprevention strategies.

Chemoprevention can be defined as the use of natural or synthetic agents to reverse or halt the progression of premalignant lesions. Chemopreventive agents are currently being tested for their efficacy in preclinical and clinical settings for many malignancies including OSCC (3, 4). However, initial promising results for OSCC chemoprevention have not been consistently reproduced and toxicity has often been significant. The issue of toxicity is particularly important in chemoprevention as prolonged therapy in the absence of a known diagnosis of OSCC may be required.

Angiogenesis is an essential phenotype in both physiologic and pathologic settings (5). Because of its critical role in cancer biology, the inhibition of angiogenesis is an attractive target for therapy. The induction of the angiogenic phenotype in OSCC is mediated by the direct and indirect production of various factors capable of inducing blood vessel growth (6). Among these, the vascular endothelial growth factor (VEGF) family is thought to play an important role. The biological effects of the VEGF ligands are mediated through their binding to members of the vascular endothelial growth factor receptor family (VEGFR-1, VEGFR-2, VEGFR-3). This interaction leads to autophosphorylation of specific tyrosine residues and subsequent downstream activation of intracellular signaling pathways, such as the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt pathways. Importantly, the induction of angiogenesis is one of the first recognizable phenotypic changes observed in both experimental models as well as in human OSCC (7-10), suggesting that inhibitors of angiogenesis may also hold promise in the field of chemoprevention.

The development, growth and survival of OSCC are also highly dependent upon the Epidermal Growth Factor Receptor (EGFR) signaling pathway. EGFR is a transmembrane glycoprotein that is a member of the ErbB/HER receptor tyrosine kinase family. Upon ligand binding, EGFR signaling is mediated by the MAPK and PI3K/Akt pathways. Increased expression of EGFR and its ligand transforming growth factor-α (TGF-α) are observed in most OSCC and premalignant oral lesions, and this expression correlates with poor prognosis (11). In addition, members of the EGFR pathway contribute to the induction of angiogenesis. For example, the expression of TGF-α or EGFR causes increased expression of VEGF (12, 13). Because of its importance in epithelial malignancies, there is considerable interest in targeting the EGFR pathway for chemoprevention.

ZD6474 (vandetanib, ZACTIMA) is an orally available tyrosine kinase inhibitor (TKI) with activity against multiple signal transduction pathways including VEGFR-2 and EGFR (14-16). In preclinical studies, ZD6474 was a potent inhibitor of angiogenesis and

proliferation of a number of different tumor cell types (17). Further, it is currently under active investigation in clinical trials for the treatment of various malignant neoplasms (17). Using the 4-Nitroquinoline 1-Oxide (4-NQO) mouse model, we have demonstrated that ABT-510 (a global inhibitor of angiogenesis) and ZD6474 (a dual tyrosine kinase inhibitor (TKI) against EGFR and VEGFR-2) significantly decreased the incidence of dysplasia and OSCC (18, 19). These data support the hypothesis that agents with anti-angiogenic activity may hold promise as chemopreventive agents for OSCC.

1.1 Background

Using the 4-NQO model, we found that ABT-510 (a global inhibitor of angiogenesis) and ZD6474 (a dual TKI against EGFR and VEGFR-2) significantly decreased the incidence of dysplasia and OSCC (18, 19). In the ZD6474 study, mice were administered 4-NQO (100 µg/ml) in their drinking water for a period of 8 weeks, returned to normal water, and then randomized to observation or daily oral gavage of ZD6474 (25 mg/Kg/day) for 24 weeks. During the 24-week chemoprevention regimen, no significant differences in food and fluid consumption or activity were observed between the groups. At the completion of the 32 week study, 71% of the control mice and 12% of the ZD6474-treated mice harbored OSCC ($p<0.001$) (Table 1). Similarly, the proportion of mice with dysplasia or OSCC was significantly different between the two groups. In the control group, 96% of the animals demonstrated dysplasia or OSCC, while 28% ZD6474 treatment group had dysplasia or OSCC ($p<0.001$). In total, this represented a 71% decrease in OSCC or Dysplasia and an 83% decrease in OSCC. ZD6474 inhibits tumor cell proliferation and angiogenesis via its dual activity against EGFR and VEGFR-2 (14-16). We performed IHC for Ki67 and CD31 as surrogate markers for proliferation and microvessel density (MVD). Overall, the proliferative index (PI) for ZD6474-treated animals was significantly lower when compared to the control mice (Table 2). The control group had a PI of 46 $\pm$ 10, while the ZD6474 treatment group had a PI of 29 $\pm$ 10 ($p<0.001$). Overall, there was a significant decrease in MVD in the ZD6474-treated mice compared to controls. The control group had a MVD score of 265 $\pm$ 60, while the ZD6474 treatment group had a MVD score of 106 $\pm$ 73 ($p<0.001$).

	Control	ZD6474	Total
Hyperkeratosis	1	18	19
Dysplasia	6	4	10
OSCC	17	3	20
Total	24	25	49

Table 1. Incidence of dysplasia and OSCC in control and ZD6474 treated mice.

	Control N=24	ZD6474 N=25
MVD	265 ± 60	106 ± 73*
Ki67	46 ± 10	29 ± 10*
pEGFR	97 ± 5	33 ± 3*
pVEGFR2	106 ± 11	32 ± 3*

* $p \leq 0.001$ for comparison to control group

Table 2. ZD6474 inhibits proliferation, microvessel density and phosphorylation of EGFR and

Vandetanib (ZD6474) is a potent inhibitor of the tyrosine kinase activity of kinase insert domain-containing receptor (KDR), an endothelial cell receptor for vascular endothelial growth factor (VEGF), and also possesses activity against epidermal growth factor receptor (EGFR). VEGF is a humoral mediator of endothelial cell proliferation, and is one of the primary growth factors responsible for the initiation of new blood vessel growth. This process, termed angiogenesis, is essential for the growth and dissemination of tumors. By specifically targeting angiogenesis, it is hoped that the growth of tumors will be controlled, with relative sparing of normal tissues.

Vandetanib has shown excellent inhibition of tumor cell growth in a broad range of pre-clinical models, including lung cancer xenografts (Calu-6 and A549). Regression of established tumors (PC-9 lung cancer and PC-3 prostate cancer) in animals was observed following oral administration. Vandetanib was considered to have an acceptable pre-clinical toxicology profile for the proposed therapeutic indication. Vandetanib also inhibits epidermal growth factor (EGF) stimulated cell proliferation, though at a concentration (the molar concentration of a compound required to produce 50% inhibition of a biological effect; IC50=170 nM) approximately 3-fold higher than that required for the inhibition of VEGF-stimulated cell proliferation (60 nM).

Vandetanib has demonstrated inhibition of both vascular endothelial growth factor receptor (VEGFR) and EGFR tyrosine kinases *in vitro*, and pre-clinical models have shown activity against non-small cell lung cancer (NSCLC) xenografts. AstraZeneca has conducted clinical studies in patients with NSCLC. In the Japanese Phase I study (TVE-15-11), 4 of 9 patients with NSCLC had confirmed partial responses (PRs). Subsequently, 2 randomized Phase II studies (6474IL/0003 and 6474IL/0006) were performed in patients with NSCLC refractory to first-line therapy. Vandetanib demonstrated an advantage in progression-free survival (PFS) compared with gefitinib in study 6474IL/0003, and in combination with docetaxel compared with docetaxel alone in study 6474IL/0006. The results of these Phase II studies led to the designs of 4 Phase III studies. Two studies investigated vandetanib in combination with chemotherapy (study D4200C00032 with docetaxel and study D4200C00036 with pemetrexed), and 2 studies investigated vandetanib as monotherapy

(study D4200C00057 compared to erlotinib and study D4200C00044 compared to best supportive care in patients who have previously received an EGFR inhibitor). In the 2 combination studies, the addition of vandetanib to docetaxel provided a statistically significant advantage in PFS compared to docetaxel alone; in the smaller study with pemetrexed, there was a positive trend for PFS in favor of the addition of vandetanib. Study D4200C00057 did not meet the goal of demonstrating superiority in PFS compared to erlotinib, but the efficacy of the 2 drugs was equivalent. Study D4200C00044 was still ongoing at the time of edition 11 of the Investigator's Brochure (IB). The most common side effects associated with vandetanib are rash and diarrhea. In addition to the studies of vandetanib in NSCLC, several other Phase I and II studies are ongoing in other tumors, and a Phase III study in patients with medullary thyroid cancer is also ongoing. [a]

[a] Vandetanib, ZD6474, Investigator's Brochure, Edition Number 10, March 2009

Summary of Adverse Events (AE) in Vandetanib (ZD6474) Phase I and Phase II Studies
The events below are discussed regardless of causality to vandetanib. Some of these events may reflect symptoms of cancer, effects of chemotherapy or radiation, or concomitant medical illness. Events that are thought likely to be causally related to vandetanib are listed in the Emerging Safety Profile section below.

Skin and Subcutaneous Tissue Disorders
The events, organized by MedDRA preferred term, that were categorized under this system organ class include rash, acne, maculo-papular rash, dry skin, night sweats, pruritus, acneform dermatitis, exfoliative dermatitis, contusion, rash photosensitivity, photosensitivity reaction, desquamation, erythema, erythematous rash, macular rash, pruritic rash, pustular rash, follicular rash, skin eruption, hyperhidrosis, nail discoloration, skin ulcer, urticaria and alopoecia.

Most of these skin disorders happened in the first 4 weeks of treatment and were CTC/CTCAE grade 1-2. There was a tendency for dose-dependent increase in incidence of drug-related adverse events. At least 2 distinct types of rash related to vandetanib therapy have been described, namely, a macular erythema in some patients and a follicular (acneform) rash in others. Also, photosensitive rash has been reported in some of these patients. When vandetanib was combined with pemetrexed, 10 patients developed skin rash; 7 of the events were considered to be vandetanib-related. None of the cases was reported to be CTCAE Grade 3 or higher. The majority of the events developed within the first 6 weeks of treatment and some of them within the first week of vandetanib exposure.

Gastrointestinal System
Events included diarrhea, nausea, vomiting, constipation, abdominal pain, upper abdominal pain, abdominal discomfort, abdominal distention, flatulence, dry mouth, dry lip, mouth ulceration, dyspepsia, dysphagia, gastroesophageal, stomatitis, aphthous stomatitis, acquired esophageal stenosis, and gingival bleeding. Most of these adverse events were CTC/CTCAE grade 1 or 2 and did not need interruption of study treatment. Routine anti-diarrheal agents are also recommended. Abdominal pain has been seen in Phase I, but was not common in Phase II studies.

General Disorders and Administration Site Conditions
Fatigue, pyrexia and peripheral edema were observed, as were asthenia, rigors, chest pain, chest tightness, mucosal inflammation, abnormal gait, and lethargy. Most of the adverse events were CTC/CTCAE grade 1-2; grade 3 was rare.

Vascular Disorders
Hypertension is considered to be a class effect for VEGF pathway inhibitors, and was a DLT for studies 6474IL/0001 and TVE-15-11. Pulmonary thrombosis and deep vein thrombosis have been observed so far. One instance of pulmonary hemorrhage after cavitation was also observed in a study of vandetanib combined with docetaxel (6474IL/0006.) It is unclear whether deep vein thrombosis and pulmonary hemorrhage may be related to vandetanib or reflect the underlying cancer or co-morbid conditions.

Respiratory System
Cough and dyspnea were common adverse events, but are common symptoms of lung cancer. Other reported adverse events included pharyngolaryngeal pain, epistaxis, dysphonia, hiccups, respiratory alkalosis, rhinorrhea, pulmonary embolism, and pulmonary artery thrombosis.

Other adverse events
Other commonly reported AEs included nervous system disorders **(**lethargy, neuropathy peripheral, headache and dysaesthesia), blood and lymphatic system disorders (neutropenia and thrombocytopenia) and metabolism and nutrition disorders (hypokalaemia).

QT/ QTc Prolongation[a]
Phase I studies
Prolongation of the ECG corrected QT interval was initially observed in Phase I and II studies, and no patients experienced symptoms definitely related to QTc prolongation. On rare occasions, patients with QTc prolongation have experienced cardiac arrhythmias; however, all patients had confounding factors that were much more likely to be the cause.

Phase II studies
Prolongation of the QTc interval, using Bazett's correction, was seen in Phase II studies. No significant changes in heart rate were observed across any of the doses studied. No patient developed symptomatic ventricular arrhythmias, although 1 patient with pneumonia and QTc greater than 600 ms was noted to have a non-sustained run of ventricular tachycardia while in a monitored hospital setting (see below). Using extensive ECG monitoring to assess the QTc prolongation more closely, at a dose of 300 mg/day, QTc prolongation resulting in dose reduction has been seen in approximately 5% of patients, and at a dose of 100 mg in combination with chemotherapy in <2% of patients.

Phase III studies
In the Phase III studies, the incidence of prolongation of the ECG QTc interval was seen in 1.9% of patients treated with vandetanib 100 mg plus docetaxel and in 0.4% of patients treated with vandetanib 100 mg plus pemetrexed. No patients receiving vandetanib 100 mg experienced torsade de pointes or other arrhythmia attributed to prolongation of the QTc interval. In study D4200C00057, 5% of patients receiving vandetanib 300 mg experienced

prolongation of the QTc interval, and there was 1 case or reversible, non-fatal torsade de pointes. The QTc prolongation was managed by dose interruption followed by dose reduction. A non-linear relationship between QTc and vandetanib plasma concentration has been determined using pharmacokinetic/pharmacodynamic modeling.

[a] Above Summary of Adverse Events taken from Vandetanib, ZD6474, Investigator's Brochure, Edition Number 10, March 2009.

Emerging Safety Profile[a]
Vandetanib produces repolarization abnormalities in human myocardium that are consistent with blockade of the IKR (potassium) channel. The most consistent electrophysiologic effects are a change in T-wave morphology (flattening, broadening or notching) and prolongation of the QT interval, both of which occur more commonly as the dose is increased. Vandetanib can cause rash, diarrhea and hypertension, all of which appear to be dose-related and are likely to be related to the pharmacologic activity of vandetanib.

The drug-related AEs seen with vandetanib monotherapy are also expected to occur in combination with chemotherapy. All drug-related AEs expected to occur in association with the concomitant chemotherapeutic agent(s) (as defined and listed in the package insert[s]) will be expected to occur when used in combination with vandetanib. The relevant product information for the concomitant chemotherapy should be used to determine these expected, drug-related AEs.

Reported adverse events that may be related to vandetanib are listed below by body system:

Cardiovascular
Abnormal ECG (with or without QT prolongation; i.e. either T-wave or ST-segment changes consistent with repolarization abnormalities), torsade-de-pointes and ventricular tachycardia (both at 300 mg daily dose) and hypertension.

Cardiac failure (300 mg daily dose) (See Appendix C for the New York Heart Association (NYHA) Cardiac Classifications.)

Central Nervous System –headache, Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Digestive – constipation, diarrhea, nausea, vomiting

Hematologic and Lymphatic – ecchymosis and thrombocytopenia

Investigations – elevated liver function tests (generally CTC/CTCAE grade 1-2, weight loss

Metabolic and nutritional – dehydration, hypokalemia, hypomagnesemia, hypophosphatemia

Skin and Appendages – acneform rash, pruritus, macular or macupapular rash (generalized or localized), localized and generalized erythema, photosensitivity reaction, sweating. On occasion (especially when given with chemotherapy) these have progressed to more serious conditions to include exfoliative dermatitis, skin desquamation, erythroderma, toxicoderma, toxic epidermal necrolysis, erythema multiforme

Respiratory – interstitial lung disease (ILD). A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough due to inflammation or scar tissue formation in the lungs (although this could be due to the underlying lung cancer)

Renal – proteinuria, hematuria

Vascular – Arterial ischaemic events (including myocardial infarction, stroke, peripheral ischaemia)

Psychiatric - Mood disorders (anxiety, depression, insomnia). It is possible that these events are not direct effects of vandetanib, but rather are secondary to symptoms of cancer or to other effects of vandetanib (rash, etc.).

General – asthenia, fatigue

[a] Above text taken from Vandetanib, ZD6474, Investigator's Brochure, Edition Number 10, March 2009.

For additional details on vandetanib, please refer to the current Vandetanib Investigator's Brochure.

Rationale
Our data support the hypothesis that agents with anti-angiogenic activity may hold promise in chemoprevention. Therefore, we will conduct a double-blind, placebo-controlled, randomized phase II trial that will assess the pharmacodynamic effects of ZD6474 in high-risk patients. The primary endpoint will examine the ability of ZD6474 to inhibit angiogenesis, as measured by MVD. Secondary endpoints will include inhibition of proliferation, modulation of EGFR and VEGFR2 phosphorylation, tolerability and feasibility of administration, and development of OSCC. We hypothesize that ZD6474 will inhibit angiogenesis in preneoplastic tissues compared to placebo. These results will serve as proof of principle to implement larger prospective chemoprevention trials of anti-angiogenic or anti-EGFR inhibitors in high-risk patients.

Study Design: This will be a randomized, double-blinded, placebo controlled study with a primary endpoint of reducing MVD in preneoplastic lesions at 3 months compared to baseline. We will administer ZD6474 or placebo for 6 months and monitor subjects for up to 3 years. Biopsies will be obtained at baseline, 3 months, and 6 months from the same area of known dysplasia and banked in the Biobanking and Pathology Core. A placebo control group is

necessary due to the lack of validated historic controls in this population and ethical because standard of care in these patients would be active surveillance.

Proposed study population: Only subjects felt to be at high risk for OSCC will be enrolled to maximize risk/benefit ratio. Subjects will be required to have an area of dysplasia on prior biopsy or a history of OSCC. Using these criteria, subjects would be expected to have a significant cumulative lifetime risk of developing OSCC of ~50%. Other eligibility criteria are will include normal organ function, QTc interval < 450ms, performance status ≥ 70% on the Karnofsky scale, and age ≥ 18 years.

Choice of primary endpoint: Despite extensive studies to identify patients at risk for developing OSCC, there are no established chemopreventive agents. Prior Phase III studies have been negative due to a lack of efficacy, inadequate understanding of molecular mechanisms underlying the intervention, or tolerability of the agent for long periods of time. Therefore, with preclinical and safety data strongly supporting the rationale for administering ZD6474 as a chemopreventative agent, this study will assess two critical limitations of prior approaches. The primary endpoint reflects an effect of ZD6474 on microvessel density (MVD) in preneoplastic lesions which correlated strongly with OSCC inhibition in the preclinical model and serves as a surrogate for the latter. We will also assess tolerability and feasibility of administering ZD6474 for 6 months (see below). The results of this trial would inform the planning of larger studies of this approach in preventing OSCC.

Secondary Endpoints: The trial will examine endpoints related to putative targets of ZD6474, safety and tolerability, and OSCC development. To assess the biologic effect of EGFR and VEGFR2 inhibition, tissues will be analyzed by IHC for pEGFR, EGFR, pVEGFR2, VEGFR2, and Ki-67. We hypothesize that biopsies from ZD6474 patients will exhibit significantly lower expression of pEGFR and VEGFR2 and proliferation indices.

A critical parameter of successful chemoprevention efforts is adherence and safety. Ideally, an agent would be easily administered for a duration that will affect the natural history of the disorder and be well tolerated. ZD6474 is an orally available, well-tolerated drug with demonstrated anti-angiogenic and EGFR inhibitory properties that has been administered safely to patients for prolonged periods. ZD6474 has been studied in 37 clinical trials involving over 2000 subjects. The agent is administered once daily with predictable pharmacokinetics and without significant food-drug or drug-drug interactions. In general, the agent has been well tolerated even for long-term administration with the most common adverse events being rash, nausea, diarrhea, fatigue, and hypertension. Reversible and dose related QT prolongation has been observed with ZD6474. At 300 mg daily, dose reduction has been required in approximately 15% of subjects for QTc prolongation. Deep venous thrombosis has been observed with ZD6474 but these events are rare (1% incidence) and it is unclear whether they are causally related to the agent. Recently a placebo controlled, phase 3, 2:1 randomized study administering ZD6474 in patients with medullary thyroid cancer was reported. The primary endpoint of progression-free survival significantly favored ZD6474 (Hazard ratio = 0.46 (0.31–0.69), $p<0.0001$). Among the 231 subjects enrolled to receive ZD6474, median duration of therapy was 90 weeks with only 12% of subjects discontinuing therapy due to an adverse event. The most common grade 3 or greater adverse events and

their frequency were diarrhea (11%), hypertension (9%), and QT prolongation (8%). Thus, in large randomized trials, ZD6474 can be safely and feasibly administered for prolonged periods.

Adherence in both arms will be monitored by self-administered patient diaries. Remaining pill counts will be performed to determine reliability of self-reporting. Subjects will be seen upon starting therapy, at weeks 1, 2, 4, 5, 8, 9, 13, 17, 21, 25; months 6, 9, and 12; and at least every 6 months for 2 years. Subjects will be followed and monitored for oral and other cancers. We expect that ZD6474 treated patients will have a lower incidence of OSCC. However, the study is clearly underpowered to demonstrate a statistically significant difference between groups.

Study Feasibility: The Head and Neck Cancer Program at the University of Chicago has a strong record of multi-disciplinary care with expertise in all aspects of the disease including head and neck cancer surgery, radiation therapy, medical oncology, and oral pathology. In 2009 the program registered over 800 unique patient visits and performed approximately 300 new patient consults. A High Risk Clinic to specifically deal with the needs of patients without active disease but who are at increased risk to develop HNSCC is available and overseen by Dr. Elizabeth Blair. These patients often have a personal or strong family history of HNSCC, engaged in behavior associated with developing OSCC (e.g. tobacco use), or harbor a pre-neoplastic lesion. The clinic will serve as the setting to screen prospective patients, obtain tissue, and perform the clinical study. We recognized the importance of OSCC chemoprevention and have participated in three such studies that are either already closed or are anticipated to complete accrual prior to the initiation of this proposed trial.

Dr. Lingen is a Board Certified Oral & Maxillofacial Pathologist. His outreach service receives biopsies from dentists throughout Illinois and Northwestern Indiana. Drs. Dennis Solt and Reza Mostofi are oral pathologists with outreach services in Chicago. The 3 services have a combined total of ~10,000 cases/year, and approximately ~100 dysplasia cases. All 3 biopsy services have contributed patients for the EPOC prevention trial currently underway with the MD Anderson. Therefore, the involvement of these biopsy services will be important for the accrual of subjects for the proposed study.

In order to achieve the target sample size, accrual for this trial must be 2 patients per month.

Rationale for Collection of Blood Samples for Biomarker Analysis

There are currently no known markers that are predictive of response or resistance to VEGF signaling inhibitors including vandetanib. By collecting and storing serial samples of plasma and serum for the first months of treatment with vandetanib it will be possible to explore relationship between changes in biomarkers and response and to explore the mechanisms underlying the biological response and resistance to VEGF signaling inhibitors. It is likely that additional information and assays for biomarkers that are important for the response to vandetanib will become available in the future. It is, therefore, important to be able to store samples in order to retain the possibility of investigating biomarker changes in the context of vandetanib treatment in the future.

2. STUDY OBJECTIVES

2.1 Primary Objective

Determine the effect of ZD6474 compared to placebo on MVD from baseline to 3 months in patients at risk for OSCC with preneoplastic lesions.

2.2 Secondary Objectives

- Change in MVD over 6 months
- Change in putative targets of ZD6474
  - tissues will be analyzed by immunohistochemistry (IHC) for pEGFR, EGFR, pVEGFR2, VEGFR2
- Change in proliferative index as measured by Ki-67 IHC
- Safety, tolerability, and adherence to ZD6474 for 6 months in patients at risk for OSCC

2.3 Exploratory Objectives

- Compare OSCC incidence in both study arms (ZD6474 and placebo)

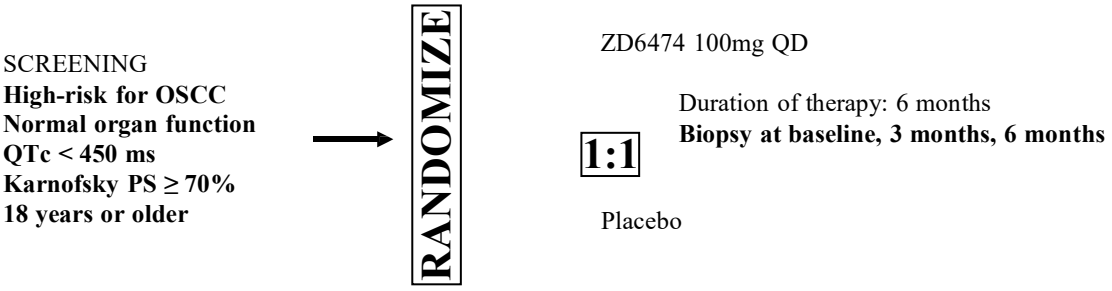
3. STUDY PLAN AND PROCEDURES

3.1 Overall Study Design

- Placebo-controlled, double-blind study of single agent ZD6474
- A total of 54 patients will be enrolled to allow for 20% loss-to-follow up and unevaluable samples
- Subjects will be randomized 1:1, ZD6474 vs. placebo without stratification
- Primary variable will be change in within-patient MVD scores from baseline to 3-months of treatment (ΔMVD) will be compared between the treatment arms using a two-sample t-test with unequal variance.
- Subjects will be required to have an area of dysplasia on prior biopsy or a history of OSCC
- ZD6474, 100 mg, or placebo will be administered PO daily for 6 months. Subjects will be followed for a minimum of 3 years.

- Data and safety monitoring will be conducted through the University of Chicago, Head and Neck Cancer program on a weekly basis
- There are no planned interim analyses

3.2 Study Plan



Study Plan

	Screen	Cycle 1				Cycle 2				Cycle 3	Cycle 4[c]	Subsequent Visits[†]
Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**13**	
Informed consent	X											
Medical history	X											
Inclusion/ Exclusion	X											
Physical examination	X					X				X	X	X
Vital signs	X	X	X			X				X	X	X
Electrocardiogram	X[a]	X[b]	X[b]			X[b]				X[b]	X[b]	
Hematology/ clinical chemistry ^	X	X	X			X				X	X	X
Urinalysis	X	X				X				X	X	X
Pregnancy test[e]	X					X				X	X	X[e]
Performance Status[@]	X					X				X	X	X
Randomization		X[§]										
Study medication dispensing[d]		X									X	
Tolerability/ AE reporting	X	X	X			X				X	X	X
Assessment of Concomitant Medication	X					X				X	X	X
Lesion measurement*		X				X				X	X	X
Tissue Sample[#]	X										X	X (only month 6)

a: 12-lead ECG must be performed at screening (within 7 days before first dose.) The screening QTc must be < 450 msec. Up to 3 ECGs may be obtained at screening, and the mean QTc value used to determine eligibility.

b: On day 1/visit 1, 12-lead ECGs are to be performed pre-dose. Baseline QTc will be determined by the average of no less than 3 consecutive ECGs (within 5-10 minutes of one another) on day 1. If the screening QTc is obtained with 3 consecutive ECGs within 3 days before day 1, then the screening QTc will be considered to be the baseline, and repeat ECGs will not be necessary on day 1. When possible, ECGs should be performed at the same time throughout the study (performed 4-8 hours after the patient takes their oral medication **ECGs must be done at weeks 1, 2, 5, 9, 13, 17, 21 and 25; at discontinuation; and as clinically indicated. In addition, upon occurrence of electrolyte disturbance or severe diarrhea, close monitoring of ECGs is recommended.**

c: Study assessments repeated every 4 weeks until month 6.

d: 100 – Vandetanib 100mg on Cycle 1 and 4.to be dispensed.

e: For women of child-bearing potential only. Negative pregnancy test required at baseline; every 28-30 days while receiving the study medication and for 2 months after the last dose.

^ CBC, complete metabolic profile, magnesium

@ Karnofsky Performance Status

* Only in subjects with visible lesions

Tissue collection will consist of serum and biopsy of previous area of dysplasia (see Section 4). At screen, DNA from peripheral blood and plasma will also be obtained as part of tissue collection (see Scetion 4). Collection should occur on Cycle 4, Day 1 and Cycle 6, day 28.

†Every 6 months for a total of 3 years from the start of therapy.
§Randomization can occur at any time after the subject is deemed eligible and screening procedures are completed. The subject must start therapy within 4 weeks of randomization.

3.3 Selection of Study Population

3.3.1 Study Selection Record

A record of patients who were considered for enrollment, but were never enrolled, along with the reasons for not enrolling will be kept.

3.3.2 Inclusion Criteria

1. Histological/cytological confirmation of oral cavity dysplasia or prior history of OSCC

2. Provision of informed consent

3. Age ≥18 years

4. Females of child bearing age must have a negative serum pregnancy test within 7 days of first dose of study drug.

5. Patients must not have been taking steroids or are on a stable dose of steroids for at least 14 days before enrolment

6. Patients must have a Karnofsky Performance Score of 70% or above

3.3.3 Exclusion Criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. History of malignancy within the last 2 years other than squamous cell carcinoma of the head and neck (SCCHN) and superficial non-melanoma skin cancer. Patients with a history of SCCHN must be free of active carcinoma.

2. Currently receiving treatment for any malignancy.

3. Laboratory results:
   - Serum bilirubin >**1.5x** the upper limit of reference range (ULRR)
   - Creatinine clearance ≤ 30 mL/minute (calculated by Cockcroft-Gault formula.)
   - Potassium, <4.0 mmol/L despite supplementation; or above the CTCAE grade 1 upper limit.
   - Magnesium below the normal range despite supplementation, or above the CTCAE grade 1 upper limit.
   - Serum calcium above the CTCAE grade 1 upper limit. In cases where the serum calcium is below the normal range, 2 options would be available: 1) the calcium adjusted for albumin is to be obtained and substituted for the measured serum value. Exclusion is to then be based on the adjusted for albumin values falling below the normal limit. 2) Determine the ionized calcium levels. If these ionized calcium levels are out of normal range despite supplementation, then the patient must be excluded.

35 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > **2.5** 3 ULRR
17 2
or alkaline phosphatase (ALP) >2.5 x ULRR**.**

4. Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol.

5. Clinically significant cardiovascular event (e.g. myocardial infarction, superior vena cava syndrome (SVC), New York Heart Association (NYHA) classification of heart disease $\geq$2 within 3 months before entry; or presence of cardiac disease that, in the opinion of the Investigator, increases the risk of ventricular arrhythmia.

6. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation), which is symptomatic or requires treatment (CTCAE grade 3) or asymptomatic sustained ventricular tachycardia. Atrial fibrillation, controlled on medication is not excluded.

7. QTc prolongation with other medications that required discontinuation of that medication.

8. Congenital long QT syndrome or 1st degree relative with unexplained sudden death under 40 years of age.

9. Presence of left bundle branch block (LBBB.)

10. QTc with Bazett's correction that is unmeasurable or 24 450 msec on screening ECG. (Note: If a subject has a QTc interval 24 450 msec on screening ECG, the screen ECG 12 12 may be repeated twice [at least 24 hours apart]. The average QTc from the three screening ECGs must be <450 msec in order for the subject to be eligible for the study.)

11. Any concurrent medication with a known risk of inducing Torsades de Pointes, that in the investigator's opinion cannot be discontinued.

12. Concomitant medications that are potent inducers (rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital and St. John's Wort) of CYP3A4 function.

13. Hypertension not controlled by medical therapy (systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg).

14. Currently active diarrhea that may affect the ability of the patient to absorb the ZD6474 or tolerate diarrhea.

15. Women who are currently pregnant or breast-feeding.

16. Receipt of any investigational agents within 30 days prior to commencing study treatment.

17. Previous enrollment or randomization of treatment in the present study.

18. Major surgery within 4 weeks or incompletely healed surgical incision before starting study therapy.

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

3.3.4 Restrictions

1. Patients who are blood donors should not donate blood during the trial and for 3 months following their last dose of trial treatment.

2. Due to the experimental nature of vandetanib, female patients must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception during and continued after the last dose of study medication (oral contraceptives, barrier methods in conjunction with spermicide, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation). Contraceptive use will continue for at least two months, five half-lives, after the last dose of study medication. All women of child-bearing potential will require a pregnancy test every 28-30 days while taking the study medication and for at least 2 months after the last dose. If a subject becomes pregnant while taking vandetanib, the study medication must be permanently discontinued.

3.4 Registration Procedures

3.4.1 Guidelines for Lead Institution

All patients should be registered by the responsible Clinical Research Associate and/or Research Nurse in the eVelos Database prior the start of study. All selection criteria listed in Section 3.3 should be confirmed prior to registration.

3.4.2 Guidelines for Participating Sites

Eligible participants will be entered on study centrally at the University of Chicago by the Lead Clinical Research Associate. All sites should confirm all selection criteria listed in Section 3.3 and then complete the Subject Registration Form and call the lead site at (773) 702-0712 or email Shane Small at Ssmall@medicine .bsd.uchicago.edu with the following information prior to start of study.

- Provider of information
- Study # and Institution
- Treating Physician
- Patient name/initials and hospital ID number

- Patient's zip code of residence
- Date of signed informed consent
- Gender
- Date of birth of patient
- Diagnosis and date of initial diagnosis
- Anticipated start date
- All source docs used to confirm eligibility (labs, physical exam, etc.).
- Consent and Inclusion and Exclusion checklist

A confirmation of registration and randomization assignment will be issued by the lead site upon receipt of the completed registration form.

Affiliate patients eligibility must be confirmed with the Leading Institution (University of Chicago) prior to the starting the study.

3.5 Precautions for Treatment

Vandetanib should not be administered to pregnant women. A negative pregnancy test should be confirmed before start of administration of vandetanib and prior to the start of each cycle.

The exposure to vandetanib is unchanged whether given in the fasted state or with food and thus a restriction on dosing with food is not required.

Exposure to vandetanib is increased with renal impairment thus caution must be adopted if being given to such patients, especially those with severe renal impairment where the exposure could potentially double.

There is no known antidote for vandetanib, and treatment of AEs associated with its use should be for the underlying adverse symptoms.

If a patient develops torsades de pointes or ventricular tachycardia, vandetanib therapy must be stopped. Vandetanib may be resumed at a lower dose when the arrythmia has resolved and the ECG QT interval has returned to normal, if clinically appropriate.

Reversible posterior leukoencephalopathy syndrome, a syndrome of subcortical vasogenic edema diagnosed on magnetic resonance imaging of the brain, has been diagnosed in a patient receiving vandetanib. This syndrome should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function and hypertension, as the syndrome is expected to be reversible if vandetanib is stopped.

There is no specific treatment for an overdose of vandetanib. In clinical trials, single doses of 1200 mg have been given to healthy volunteers with minimal symptoms. Chronic dosing of 600 mg has resulted in diarrhea and other AEs. In case of overdose, vandetanib therapy may be interrupted, and any adverse reactions treated symptomatically.

3.6 Guidance on the Management of Toxicity

In all cases where the dose of study treatment has been reduced/modified or the patient withdrawn due to unusual or unusually severe toxicity considered related to study treatment, the investigator must contact and inform the AstraZeneca study physician.

All patients who experience any NCI CTCAE grade 3 or 4, including QTc changes (see below), skin, gastrointestinal and other adverse events must be permanently discontinued from study treatment and monitored until resolution or return to baseline.

For guidance on the management of QTc prolongation, see Figure 1 below. Also see Appendix A - Medications Known to Prolong the QT Interval and/or Induce Torsades De Pointes (TDP).

For all other toxicities, the dose of study treatment will be withheld for up to 3 weeks until the toxicity has resolved to CTCAE grade 0 or baseline. Study treatment may then be restarted at a reduced dose (see Table 3 below). Patients will be withdrawn from the study if toxicity does not resolve to CTCAE grade 0 or baseline within 3 weeks. If grade 1 or 2 toxicity recurs after dose reduction, the patient must be permanently discontinued from study treatment.

A guideline for dose reduction is shown in the table below.

Table 3 Dose Reduction

Original dose	Reduced dose	Vandetanib dispensed for reduced dose	Tablets per daily dose
100 mg	100 mg **every other day**		1 every other day

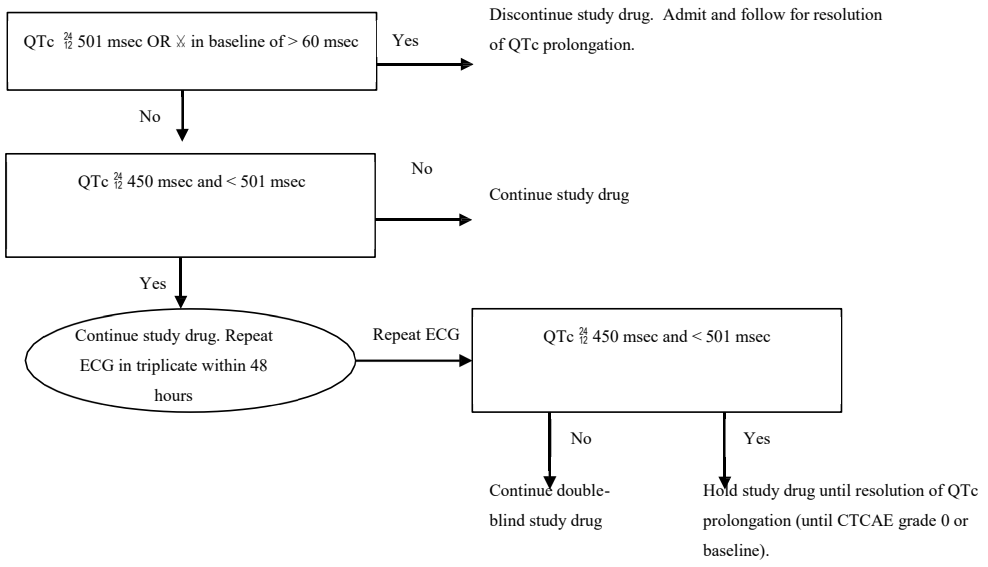
3.6.1 QTc Prolongation

Patients will have ECGs performed to monitor QTc interval (using Bazett's correction) as outlined in the study plan.

QTc prolongation is defined as:

- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs):
  - A QTc interval 450 msec **OR**
  - An increase of > 60 msec from baseline QTc.

Figure 1 Flowchart detailing management of QTc prolongation



Management of Patients with QTc Prolongation

For a single QTc value of > 450 msec but < 500 msec, vandetanib may be continued but a repeat ECG (in triplicate) must be obtained within 48 hours. If QTc prolongation is confirmed, vandetanib must be held. ECGs and electrolytes should be followed 3 times a week until QTc falls below 450 msec or baseline whichever is higher. Vandetanib treatment may be resumed at a lower dose after the QTc recovers to < 450 msec or baseline whichever is higher.

If the patient does not meet the criteria for QTc prolongation at the repeat ECG, then the patient should continue treatment and resume the ECG schedule as outlined in the Study Plan.

Patients experiencing NCI CTCAE grade 3 or 4 QTc prolongation, i.e. QTc ≥ 501 msec or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia must discontinue treatment AND admitted to hospital for monitoring until resolution or return to baseline.

3.6.2 Management of Skin Toxicity

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 to the Investigator 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, topical or systemic antibiotics, topical or systemic antihistamines, and occasionally retinoid creams.

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

- If a rash of CTCAE grade 2 is detected, immediate symptomatic treatment should be provided.

- If a rash of CTCAE grade 3 or higher is detected, vandetanib should be discontinued.

If severe cutaneous toxicity recurs at reduced dose of vandetanib, the patient will permanently discontinue study treatment of vandetanib. If vandetanib must be withheld for >3 weeks due to cutaneous toxicity, the patient will be discontinued.

3.6.3 Management of Gastrointestinal (GI) Toxicity

Nausea, vomiting, or both may be controlled with antiemetic therapy. In subjects who have emesis and are unable to retain vandetanib/ placebo, every attempt should be made to obtain control of nausea and vomiting. The dose of vandetanib/ placebo may be repeated if emesis occurs within 30 minutes of taking the tablet. Diarrhea should be treated with standard medications to avoid dose modification or interruption, if possible. Electrolyte supplementation with regular laboratory monitoring should be used, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation. If grade 1 or 2 diarrhea develops, vandetanib should be withheld until diarrhea resolves to grade 0 or baseline. Patients who are clinically unstable because of diarrhea or other intercurrent medical illness must be admitted and evaluated using telemetry, until clinically stable. Upon recovery, treatment may resume at a permanently reduced dose (refer to section 3.3.5.) If vandetanib must be withheld for more than 3 weeks for resolution of diarrhea, the patient will not restart treatment with study medication. If grade 1 or 2 diarrhea recurs after this dose reduction, the patient must permanently discontinue study treatment.

3.6.4 Other Toxicity

If any other CTCAE grade 3 or 4 toxicity that is not outlined in Sections 3.3.6.1 to 3.3.6.3 develops and is attributable to vandetanib, vandetanib should be permanently discontinued.

If study treatment must be interrupted for more than 3 weeks to allow for toxicity to resolve, the patient's vandetanib will be discontinued.

Table 4 Summary of Guidance on the Management of Toxicity for Vandetanib

Toxicity	Vandetanib
QTc value ≥501 msec or prolonged ≥60 msec from baseline	Discontinue vandetanib AND admit to hospital for monitoring until resolution or return to baseline.
Grade 3 or 4 cutaneous	Discontinue vandetanib and monitor until resolution or return to baseline.
Other grade 3 or 4 toxicity related to vandetanib	Discontinue vandetanib and monitor until resolution or return to baseline.

3.7 Discontinuation of Subjects from Treatment or Assessment

3.7.1 Criteria for Discontinuation

Subjects should be discontinued from study for the following reasons:

- Completion of protocol intervention and required follow-up
- Diagnosis of cancer
- Disease progression requiring alternative therapy in the opinion of the Principal Investigator
- Adverse event/serious adverse event including grade 1 toxicity that is unacceptable to the patient or physician
- Repeated grade 1 or 2 toxicities or grade 3 or 4 toxicity that is believed to be possibly, probably or definitely related to study medication
- Pregnancy
- Allergic reaction to the study medication
- Inability or unwillingness to adhere to protocol procedures and instructions
- Medical contraindication
- Withdrawal of informed consent
- Patients who require medication that may prolong the QT interval while on study that the investigator's opinion cannot be discontinued, should be discontinued from the study. Refer to Appendix A for a list of medications known to induce Torsades de Pointes.

3.7.2 Procedures for Discontinuation

If a subject discontinues study, reason for discontinuation must be documented and attempts to retrieve all study drug should be undertaken. If possible, subjects should be assessed within 30 days of study discontinuation. If a subject discontinues drug, attempts should be made to follow outcome for at least 2 years after discontinuation as outlined in Study Plan.

3.8 Treatments

3.8.1 Investigational Products

3.8.1.1 Identity of Investigational Product and Comparators

Subjects will be randomized to receive ZD6474 (vandetanib,) versus placebo for up to 6 months.

3.8.1.2 Doses and Treatment Regimens

ZD6474 100 mg QD PO
Matching placebo will be supplied by AstraZeneca

If subject(s) cannot swallow tablets, see Appendix E for Instructions for Dispersing Vandetanib Tablets.

Missed or Forgotten Doses
If the subject inadvertently does not take the dose in the morning, he or she may take that day's dose any time up to 10 pm that same day. However, if a subject misses taking their scheduled dose and is unable to take the missed dose on the same day, he or she must take the next scheduled dose and the missed dose will not be made up. The dose of study medication may be repeated if vomiting occurs within 30 minutes of taking the study treatment.

3.8.1.3 Labeling

Labeling of the investigational product will be performed in accordance with Good Manufacturing Practices (GMP.) AstraZeneca, or a company acting on their behalf, will pack tablets into high-density polyethylene (HDPE) bottles with child-resistant tamper-evident closures. Each bottle will be labeled with the statement: "Caution: New Drug - Limited by Federal (or USA) Law to Investigational Use". Instructions stating that the tablets are to be taken orally "as directed by your doctor" will be included. Information on the label will indicate the identity and quantity of tablets and storage conditions. Additional subject information will be identified as dictated by the protocol; it may be necessary for information to be recorded on the label by the investigator at the time the bottle is dispensed.

3.9 Drug Supply Information

3.9.1 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. Descriptions of the appropriate storage and shipment conditions are specified on the investigational product label and investigator brochure. The stored study drug supplies must be accessible to authorized staff only. The storage area must also have adequate control of temperature in order to maintain stability and potency of study drug supplies. The tablets

should be stored in the original pack until use. For further information, investigators should refer to the investigational product label.

3.9.2 Accountability

All subjects will maintain a drug diary documenting drug administration and adverse events (Appendix B). At each visit, subjects will return any unused drug and pill counts will be performed to account for drug administration.

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drug must be accounted for, including study drug accidentally or deliberately destroyed. All discrepancies between amounts of study drug dispensed and amounts returned must be documented. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol without prior AstraZeneca approval. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

3.9.3 Mechanism of Drug Destruction

At the conclusion of the study, unused containers of the investigational drug are inventoried and prepared for return to the sponsor or destroyed in accordance with the requirements of the sponsor or the manufacturer or the state board of pharmacy. All documentation regarding receipt, storage, dispensing, and return of used containers must be complete and accurate.

** Unused expiring drug **
The expiration date of the drug should be noted, and the drug should be returned, disposed of, or destroyed in accordance with the approved protocol when the drug expires. An ongoing audit of drug expiration will be performed as the medication is received and as the medication is dispensed. In addition, a random audit of medication supplies and expiration dates will be performed weekly on 10 active protocols. Documentation indicating study drug was destroyed will be sent to AstraZeneca.

3.9.4 Blinding and Procedures for Unblinding the Study

Methods for ensuring blinding
A secure online registration interface has been developed to register patients, and it is integrated with the randomization component. This type of an interface has been used successfully in other Head and Neck cancer clinical trials at the University of Chicago (e.g. DeCIDE). At the time of patient registration an electronic notification will be sent to the study pharmacist. To randomize the patient, the pharmacist will securely login into the registration system, which will provide the randomized treatment assignment. Only the pharmacist will have access to the treatment assignment to maintain the blinding.

Methods for unblinding the study
In the event of an **emergency**, Dr. Jonas De Souza at the University of Chicago shall be contacted at the 24-hour pager number: (773) 702-4400, which will be printed on the study

medication label. **Remember, this is only in the event of an emergency.** The protocol number, the patient study ID number, and the patient's initials (e.g., "FL") or name will be required to unblind the patient. Once Dr. De Souza concurs that unblinding is appropriate, he will ascertain the treatment assigned to that patient by securely logging into a designated website, and inform the caller of the patient's treatment. **If a patient is emergently unblinded, he/she is considered to be off treatment, but should continue to be followed for outcome evaluations.**

3.9.5 Pre-Study, Concomitant and Post-Study Treatment(s)

Concomitant use of any therapy during study must be documented and should be approved by the treating physician prior to initiation. Concomitant use of the known potent inducers of CYP3A4: rifampicin, phenytoin, carbamazepine, barbiturates and St. John's Wort are not allowed within 2 weeks of study or during the study. Until the effect of CYP3A4 inducers in the exposure to vandetanib in humans has been assessed, the co-administration of such inducers with vandetanib is not allowed. However, it has been shown that CYP3A4 inhibitors have little effect on the exposure to vandetanib in humans, and therefore these can be co-administered with vandetanib.

A potent CYP3A4 inducer has been shown to reduce the exposure to vandetanib by 40% thus the co-administration of such inducers with vandetanib is not allowed. A potent CYP3A4 inhibitor has been shown have little effect on the exposure to vandetanib and therefore these can be co-administered with vandetanib.

In vitro data has shown vandetanib inhibits CYP2D6 and CYP2C8. Based on the maximum steady state total plasma concentrations observed in patients the I/Ki ratio for both these is less than 0.10, and a SimCYP simulation for the potential inhibition of CYP2D6 (lower IC50 and Ki), concluded there would be little effect on CYP2D6 substrates. Thus substrates of both CYP2D6 and CYP2C8 may be co-administered with vandetanib.

Patients who require medication that may prolong the QT interval while on study: antiarrhythmic 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 cloroquine, clarithromycin, dolasetron, granisetron, haloperidol, methadone, moxifloxacin, and pimozide), that the investigator's opinion cannot be discontinued, should be discontinued from the study. Refer to Appendix A for a list of medications known to induce Torsades de Pointes.

3.10 Safety Measurements and Variables

3.10.1 Adverse Events

3.10.1.1 Definitions

The definitions of Adverse Events (AEs) and Serious Adverse Events (SAEs) are given below. It is of the utmost importance that all staff involved in the study be familiar with the content of this section. The Principal Investigator is responsible for ensuring this.

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

Any detrimental change in a patient's condition subsequent to them entering the study and during the follow-up period should be considered an AE. When there is a deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the reporting physician considers that study treatment contributed to the deterioration or local regulations state to the contrary, the deterioration should be considered a lack of efficacy. Signs and symptoms of disease progression are therefore not considered AEs.

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

Serious Adverse Event
A Serious Adverse Event (SAE) is an AE occurring during any study phase (e.g., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

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

Any event or hospitalization that is unequivocally due to progression of disease, as determined by the investigator, must not be reported as an SAE, however should be communicated to AstraZeneca

The causality of SAEs (their relationship to all study treatment) will be assessed by the investigator(s) and communicated to AstraZeneca.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)

A serious adverse event is considered to be a suspected adverse reaction if there evidence to suggest a causal relationship to the adverse event. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater frequency than expected from historical controls, or occurs at a greater frequency in the investigational versus the placebo arm of the study.

Unexpected events are those not listed at the observed specificity or severity in the protocol, consent, investigator brochure, FDA-approved package insert, or elsewhere in the current IND application. This includes adverse events listed in the protocol, consent or IND as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which have not been previously observed with this investigational agent.

ALL SUSARS occurring on this clinical trial must be reported to the FDA. Refer to Section 3.10.1.6 for reporting guidelines.

3.10.1.2 Reporting of Adverse Events

Adverse events will be recorded at each study visit, graded using Common Toxicity Criteria Version 4.0, and assigned an attribution to study drug from 1-5 (not related, unlikely related, possibly related, probably related, definitely related). Adverse event onset, resolution, action taken, and whether it constitutes a serious adverse event will be recorded.

Pregnancy should be excluded before randomization. Should a pregnancy occur during study participation, it must be reported in accordance with the procedures described in Section 7.1, Procedures in Case of Pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication

All non-serious adverse events will be reported to AstraZeneca at the conclusion of the study.

3.10.1.3 Reporting of Serious Adverse Events

The principal investigator and other designated site personnel are responsible for informing the University of Chicago Comprehensive Cancer Center (UCCCC) Cancer Clinical Trials Office (CCTO) of any serious and unexpected adverse events. AstraZeneca must also be notified of all such adverse events. Events that qualify as a SUSAR or other reportable events be reported to the FDA. Refer to Section 3.10.1.6 for details of FDA reporting requirements.

Guidelines for reporting to each of these groups are provided below.

3.10.1.4 University of Chicago Comprehensive Cancer Center

Events Occurring at the University of Chicago:

All serious adverse events (as defined in Section 3.10.1.) and protocol deviations must be reported to the University of Chicago Comprehensive Cancer Center (UCCCC) Cancer Clinical Trials Office (CCTO) using the eVelos database. The Research Nurse or other designated individual should report the SAE/deviation to the UCCCC Quality Assurance (QA) Coordinator by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Each event report must indicate where the event meets the University of Chicago Institutional Review Board's (UCIRB) Unanticipated Problem reporting criteria.

Events Occurring at Participating Site(s)
For serious and unexpected adverse events occurring at a participating site it is the responsibility of the research nurse, study coordinator, or other designated individual at the site where the event occurs to notify the UCCCC of the adverse event. Events should be reported to the UCCCC QA Coordinator be email: QACCTO@bsd.uchicago.edu or by fax at (773) 834-5800.

For unexpected and serious suspected adverse reactions which FDA require reporting as a single occurrence, Form 3500a (MedWatch) must be completed by the designated site personnel and returned to the UCCCC QA Coordinator according to the timeframes in Section 3.10.1.6.

3.10.1.5 Institutional Review Board

Events meeting current IRB reporting criteria must be submitted by the principal investigator via the IRB's electronic submission system within **the IRB's designated reporting timeframes**. Details of the IRB's current reporting policy and timelines can be found on their website at: http://bsdirb.bsd.uchicago.edu/forms-guidelines/up.html.

The responsible research nurse or other designated individual are responsible for entering the appropriate information into the IRB's electronic submission system and forwarding the completed submission to the principal investigator for reporting to the IRB.

Events occurring at a participating site should be reported to the local IRB of record according to their policies and procedures and may be reported to the University of Chicago IRB if they meet current reporting criteria.

3.10.1.6 FDA

This study will be conducted under an IND held by Jonas De Souza at the University of Chicago.

Per 21 CFR 312.32, the sponsor-investigator is required to notify the FDA and all participating investigators of potential serious risks within 15 calendar days. Unexpected fatal or life-threatening adverse events must be reported to the FDA by the sponsor-investigator via phone or fax within 7 calendar days.

Current FDA regulations require that all SUSARs (see definition in Section 3.10.1.1) occurring on this trial, other findings that suggest a significant risk to humans exposed to the investigational drug (e.g. information from pooled analysis of multiple studies), and any clinically significant increase in the rate of an expected serious adverse reaction be reported as an IND Safety Report. Refer to Table A below for guidelines for reporting these events to the FDA.

In order to meet these requirements, the sponsor-investigator will review all reported serious adverse events as they occur and will conduct a literature search to seek new safety information and review and analyze all safety information from this clinical trial at least annually and more frequently as appropriate.

Table A: FDA Reporting Requirements

Report Type	Method of Report	Responsible Party	Timeline[1]	
			Fatal/Life-Threatening Event	
			Yes	No
Individual Report	Form 3500A (MedWatch)[7]	RN/CRA	4 calendar days[5]	10 calendar days[5]
Other Findings that Suggest *Significant Risk*[2]	Narrative[3]	PI	4 calendar day[6]	10 calendar days[6]
Clinically Significant Increased Frequency of Suspected Adverse Reactions[4]	Narrative	PI	4 calendar days[6]	10 calendar days[6]

1: Report Due to CCTO IND Coordinator according to the specified timeline regardless of whether or not all information regarding the event is available. If applicable, a follow-up report should be provided to the IND Coordinator once additional information on the event is available.
2: An IND Protocol Amendment is also required to describe any changes to the protocol, consent, or overall conduct of the study made as a result of this information. All revised documents should be made available to the CCTO IND Coordinator at the time of IRB submission.
3: Copy of relevant publication(s) should be included if applicable.
4: Details of individual cases should be included as appropriate
5: From date event was reported to the sponsor-investigator
6: After information is received by the investigator and determined to meet reporting criteria
7: Copy should be maintained in the subject research chart and master IND file in the CCTO.

All other events (e.g. protocol deviations or other safety concerns) not meeting the requirements for IND Safety Reporting (per 21 CFR 312.32) but which require reporting to

the IRB as an Unanticipated Problem will be reported to the FDA as an informational amendment or with the annual report as appropriate.

3.10.1.7 Participating Sites

It is the responsibility of the designated Regulatory Manager on behalf of the sponsor-investigator to notify all participating sites of all unexpected and serious suspected adverse reactions that occur on this clinical trial and which are reported to the FDA as an IND Safety Report (21 CFR 312.32). A copy of the completed Form 3500A (MedWatch) and/or IND Safety Report Narrative will be provided to the responsible Regulatory Manager by the IND Coordinator for distribution to all participating sites.

3.10.1.8 AstraZeneca

All serious and unexpected adverse events must also be reported to AstraZeneca. It is the responsibility of the research nurse or other designated member of the research team at the site where the event occurred to report these events to AZ.

Reports should be submitted to by ***fax to AstraZeneca's designated fax line: (800) 972-4533, Attention Oncology ISS Safety Representative.****

A cover page with the following information should accompany the completed MedWatch form:

- Vandetanib Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca reference number

***** It must be indicated, either in the SAE report or the cover page, the **causality** of events **in relation to all study medications** and if the SAE is **related to disease progression**, as determined by the principal investigator.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code-break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the *30 day follow-up* period. (See Appendix D for the Non-Serious Adverse Event Reporting Template.) After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution.* All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the FDA and AstraZeneca). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

4. PHARMACOKINETICS & PHARMACODYNAMICS

4.1 Pharmacodynamics

Biopsy:
A biopsy will be performed prior to starting therapy (baseline), 3 months, and 6 months. The primary endpoint of the study will be to assess the change in MVD from baseline to 3 months in subjects receiving ZD6474 versus placebo. Therefore, biopsy is mandatory for all subjects. Tissue should be obtained in the area of prior or current dysplasia or cancer. Anatomic biopsy location must be documented textually and diagrammatically to insure that the same area is biopsied at each time point. Biopsies will consist of either a 5 mm or an 8 mm punch biopsy of the oral mucosa. Tissue specimens will be bisected, with half of the specimen immediately embedded in OCT and frozen at -80 C with the other half placed in 10% buffered formalin, processed and embedded in paraffin.

Immunohistochemistry:
For detection of CD34, antigen retrieval will be achieved by using DAKO Proteinase K (Cat # S3004) treatment for 15 minutes at room temperature. Endogenous peroxidase activity will be quenched with 1% hydrogen/methanol. The primary antibody for CD34 (Vector, Catalog # VP-C345) will be applied at 1: 50 dilution for a one hour incubation at room temperature, followed by anti-rabbit polymer labeled HRP bound secondary reagent (DAKO Envision+System-HRP).

For detection of phosphorylated EGFR (pEGFR) and phosphorylated VEGFR-2 (pVEGFR-2), antigen retrieval will be achieved using Immuno/DNA retriever with citrate (BioSB, SantaBarbara, CA Catalog # BSB0021). Endogenous peroxidase activity will be quenched with Mouse/Rabbit ImmunoDetector Peroxidase Block Kit. Sections will be incubated using primary antibody to pVEGFR-2 1:300 (Abcam, Cambridge, MA; Catalog # ab38464) or pEGFR 1:250 (Cell signaling, Danvers, MA Catalog #4407) for one hour at room temperature. Antibody binding will be visualized by using Mouse/Rabbit ImmunoDetector HRP/DAB Detection System (BioSBSanta Barbara, CA Catalog # BAB0003).

For detection of Ki-67, antigen retrieval will be achieved using 10mM TrisBase, 1mM EDTA pH 9.0. Endogenous peroxidase activity was quenched with 1% hydrogen peroxide/Methanol. The primary antibody for Ki67 (NeoMarkers, Fremont, CA; Catalog # RM-1906), sections will be incubated at a 1:300 dilution at room temperature for one hour followed by anti-rabbit polymer labeled HRP bound secondary reagent (Envision+system-HRP).

All immunohistochemistry stains will be developed with DAB chromogen and counterstained with hematoxylin. Corresponding negative control experiments were performed by omitting the incubation step with the primary antibody.

Scoring of immunohistochemical staining will be performed using the Automated Cellular Imaging System (Aperio Image Analysis Workstation). Stained sections will be scanned and acquired using an Aperio imaging/microscopy system. Proliferation will be measured by calculating the average labeling percentage of the epithelial compartment for Ki67 for each specimen. For determination of microvessel density (MVD), the total number of CD34-stained clusters or single cells, with or without a lumen, was quantified for each specimen. For pVEGFR-2 and pEGFR quantification was, an index of staining will be calculated and expressed as the percentage of staining multiplied by staining intensity after subtracting the index staining of corresponding negative controls.

DNA from peripheral blood:
A 10 ml purple-top (EDTA-containing) vacutainer will be used to draw blood at baseline. The site coordinator or designee at each site will separate plasma from buffy coat by centrifugation at 3500 rpm at 4°C for 15 minutes. Plasma will be aliquoted into 2 ml cyrovials and stored at -80°C for future biomarker studies. The buffy coat of cells will be transferred to a separate tube, to which 5 mL of PBS will be added and mixed with the buffy coat. The buffy coat tube + PBS will be centrifuged for 5 min at 3000 RPM, the supernatant will be removed and the cell pellet will be stored at -80 for LOH and other biomarker analysis.

Serum:
Serum samples will be collected prior to therapy on all patients and at 3 and 6 months in two 7-10 cc SST tubes. Blood in the serum collection tube should be allowed to clot for 60 minutes and then centrifuged to separate serum. Serum should be stored in 2 mL cryovial tubes (Nalgene Cat# 5000-0020) in 410uL aliquots. Samples should be labeled with institution, protocol number, patient initials, patient registration number, and the date and time of draw. Serum samples should be stored at -80°C.

Saliva collection, stabilization and processing
Unstimulated saliva samples will be procured from subjects prior to starting therapy, at 3 and 6 months. Subjects will be asked to refrain from eating, drinking, smoking, or oral hygiene procedures for at least one hour prior to the collection. Saliva samples will be centrifuged at 2,600 x g for 15 min at 4°C. The supernatant will be removed from the pellet and immediately mixed with SUPERase•In (Ambion Inc., TX) or with a cocktail of protease inhibitors (Roche, USA).

Sample shipping and Storage:

All the tissue samples will be packaged and transported by carrier service in batched samples following the government regulation 42 CFR Part 72 – "Interstate Shipment of Etiologic Agents," which describes the requirements for the proper packaging and shipping of infectious substances and other biomedical material. All the samples will be packaged and delivered in such a way that the contents will not leak and will arrive in good condition. The tissue will be transported in the packages with the biohazard label on the front to the Human Tissue Resource Center at the University of Chicago (address below). Paraffin-embedded tissue blocks should be shipped at ambient temperature. All institutional requirements for safety and confidentiality will be met during specimen transmittance.

Human Tissue Resource Center (HTRC)
University of Chicago
5835 S. Cottage Grove, Room Room P-616A
Chicago, IL 60637
Phone: 773-834-8391
Fax: 773-834-8740
e-mail: tissuebank@bsd.uchicago.edu

4.2 Electrocardiogram (ECG) Assessments for Study Plan

- Baseline QTc (Bazett's) will be determined by the average of no less than three (3) consecutive ECGs (within 5-10 minutes of one another.)

  ECGs will be repeated at **weeks 1, 2, 5, 9, 13, 17, 21 and 25**; at discontinuation; and as clinically indicated (ECGs to be consistent with the chemotherapy schedule, where relevant.) In addition, upon occurrence of electrolyte disturbances or severe diarrhea, close monitoring of ECGs is recommended.

- If QTc prolongation occurs at one of the usual assessment times, or at any other time, the QTc will be re-evaluated with no less than 3 consecutive ECGs (within 5-10 minutes) of one another, as per baseline (Refer to Section 3.3.6.1, "QTc Prolongation.")

4.3 Imaging

Not applicable to study. Imaging should be performed as clinically indicated.

4.4 Response Data

Visible lesions will be measured at each visit and change in size or appearance will be documented.

5. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

5.1 Statistical Evaluation – General Aspects

This is a randomized, double-blind, placebo-controlled study with a primary endpoint of reducing microvessel density (MVD) in preneoplastic lesions at 3 months compared to baseline. A placebo control group is necessary due to the lack of validated historic controls in this population and is ethical since the standard of care for these patients would be active surveillance. Patients eligible to participate in this trial will be at high risk of developing oral cancer, but will be free of disease when enrolled on the study. Thus, commonly used clinical trial endpoints such as response rate or progression-free survival are not applicable to this patient population. Time to disease recurrence could be used as the primary endpoint, but due to the incidence of cancer development even among the high-risk patients, this endpoint will require too large a sample size to be feasible at this point.

Eligible patients will be randomized to ZD6474 (treatment) or placebo (control) arms for 6 months and monitored for up to 3 years. Tissue biopsies from the same area of known dysplasia will be obtained at baseline, 3 months, and 6 months, and will be banked by the Biobanking and Pathology Core. Statistical analyses will be performed using SAS or Stata statistical software. Analyses will be performed by the study statistician, Dr. Kocherginsky.

5.2 Description of Outcome Variables in Relation to Objectives and Hypotheses

Despite extensive studies to identify patients at risk for developing OSCC, there are no established chemopreventive agents. Prior Phase III studies have been negative due to a lack of efficacy, inadequate understanding of molecular mechanisms underlying the intervention, or lack of tolerability of the agent for long periods of time. Therefore, with preclinical and safety data strongly supporting the rationale for administering ZD6474 as a chemopreventative agent, this study will address these critical limitations of prior approaches. The primary endpoint was chosen to reflect the effect of ZD6474 on microvessel density (MVD) in preneoplastic lesions which correlated strongly with OSCC inhibition in the preclinical model and serves as a surrogate for the latter. Secondary endpoints will include feasibility, safety and tolerability of ZD6474, development of OSCC, as well as molecular studies of putative targets of ZD6474.

5.3 Description of Analysis Sets

Full Analysis Set (intention-to-treat population): The full analysis set is the primary analysis population and will consist of all randomized patients.

Safety Set: The safety set will consist of all randomized patients who received trial medication at least once. This set will be used for safety analyses.

5.4 Method of Statistical Analysis

Primary Endpoint: The primary endpoint of this study is the comparison between treatment groups of the within-patient change in MVD score from baseline to 3-months following treatment initiation (ΔMVD). The primary analysis upon which the sample size calculations are based is the comparison of ΔMVD between treatment arms using a two-sample *t*-test with unequal variances. A Wilcoxon ranksum test may be used if the normality assumption is not

satisfied. Alternatively, ΔMVD may be transformed (e.g. log-transformation) to satisfy the normality assumption. Additional analyses of the primary endpoint will include linear regression models with treatment effect and other prognostic factors as covariates. Model selection will follow strategies described in Harrell (2001).

Secondary Endpoints: ZD6474 has been studied in 37 clinical trials involving over 2000 subjects. In general, the agent has been well tolerated even for long-term administration with the most common adverse events being rash, nausea, diarrhea, fatigue, and hypertension. Adverse events data will be collected, and event rates will be summarized using frequency tables. Event rates will be compared between treatment arms using a Chi-squared test or Fisher's exact test.

Adherence to treatment will be monitored by self-administered patient diaries. Remaining pill counts will be performed at each visit, and pill counts will be compared with those reported on patient diaries to determine the reliability of self-reporting. Adherence rates will be defined as the number of doses administered divided by the total number of doses that was prescribed, and will be summarized for each 3-month period. Agreement between pill counts and self-reported doses administered will be analyzed using the kappa coefficient and Bland-Altman plots.

Subjects will be monitored for the development of oral and other cancers. We expect that ZD6474 treated patients will have a lower incidence of OSCC. Time to cancer development will be summarized using the method of Kaplan and Meier for each treatment arm, and compared between arms using the logrank test. In addition, yearly incidence rates will be reported. However, the study is clearly underpowered to demonstrate a statistically significant difference between groups with respect to time-to-event or incidence rates due to the low expected overall number of cancer cases.

To assess the biologic effect of EGFR and VEGFR2 inhibition, tissues will be analyzed by IHC for pEGFR, EGFR, pVEGFR2, VEGFR2, and Ki-67. We hypothesize that biopsies from ZD6474 patients will exhibit significantly lower expression of pEGFR and VEGFR2 and proliferation indices. Expression levels will be measured on a continuous scale, and within-patient changes in expression will be compared between treatment arms using a t-test or Wilcoxon ranksum test as appropriate.

5.5 Determination of Sample Size

Changes in within-patient MVD scores from baseline to 3-months of treatment (ΔMVD) will be compared between the treatment arms using a two-sample *t*-test with unequal variance. We assume that baseline mean and variance will be similar to what is reported in Li et al (29) who examined MVD in 52 samples with mild, moderate and severe dysplasia. To calculate sample size we make the following assumptions:

- baseline average MVD = 30.1 (the weighted average of all dysplastic samples in Li et al);

- coefficient of variation CV = 40%, both at baseline and at 3 months (CV in Li et al ranged from 30%-56% across dysplastic groups; Michailidou et al (30) report CV = 28% in leukoplakia with dysplasia);
- 10% increase in MVD in the placebo arm, which corresponds to a difference between mild vs. moderate or moderate vs. severe dysplasia in Li et al.(29);
- 25% decrease in MVD in the ZD6474 arm, which corresponds to a difference between moderate dysplasia vs. normal epithelia in Li et al(29). Similarly, MVD was 35% lower in normal mucosa than in leukoplakia with dysplasia tissue samples in Michailidou et al.(30);
- within-patient correlation between baseline and 3-month MVD ranging between 0.25-0.75.

Based on these assumptions, expected baseline MVD is 30.1±12.1, and 3-month MVD will be 33.2±13.3 and 22.6± 9.0 in the placebo and ZD6474 arms, respectively. This corresponds to an average change ΔMVD of 3 and -7.5 in each treatment arm.

Table 5 lists the sample sizes required to attain 80% power with two-sided α=0.05 to detect differences in ΔMVD for various levels of within-patient correlation. Assuming a moderately high within-patient correlation ρ=0.50, 22 patients per arm will be required. A total of 54 patients will be enrolled to allow for 20% loss-to-follow up and unevaluable samples. These calculations are somewhat conservative because much larger change in MVD (40% decrease) was observed in ZD6474-treated mice in the 4NQO mouse model. Also, a somewhat conservatively high CV=40% is assumed.

Rho	Placebo SD_Δ	ZD6474 SD_Δ	N (per arm)
0.25	15.5	13.1	31
0.50	12.7	10.9	22
0.75	9.0	8.0	12

Table 5. Calculation of number of patients required per arm of the clinical trial.

Study Feasibility: The Head and Neck Cancer Program at the University of Chicago has a strong record of multi-disciplinary care and expertise in all aspects of the disease. In 2009 the program registered over 800 unique patient visits and performed approximately 300 new patient consults. A High Risk Clinic to specifically deal with the needs of patients without active disease but who are at increased risk to develop HNSCC is available and overseen by Dr. Elizabeth Blair. These patients often have a personal or strong family history of HNSCC, engaged in behavior associated with developing OSCC (e.g. tobacco use), or harbor a pre-neoplastic lesion. The clinic will serve as the setting to screen prospective patients, obtain tissue, and perform the clinical study. The Head and Neck Cancer Program has recognized the importance of OSCC chemoprevention and participated in three such studies that are either already closed or are anticipated to complete accrual prior to the initiation of this proposed trial.

Dr. Lingen is a Board Certified Oral & Maxillofacial Pathologist. His outreach service receives biopsies from dentists throughout Illinois and Northwestern Indiana. Drs. Dennis

Solt and Reza Mostofi are oral pathologists with outreach services in Chicago. The 3 services have a combined total of ~10,000 cases/year, and approximately ~100 dysplasia cases. All 3 biopsy services have contributed patients for the EPOC prevention trial currently underway with the MD Anderson. Therefore, the involvement of these biopsy services will be important for the accrual of subjects for the proposed study. In order to achieve the target sample size, accrual for this trial must be 2 patients per month. ZD6474 and placebo will be supplied by AstraZeneca. The study will be conducted under an IND held by the protocol principal investigator, Dr. Jonas De Souza .

5.6 Interim Analyses

Not applicable.

5.7 Data and Safety Monitoring Board

Subject enrollment, clinical response, and toxicity will be reviewed on a weekly basis during the Head and Neck Cancer Data and Safety Meeting. Since the study is blinded, an independent Data and Safety Monitoring Board (DSMB) will be convened annually. This board will consist of a medical oncologist and statistician who are independent of the study. DSMB minutes will be reported to the principal investigator, FDA, IRB, and AstraZeneca. The protocol will be reviewed annually by the Institutional Review Board and the Scientific and Accrual Committee at the University of Chicago. An annual report to the FDA for IND renewal will be submitted.

5.8 Study management

5.8.1 Training of site personnel

A data manager and research nurse will be assigned to the study. All study procedures and data collection parameters will be reviewed with them. A study database will be established in The University of Texas M.D. Anderson Cancer Center DMI Portal with web-based case report forms (CRF). All study personnel will be required to complete and document clinical research training as mandated by each institution.

5.8.2 Source data

All data will be stored electronically in the secure The University of Texas M.D. Anderson Cancer Center DMI Portal.. A designated data manager will extract and enter data from source documents. Data elements will include, but not be limited to, age; sex; performance status; prior history and therapy for cancer or preneoplasia; tobacco use and other risk factor history; concomitant medications; adverse events; lesion location and response; drug administration; date and nature of progression; incident cancers; and date and cause of death.

5.8.3 Multi-center Guidelines

5.8.3.1 Study Documents

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the lead site. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.) and summary of unanticipated problems or protocol deviations. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

A completed FDA Form 1572 and investigator CVs must be received by the lead site prior to start of enrollment at the participating site.

5.8.3.2 Data Submission Instructions for Participating Site(s)
Investigators must record the information required by the protocol. Electronic Case Report Forms (CRF) will be made available for all data elements required by the study.

5.8.4 Study timetable and end of study

The end of the entire study is defined as "the last visit of the last subject undergoing the study". The study is expected to start in Spring 2011 and to be completed by Spring 2013. AstraZeneca may terminate the study prematurely if concerns for safety arise within this study or in any other study involving vandetanib.

6. ETHICS

6.1 Ethics Review

The final study protocol, including the final version of the written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB.

The principal investigator is responsible for informing the IRB of any amendments to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious, unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The principal investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the principal investigator.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each participating institution prior to implementation.

The Protocol Chair (or his/her designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating site(s). Documentation of local IRB approval must be received by the lead site within 90 days of distribution.

6.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

6.3 Written Informed Consent

Provision of written Informed Consent must be obtained prior to any study-related procedures. The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

Where genetic analyses are included, special account of these will be made in the consent form, as it is recognized that special provisions need to be made to retain confidentiality of medical information. These factors have been taken into account in the design of the consent form. Consent forms specific for the collection of genotyping samples will be used; the format depends on the design of the study.

The subject's signed and dated informed consent(s) must be obtained before conducting any procedure specifically for the study. The principal investigator(s) must store the original, signed written Informed Consent Form(s.) A copy of signed written Informed Consent Form(s) must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

6.4 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to AstraZeneca and/or allow AstraZeneca, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

7. EMERGENCY PROCEDURES

7.1 Procedures in Case of Pregnancy

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. Should pregnancy occur during a female subject's trial participation, the female subject will immediately be discontinued from the trial and followed-up per protocol.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be followed-up, documented and reported to AstraZeneca. The site will complete and forward to AstraZeneca their site-specific pregnancy form. The following information must be reported to AstraZeneca:

- DOB, Occupation
- Relevant medical history (pregnancy risk factors, smoking alcohol, etc.)
- Relevant family history
- Previous pregnancies (overall number, deliveries, spontaneous miscarriage, etc)
- Current pregnancy (LMP, expected delivery date, any amniocentesis, chorionic villus sampling, in-vitro fertilization)
- Concomitant medications taken during pregnancy (name, total daily dose, therapy duration, indication)
- Outcome of pregnancy (i.e., full-term, premature birth, spontaneous miscarriage, elective termination. If premature birth, specify gestational age in weeks. If elective abortion, specify if any medical reason.)
- Details of birth (i.e., DOB, weight, sex, healthy baby, sick baby, congenital anomaly/birth defect, still birth, multiple births, sickness manifestations, etc.)
- Any complications, infections, illness during pregnancy

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Appendix A
Medications Known To Induce Torsades De Pointes (TDP)

MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES (TDP)

Appendix A updated 19 August 2011

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsades de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

Group 1. Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes

Concomitant use of these drugs is not allowed during the study or within 2 weeks of randomization (at least four weeks for levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of 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	

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
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	
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

Source: www.QTdrugs.org

Group 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.

Concomitant use of these drugs is not allowed within 2 weeks of randomization or during the study. These drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes (reference section 5.6.2 of the protocol).

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	

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
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	
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	

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Voriconazole	Anti-fungal / anti-fungal	
Ziprasidone	Anti-psychotic (schizophrenia)	

Source: www.QTdrugs.org

Appendix B. Drug Administration Diary

Site Number	Subject Number	Subject Initials	Cycle

Subject Drug Diary
Bring your diary and study drug bottles (containing unused drug and empty bottles) to EACH appointment with the research nurse.

Please complete the diary every day. Write the date and time of each dose of drug you take. If you did not take your daily dose, or did not take your full dose, please write down the actual amount taken. If you experience any health/medical complaints, please record this information.

Day	Date	time of dose	# of Tablets
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			

12			
13			
14			
15			
16			
Day	**Date**	**time of dose**	**# of Tablets**
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			

Health / Medical Complaints

Please describe what you experienced	**Date started**	**Dated stopped**

Other Medication

Record only medication (prescription and/or over-the counter, including herbal medications and vitamins) taken other than study drug.

Name of Medication	Why did you take the medication?	Date started	Dated stopped

Appendix C

New York Heart Association (NYHA) Cardiac Classification

The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix D

Non-Serious Adverse Event Reporting Template

Patient Identifier	Adverse Event Term	CTC Grade	Treatment (if required)	Causality (Y or N)	Event Became Serious (Y or N)	Withdrawn from Study (Y or N)	Additional Comments

Appendix E

Instructions for Dispersing Vandetanib Tablets

Do not crush tablets. Drop the number of vandetanib tablets required for a single dose into an appropriate container (ideally glass to help confirm removal of all the dispersed material) containing approximately 2 ounces (or 50 mL) of water (either drinking water, sterile water for injection, or purified water) at room temperature. Stir the liquid occasionally to ensure complete break-up of the tablets. When the tablets have broken up into a fine dispersion (approximately 10 to 15 minutes) it can be administered to the patient. Administration to the patient should occur immediately after dispersion is complete whenever possible.

To ensure delivery of the whole dose, rinse the container with a similar amount of water to ensure removal of any material adhering to the walls of the container and administer the additional water to the patient.

Glass Contamination
As long as the glassware is cleaned thoroughly after use, using standard washing detergent or in a dishwasher then the risk of glass contamination is minimal. As an extra precaution, it could be suggested that the patient dedicates one glass for preparation of the oral dispersion, which is not used by other members of the household.

Spillage
If the oral dispersion is spilled, it should be cleaned up using plenty of water and the area washed with water until no residual drug remains. If the dispersion is spilled on the skin, the skin should be washed with plenty of clean water. If there is any contact with eyes, they should be irrigated with plenty of clean water for at least 10 minutes.

Stability Summary
Experimentation has shown that vandetanib tablets will break up into a fine dispersion within 10 to 15 minutes when they are dropped whole into water (either drinking water, sterile water for injection, or purified water) at room temperature. The dispersion should be administered to the patient immediately if possible. In the event of a delay in administration, the dispersion is chemically stable up to 4 hours after preparation.

The data confirms that aqueous dispersal of vandetanib (as described above) has no detrimental effects on the release of the active pharmaceutical ingredient (API) when compared to administration of the intact tablet and that a delay of up to 4 hours between preparation of the dispersion and administration will not have any detrimental effect on the assay and degradation products or the release of API in the dispersed tablet.

Effect of Variation in pH and Temperature of Water for Dispersion
The temperature and pH of the water used to prepare the dispersed tablet may vary in the clinic. The effect of pH of the water used for dispersion was evaluated over the range pH 5 – 8. Over this range, the pH of the water used for dispersing the tablets has no significant effect on the dispersion times.

The temperature range defined in the USP for controlled room temperature excursions that are experienced in hospitals is 15 °C to 30 °C. Over this range, the temperature of the water does have an effect on tablet dispersion times with the tablets taking longer to disperse at lower temperatures. All tablets tested dispersed within 10 minutes.

Compatibility With Delivery Devices

The dispersed tablet may be administered by nasogastric tube or gastrostomy tube. To ensure that the dose is not affected by the method of delivery, the vandetanib content and degradation products were determined after the dispersion had been passed through the delivery tube. See Table1 for details of the feeding tubes tested.

Table 1 Feeding tube equipment tested

Tube No	Feeding tube type	Product details	Product Code	Lot No
1	Nasogastric	Flocare nasointestinal feeding tube from Nutricia (CH10). (PD Ref. P/4163/07)	35231	200509353
2	Gastrostomy	Flocare PEG set from Nutricia (CH14). (PD Ref. P/4163/08)	35428	200506132
3	Nasogastric	CORFLO Controller PILL-NG enteral feeding tube from Viasys (10FR). (PD Ref. P/4163/011)	20-2551	18864

No significant difference was observed between the delivered dose obtained for the feeding tubes and the content of vandetanib in the control sample, indicating that the patient should receive the full dose when the dispersed tablet is administered using a feeding tube.

For the assay and degradation products results, no significant difference was observed between the results obtained for the feeding tubes and those obtained for intact tablets indicating that there are no compatibility issues with any of the tubes.

The administration method and any change in that method must be recorded on the appropriate CRF.