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DCP Protocol #: UWI2016-07-01

Phase IIB Randomized, Placebo-Controlled Trial of ACTOplus met® XR in Subjects with Stage I-IV Squamous Cell Carcinoma of the Oral Cavity or Oropharynx Prior to Definitive Treatment

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SCHEMA

Phase IIB Randomized, Placebo-Controlled Trial of ACTOplus met® XR in Subjects with Stage I-IV Squamous Cell Carcinoma of the Oral Cavity or Oropharynx Prior to Definitive Treatment

Patients ≥ 18 years of age with a newly diagnosed stage I-IV squamous cell carcinoma or squamous cell carcinoma in situ of the oral cavity or oropharynx who will be undergoing surgical, radiation or combined modality treatment. Patients with a lesion suspicious for cancer that has not yet been biopsied may also be screened for this protocol but will be randomized only if the presence of squamous cell carcinoma/carcinoma in situ is confirmed on biopsy.

Screening/Baseline Visit

(Procedures to be completed within 30 days prior to randomization)

Informed consent obtained. Participant registered. Medical/Surgical history, concomitant medications, baseline symptom assessment, physical exam and vital signs, height and weight, ECOG performance status. Baseline tobacco and alcohol use questionnaires administered. Clinical safety/eligibility labs and blood for pioglitazone analysis obtained.

Eligibility Questionnaire completed. After eligibility is determined and verified by a study investigator, biopsies of tumor and visually normal appearing tissue adjacent to the tumor are obtained for tissue biomarker analysis.

If a standard of care staging PET/CT is planned, the results will be documented and used for an exploratory analysis of the effect of the study agent on tumor burden and FDG uptake.

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Randomization to one of the following treatment groups (2:1 active treatment: placebo)

Group 1: ACTOplus met® XR
(30 mg pioglitazone/1000 mg metformin HCl):
[One (1) tablet, taken daily by mouth with a meal for 10 to 21 days.]

Group 2: Placebo:
[One (1) tablet, taken daily by mouth with a meal for 10 to 21 days.]

Day 1 = Date of first dose of study agent

During Study Intervention

Day 5-7 Phone Contact: Review baseline symptoms and concomitant medication. Assess adverse events and compliance with study agent dosing and completion of Pill Diary. Instruct participant when they should take their dose of study agent the day prior to pioglitazone PK assessment.

Final Dose Reminder Phone Contact: 12-72 hours prior to the time the participant was instructed to take their pre-pioglitazone PK dose of study agent.

End of Study (Day 11-22) or Early Termination

FDG-PET/CT skull base to thigh prior to collection of the end of study tissue samples (only for participants who had a standard of care staging FDG-PET/CT scan prior to starting study intervention). Review baseline symptoms, adverse event and concomitant medications. Collect blood for clinical safety labs and pioglitazone trough levels. Physical exam, vital signs and weight. Follow-up tobacco and alcohol use questionnaire administered. Biopsies of tumor and visually normal appearing tissue adjacent to the tumor are obtained for tissue biomarker analysis. If the participant is having their cancer surgically excised, these tissue samples may be obtained during surgery.

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Endpoints

Primary: effect of study agent dosing on Ki-67 expression in tumor tissue.

Secondary: Compare pre/post-study treatment differences in the following areas:

In tumor and visually normal appearing oral/oropharyngeal tissue: apoptosis and human RNA-seq gene analysis.

In visually normal appearing tissue: Ki-67 expression.

In tumor tissue alone: biguanide and PPARγ associated pathway biomarkers and immune microenvironment.

In pre-treatment tumor tissue: determine HPV status using p16

Exploratory Analysis: FDG-PET/CT: FDG uptake/metabolism and tumor burden (only for participants who had a standard of care staging FDG-PET/CT scan prior to starting study intervention)

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1. OBJECTIVES

1.1 Primary Objectives – The primary objective of this protocol is to determine whether 10-21 days of treatment with ACTOplus met® XR will result in a decrease in proliferation index (Ki-67) expression in oral cavity/oropharyngeal tumor tissue as compared to placebo.

1.2 Secondary Objectives –

1.2.1 Compare differences in proliferation index (Ki-67) expression from baseline to post-exposure in visually normal appearing oral cavity/oropharyngeal tissue.

1.2.2. Compare immunohistochemical differences in the apoptosis biomarker Cleaved Caspase 3 from baseline to post-exposure in oral cavity/oropharyngeal adjacent visually normal appearing tissue and tumor tissue samples.

1.2.3. Compare immunohistochemical differences from baseline to post-exposure in oral cavity/oropharyngeal tumor tissue samples with regard to Cyclin D1, p21 and biguanide or PPARγ associated pathway biomarkers. Prospective biomarkers on the panel will include pAKT, pAMPK, pS6 (Metformin), and PPARγ.

1.2.4. Compare immunohistochemical differences from baseline to post-exposure of oral cavity/oropharyngeal tumor tissue samples with regard to tumor infiltrating immune cells (effector CD8 (CD8+), regulatory CD4 Treg (CD4+Foxp3+), tumor associated myeloid cells (CD68), PD1 and PD-L1.

1.2.5. Compare and correlate pre- and post-ACTOplus met® XR treatment Human RNA-seq gene analysis on total RNA samples from oral cavity/oropharyngeal adjacent visually normal appearing tissue and tumor tissue pre-and post-study treatment.

1.2.6. Determine HPV status in pre-treatment tumor tissue using p16 immunohistochemistry.

1.3 Exploratory Analysis –

1.3.1 Compare pre- and post-study treatment FDG-PET/CT scans with regard to SUV (Standardized Uptake Value) of FDG and tumor burden using RECIST v 1.1 in those participants with a pre-intervention standard of care staging FDG-PET/CT.

2. BACKGROUND

2.1 *Study Disease*

There are at least 55,000 newly diagnosed head and neck cancers yearly and at least 180,000 new lung cancer diagnoses. There are no current effective chemoprevention agents in either a primary setting for precancerous disease or for secondary chemoprevention. Aerodigestive malignancies (head and neck, upper esophagus or lung) affect millions worldwide. Approximately 90% of these malignancies are contributed to by tobacco use. Those treated for an initial malignancy are at risk for second primary malignancies because of "field cancerization"[1]. Minimal change in survival for either malignancy for over a generation mandates new approaches to prevention and treatment.

2.2 *Study Agent*

2.2.1 Targeting Inflammation in Aerodigestive Cancers:

Virchow made the initial observations that cancer often occurs at sites of chronic inflammation approximately 150 years ago, and inflammation is implicated as a causative agent of approximately 15-20% of malignancies worldwide. In tobacco-associated precancerous conditions (e.g. oral leukoplakia, lung metaplasia), the links are a bit more elusive, but recent evidence suggests chronic inflammation is a predisposing factor to the development of lung and oral carcinoma [2-5]. It is well established that NFκB-dependent cytokines are elevated in both aerodigestive preneoplastic conditions. Tobacco carcinogens, one of the most commonly accepted risk factors for the development of oral cavity cancer, have been shown to increase NFκB activation in oral and lung preneoplastic epithelial cells [6-9]. Principal phenotype alterations by NFκB in aerodigestive cancer include increases in cyclin D1-associated cell proliferation [10], MMP-associated invasion [11], and IL-8-associated angiogenic processes [12].

Loss of p53 function contributes to NFκB activation in aerodigestive malignancies. Recent data demonstrates the necessity of NFκB activation for the development of spontaneous adenomas in transgenic mice containing p53 loss and KRAS expression, a common precursor genetic state in the lung [13; 14]. Interestingly, abrogation of NFκB signaling has been shown to be associated with increased efficacy of erlotinib in tumor cells modified to harbor EGFR exon 19 mutations [15]. Several lines of evidence point to inflammation-associated processes linked to chronic tobacco use, and COPD can result in NFκB upregulation. This in turn provides a permissive proinflammatory milieu, which may allow for the development of aerodigestive cancers.

2.3 *Rationale*

2.3.1 Thiazolidinediones: Pioglitazone**:**

The peroxisome proliferator-activated receptor γ (PPARγ) is a ligand-activated nuclear transcription factor belonging to the steroid receptor superfamily that is a key regulator of adipogenic differentiation. While originally believed to be highly adipocyte-specific, accumulating data show that PPARγ is also expressed in normal and neoplastic tissue, including breast, colon, prostate, and lung, and that ligand activation in breast and colon cell lines, as well as liposarcomas, leads to differentiation and/or apoptosis [16-21]. Ligands of PPARγ include the prostaglandin derivative 15deoxy-Δ2,14-prostaglandin J2 (15d-PGJ2) and the thiazolidinedione class of antidiabetic agents including pioglitazone. Mouse xenograft studies using breast and colon cancer cell lines have shown significant reduction in tumor size after treatment with PPARγ ligands compared with vehicle controls, with induction of apoptosis in the breast tumors [17; 18]. Pioglitazone (1.5 and 4.5 mg/kg-bw/day) was also effective in reducing colon tumor size, multiplicity, and incidence in the 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis model in male Wistar rats [22].

In vitro studies support the use of PPARγ ligands in the treatment and prevention of aerodigestive cancers. Chang and Szabo examined the expression of PPARγ in normal lung and non-small cell lung cancer (NSCLC) cell lines and the effects of PPARγ ligands on NSCLC growth and differentiation status [21]. PPARγ messenger RNA (mRNA) is significantly expressed in normal lung and protein is detectable by immunohistochemical methods in lung epithelial cells, particularly type II pneumocytes, and in 49% of primary lung tumors. All ten NSCLC cell lines examined expressed PPARγ mRNA and protein. Treatment of multiple cell lines in monolayer culture with 15d-PGJ2 or ciglitazone (a commercially available thiazolidinedione similar to pioglitazone) led to growth arrest and ultimately cell death. In clonogenic assays, ciglitazone potently inhibited anchorage-independent growth and pretreatment with ciglitazone led to irreversible loss of the capacity for anchorage-independent growth, providing evidence that some aspects of the phenotype modulation by PPARγ ligands are irreversible.

Multiple lines of evidence support the role of PPARγ ligands in modulating early tobacco-related carcinogenesis. Pioglitazone suppressed tongue carcinoma development in a transgenic animal model of oral squamous cell carcinoma [23]. Rats carrying the human c-Ha-ras proto-oncogene were treated with the carcinogen 4-nitroquinoline 1-oxide (4-NQO) and then administered pioglitazone (500 ppm) in the diet for 11 weeks beginning one week after 4-NQO treatment. Pioglitazone significantly inhibited tongue carcinoma multiplicity compared with carcinogen-control animals. Troglitazone and rosiglitazone have also shown chemopreventive efficacy in head and neck carcinogenesis based on activity in preventing 4-NQO-induced carcinomas in F344 rat tongue. Troglitazone at 100 ppm in diet fed for 22 weeks following treatment with 4-NQO significantly decreased the incidence of squamous cell carcinomas in F344 rats from 45% to 5% compared with controls; cell proliferation (as measured by bromodeoxyribonucleotide labeling and cyclin D1 expression) and cyclooxygenase-2 expression were also decreased [24]. Finally, administration of pioglitazone (15 mg/kg body weight by gavage) in two carcinogen-treated mouse models demonstrated inhibition of both adenocarcinomas and squamous cell carcinomas [25]. Adenocarcinoma tumor load following vinyl carbamate treatment was inhibited by 64% in p53wt/wt mice and by 50% in p53wt/Ala135Val animals. Similarly, squamous cell carcinoma formation in NIH Swiss mice after treatment with topical N-nitroso-trischloroethylurea (NTCU) was significantly decreased by 35%. Induction of apoptosis was seen in both the adenocarcinoma and squamous cell models, while a statistically significant decrease in proliferation was only seen in p53wt/wt mice treated with vinyl carbamate.

In a study of male diabetics followed in Veterans Administration (VA) hospitals, Govindarajan et al. demonstrated a 33% reduction in lung cancer risk among thiazolidinedione users compared with nonusers [26]. Using the same VA database, the authors also reported a 41–55% reduction in head and neck cancer in diabetics using thiazolidinediones in combination with other agents or alone.

Based on the above data, NCI DCP sponsored three cancer prevention trials with pioglitazone. An open-label phase 2a trial conducted by Ondrey and colleagues at University of Minnesota treated subjects with high-risk (length ≥8 mm and width ≥3 mm) oral premalignant lesions (OPL) with pioglitazone (45 mg/day) for three months. Of 22 subjects enrolled, 21 subjects finished treatment, and 17 subjects (3 complete and 14 partial responses) had >50% clinical shrinkage of lesions (79% partial clinical response rate), with an average decrease in size of 79%. Histologic responses were noted in 3/21 subjects (14%), while progressive histologic disease was noted in 4/21 subjects (19%). This is an overall response rate of 15/21 subjects. No unexpected toxicities were identified and only one subject dropped out, for unknown reasons. The current UWI Chemoprevention consortium led by Dr. Ondrey performed (with MDA consortium) a phase IIb, randomized, double blind placebo-controlled trial, where individuals with high-risk OPL were randomized to receive 45 mg pioglitazone or placebo for 24 weeks. Lesions were measured and biopsied before and after treatment to evaluate the clinical and histologic response, respectively. Fifty-two participants were randomized (27 pioglitazone, 25 placebo). Pioglitazone was well tolerated, with no unexpected toxicities reported. Clinical response was observed in 46% of participants receiving pioglitazone vs. 32% of participants receiving placebo (p=0.45), with no difference in progression (19% pioglitazone vs. 20% placebo). Histologic response occurred in 8% of the subjects in each group, while progression occurred in 12% of pioglitazone-treated participants vs. 8% of placebo-treated participants. Full accrual of the trial was not met, and there was no effect on Ki-67, cyclin D1, p21, or PPARγ. In an NCI, DCP-sponsored pilot study, six participants with known or suspected Stage IA−IIIA NSCLC and ≥10 pack/year smoking history (current or former) received 45 mg pioglitazone daily for 14–42 days or until scheduled resection. Of the five participants included in the primary endpoint analyses, tumor tissue Ki-67 labeling index was uniformly reduced, with a median (range) percent change of -20% (-11.1 to -40.0%) (p=0.06). Additional tumor tissue, normal tissue, and positron emission tomography/computed tomography data were unrevealing. Analysis of gene expression from histologically normal epithelium in the surrounding field is ongoing, but initial observations indicate

significant modulation of pathways associated with lung carcinogenesis. These data are derived from a small number of participants. No grade 2 or higher adverse events were reported.

Pioglitazone, like other thiazolidinediones, can cause fluid retention when used alone or in combination with other antidiabetic agents, including insulin. Fluid retention may lead to or exacerbate heart failure. FDA has required a black box warning to be placed on the pioglitazone package insert to indicate the increased risk of congestive heart failure. In 2011, FDA updated the Warnings and Precautions section of the label for pioglitazone-containing medicines to indicate that use for more than one year may be associated with an increased risk of bladder cancer. However, a recent extended follow-up of the Kaiser Permanente Northern California observational cohort of 193,099 diabetics, as well as 464 bladder cancer cases and 464 matched controls, did not demonstrate any association between pioglitazone use and bladder cancer [27].

2.3.2 Biguanides: Metformin:

Metformin, a first-line drug commonly used to treat diabetes mellitus, also directly inhibits cell growth. Besides inhibiting gluconeogenesis, this biguanide derivative directly activates adenosine monophosphate-activated protein kinase (AMPK) in epithelial cells by a liver kinase B1 (LKB1)-dependent mechanism. AMPK appears to be a key molecular target for cancers associated with diabetes mellitus and obesity. AMPK is an intracellular regulator that is activated when the cell senses conditions of decreased energy such as low glucose, hypoxia, or ischemia [28; 29]. AMP, which is present under conditions of starvation when adenosine triphosphatase levels are low, binds to the γ subunit of AMPK allowing AMPK to be activated allosterically by LKB1. Activation of AMPK increases insulin-stimulated glucose uptake. It also inhibits mammalian target of rapamycin (mTOR) via tuberous sclerosis complex 2/1, resulting in decreased protein synthesis mediated by the downregulation of the ribosomal protein S6K. Exposure of breast cancer cells to metformin decreases phosphorylated AKT and activation of mTOR, resulting in inhibition of cell proliferation and an increase in apoptosis [30]. The cell signaling pathways of adiponectin and leptin, two other hormones implicated in obesity-associated carcinogenesis may also be mediated by AMPK, but do not appear to be affected by metformin [28; 29; 31]. Metformin also has indirect anti-proliferative effects related to lower systemic levels of insulin.

The potential cancer chemoprevention efficacy of metformin has been demonstrated in animal models of colon [32], lung [33-35], liver [36-38], mammary gland [39], oral cavity [40], and skin [41] cancer. In a published NCI, DCP-sponsored study, metformin inhibited the initiation of new neoplastic lesions, but not pre-existing lung adenomas or tumors, in mainstream cigarette smoke (MCS)-exposed mice [35]. Newborn mice were exposed to MCS for four months, followed by filtered air for 3.5 months, then administered metformin (800 mg/kg-diet) for four weeks. MCS was shown to dramatically increase lung DNA adducts and oxidative damage compared with control mice. Metformin treatment reduced MCS-induced lung DNA adducts (2.6-fold in males and 3.4-fold in females) and oxidative damage (1.4-fold in males and 1.5-fold in females) compared with untreated MCS-exposed mice. Metformin failed to inhibit MCS-induced lung adenomas and tumors, even though it reduced microadenoma incidence (55.9% vs. 35.1%, $p<0.01$) and multiplicity (8.9 vs. 4.5, $p<0.01$).

Vitale-Cross et al. [40] showed metformin prevented the development of oral squamous cell carcinomas (SCCs) in a murine model of head and neck SCC (HNSCC). 4-NQO-treated female mice were administered metformin (50 mg/kg-bw/day) by intraperitoneal injection for 22 weeks. Metformin reduced both the number ($p<0.05$) and size of oral tumors compared with saline-treated animals. Furthermore, histological analysis of HNSCC grade revealed fewer malignant conversions and lower grade dysplasias (preneoplastic lesions) with metformin. For example, SCC multiplicity was near zero ($p<0.05$), and both low- and high-grade dysplasias were significantly reduced ($p<0.01$ and $p<0.05$, respectively). Consistent with this, there was a significant reduction in Ki-67 staining of cells in metformin-treated mice ($p<0.001$).

In addition, AMPK and phosphorylated AMPK (pAMPK) levels were evaluated in human HN12 HNSCC cells in response to metformin. Metformin caused a concentration-dependent increase in pAMPK but not AMPK that correlated with cell growth inhibition. Intriguingly, metformin-mediated growth was not mediated by AMPK or pAMPK since knockdown of AMPK's activator protein, LKB1, did not result in metformin resistance to HNSCC growth. Furthermore, testing metformin in HeLa cells, which are devoid of endogenous LKB1 activity due to promoter methylation, also did not result in metformin-resistant cell growth. Consequently, metformin tumor cell growth inhibition is an AMPK independent process, possibly a result of its ability to deplete cellular energy.

In addition to its LKB 1/AMPK pathway effects, metformin has the capacity to interact with mitochondrial respiration as a mechanism to prevent tumorigenesis. Wheaton et al. were able to demonstrate that metformin at concentrations (0.25–1.0 mM) inhibited cellular oxygen consumption in human HCT116 p53−/− colon cancer cells via inhibition of mitochondrial complex 1 (MCC 1) [42]. Transfection of human analog ND11 (NADH dehydrogenase) restored oxygen consumption in this model demonstrating that the deficiency caused by metformin could be reversed.

Further evidence in support of metformin's cancer chemopreventive efficacy comes from epidemiologic studies. Population studies and several meta-analyses have revealed that treatment with metformin, a first-line treatment for patients with type 2 diabetes, is significantly associated with reduced cancer risk [43; 44], suggesting that metformin might have chemoprevention efficacy in humans. The magnitude of the risk reduction varies across studies, ranging from 10-30% decreased overall cancer risk. Several studies have focused on metformin's potential as a cancer prevention drug in common obesity-associated cancers, such as breast, prostate, pancreas, and colon [43-50].

In a recent NCI, DCP-sponsored randomized, double-blind, placebo-controlled, phase 2 study, 74 subjects with Barrett's esophagus (BE) were randomized to receive either metformin (increasing to 2000 mg/day by week 4, n = 38) or placebo (n = 36) daily for 12 weeks. Biopsy specimens were collected at baseline and at week 12 via esophagogastroduodenoscopy. The primary endpoint was the percent change in median levels of pS6K1 between subjects given metformin vs placebo. The percent change in median level of pS6K1 did not differ significantly between groups (1.4% among subjects given metformin vs −14.7% among subjects given placebo; p=0.80). Metformin had no effects on cell proliferation (on the basis of assays for Ki67) or apoptosis (on the basis of levels of caspase 3) [51].

Metformin is well tolerated, even by individuals without diabetes mellitus, and does not cause hypoglycemia if used as labeled. Its main side effects are transient nausea and diarrhea. Lactic acidosis, a major adverse effect, is rare, and seen only in those with concomitant renal failure or liver disease.

2.3.3 Metformin plus Pioglitazone:

Metformin and pioglitazone have different modes of action; thus, the combination of metformin and pioglitazone might be more effective than either agent alone in prevention of lung or head and neck cancer. In an NCI, DCP-sponsored nonclinical study, the effect of metformin plus pioglitazone on benzo[a]pyrene-induced lung carcinogenesis was evaluated in mice by Wattenberg/Ondrey [52]. Female A/J mice were administered metformin (850 or 1,000 mg/kg-bw/day), pioglitazone (15 mg/kg-bw/day), or the combination metformin (850 mg/kg-bw/day) plus pioglitazone (15 mg/kg-bw/day) beginning two weeks (early stage) or nine weeks (late stage) after the last carcinogen dose. Animals were sacrificed at week 16. For the early-stage treatment (+two weeks), metformin alone caused a 64% and 71% inhibition of tumor multiplicity at the 850 and 1000 mg/kg-bw/day doses ($p<0.01$), respectively, compared with control group. For the late-stage treatment (+nine weeks), metformin at 850 mg/kg-bw/day caused a 37% ($p<0.01$) reduction in tumor multiplicity compared with control animals. Pioglitazone alone showed 32% ($p<0.01$) and 17% (non-significant) inhibition of tumor multiplicity at the early-stage and late-stage

treatments, respectively. The metformin plus pioglitazone combination at the early-stage treatment showed a 70% inhibition of tumor multiplicity but was less effective at the late-stage treatment, with 44% inhibition vs. the control group.

The combination of pioglitazone and metformin is approved by the FDA and marketed as ACTOplus met® XR (Takeda Pharmaceuticals America, Inc., Deerfield, IL). It is available as extended release tablets in two dosage forms—15 mg pioglitazone plus 1000 mg metformin and 30 mg pioglitazone plus 1000 mg metformin. ACTOplus met® XR can cause or worsen congestive heart failure and is contraindicated in patients with severe or uncontrolled heart failure, kidney disease, and metabolic acidosis.

2.3.4 Tobacco and Alcohol Use

Tobacco and alcohol use are known risk factors for cancers of the aerodigestive system. In addition, tobacco and alcohol use may adversely affect agent intervention, for example by altering the safety profile or metabolism of a drug. Standardized assessments of tobacco and alcohol use during clinical trials will aid in understanding the potential relationship between the use of these products and clinical endpoints or cancer prevention biomarkers. NCI, DCP is including assessment of tobacco and alcohol use at baseline and end of study visits to determine the potential impact of tobacco and alcohol use on 1) treatment toxicity and symptom burden, and 2) the efficacy of treatment intervention.

3. SUMMARY OF STUDY PLAN

This is a 2:1 randomized, placebo-controlled, phase IIB oral cavity/oropharynx window of opportunity cancer chemoprevention study of ACTOplus met® XR (pioglitazone 30 mg and metformin extended release 1000 mg) daily for 10-21 days in patients undergoing planned surgery or definitive radio/chemotherapy. We plan to accrue 36 evaluable participants to this protocol. To account for an anticipated dropout rate of 8%, 39 participants will be accrued over a 12-18-month period of time. This number allows for three (3) unevaluable participants. (Note: this will start as a pilot study of the first 18 participants accrued to the protocol). Assuming a screening rate of approximately 2 participants per month and an accrual rate of 1-2 participants per month (0.5-1 per site), we expect the study to be complete within 18–24 months.

Study recruitment will occur in head and neck cancer clinics at participating institutions. Surgeons will be critical to recruitment as patients with newly diagnosed head and neck cancer will usually first meet with a surgeon.

Candidates for this protocol will be patients with newly diagnosed, histologically confirmed, stage I-IV squamous cell carcinoma or squamous cell carcinoma in situ of the oral cavity or oropharynx who will be undergoing definitive treatment (surgical, radiotherapy, chemoradiation treatment). Patients with a lesion in the oral cavity or oropharynx that is not yet biopsied, but is highly suspicious for squamous cell carcinoma, are candidates for screening but will not be randomized if the diagnosis is not pathologically confirmed. Study candidates must have a primary tumor and adjacent visually normal appearing tissue in an area that would allow for the collection of a 4 mm tissue sample from each for biomarker analysis at baseline and at the end of study.

Informed consent will be obtained prior to performance of any study procedures. The following assessments will be completed within 30 days prior to day 1 of study agent dosing. If any of these tests were conducted as part of the participant's standard medical care within the required 30 day time frame and a copy of the source document can be obtained for the study chart, those tests do not need to be repeated. If the testing is incomplete [i.e. some, but not all of the required blood tests were obtained or a

physical exam was done but did not assess for one of the required elements (ECOG performance status, edema, signs/symptoms of congestive heart failure, HEENT, Chest, Heart or Abdomen) only those required elements not assessed need to be performed]. Copies of blood test results must contain the lab's reference (normal) range for the test.

- Medical/Surgical History and Concomitant Medication assessment
- Baseline symptoms
- ECOG performance status
- Eligibility Questionnaire
- Physical Exam, height, weight and vital signs
- Clinical lab tests: CBC with differential, Comprehensive Metabolic Panel and urine pregnancy test (for women of childbearing potential)
- Baseline tobacco and alcohol use assessments

A blood sample for baseline PK analysis will also be obtained.

Patients who meet the eligibility criteria for the protocol will have baseline tissue samples for biomarker analysis obtained in clinic or in conjunction with a standard of care direct operative laryngoscopy with biopsy (DL biopsy) performed for diagnostic purposes. Two 4 mm biopsies: one of tumor and one of adjacent normal appearing tissue will be obtained. Half of each biopsy will be placed in RNAlater. The other half will be formalin-fixed and paraffin-embedded. For those participants with an undiagnosed suspicious lesion, the paraffin-embedded biopsy sample from the lesion will be submitted for pathology review.

Patients with undiagnosed suspicious lesions will not be randomized until they have a histologically confirmed cancer, and a treatment plan is established. (If the presence of cancer is not confirmed, the patient will be considered a screen failure.)

If a standard of care staging PET/CT is planned, the participant's randomization will be held until the scan is completed. The results will be documented and used in an exploratory analysis of the effect of study agent on FDG uptake and tumor burden (per RECIST v 1.1 criteria). This exploratory analysis will be performed only on those participants who have had a standard of care staging PET/CT. A staging scan is not a required baseline assessment. Those participants who have had a standard of care staging PET/CT will be asked to have a repeat scan, for research purposes only, conducted prior to the collection of their end of study tissue samples in order to complete the exploratory analysis.

Confirmation of eligibility and randomization will be performed by the Contract Lead Organization (CLO).

Once a surgery date or start date for definitive radiotherapy/chemotherapy is scheduled, participants will begin taking ACTOplus met® XR (or Placebo) orally, daily for 10 to 21 doses prior to the scheduled treatment date. The day the participant begins taking agent is considered Day 1. Participants will be contacted on Day 5-7 by telephone to assess for adverse events, compliance with study agent dosing and completion of the pill diary and to review their use of concomitant medications. At this contact, the participant will be instructed what time of day they should take their dose of study agent on the day prior to the end of study collection of blood for pioglitazone trough levels. To obtain an accurate trough level, the participant should dose approximately 24 hours (and no longer than 26 hours) prior to the time that the blood draw will occur. The participant will be contacted 12-72 hours prior to this dose time to remind them of the dose timing and to NOT take a dose of study agent on the day of the blood draw. For participants who are scheduled to have their lesion surgically excised, if the surgery is re-scheduled or delayed after the participant has started taking study agent, the participant may continue to take up to 25

doses of study agent with the final dose being taken within 26 hours of the collection of the end of study tissue samples. In the event of a cancellation or postponement of surgery beyond the maximum of 26 days after the start of study agent dosing (Day 1), if the participant is willing, the tissue samples for study end point may be collected in clinic via biopsy within the day 11 to 26 window.

For all participants, the following will be obtained after 10 to 21 (up to 25 in the case of delayed surgery) days of study agent dosing and prior to performing the end of study tissue biopsies:

- FDG PET/CT scan (this is a research only scan to be performed only if the participant had a standard of care staging PET/CT prior to starting study intervention)
- CBC with differential
- Comprehensive Metabolic Panel
- Plasma sample for pioglitazone concentration
- Physical exam
- Follow-up tobacco and alcohol use assessments

If surgery is the definitive treatment, at the time of surgery, two research biopsies will be obtained: one of normal appearing tissue adjacent to the tumor, and one of the tumor tissue itself. Half of the normal appearing tissue biopsy and a 2 mm piece of tumor tissue will be placed in RNAlater. The other half the normal appearing biopsy and the tumor tissue will be formalin-fixed and paraffin-embedded. The formalin-fixed tumor tissue will be submitted for standard of care clinical histopathology in accordance with the institution's standard procedures.

For non-surgical, radio/chemoradiotherapy participants, a post-study treatment 4mm biopsy of tumor and adjacent visually normal appearing tissue will be performed between days 11 and 22.

To protect the integrity of the cells, the formalin-fixed, paraffin-embedded tissue from each sample will remain in block form at each participating organization until the samples are requested to be submitted for analysis.

The University of Minnesota will perform analysis of Ki-67, Cyclin D1, Cleaved Caspase 3, p16 (HPV pre-treatment only), p21, pAKT, pAMPK, pS6, PPAR gamma.

Johns Hopkins University will perform analysis of PD1, PD-L1, T helper (CD4), T suppressor (CD8), Fox p3 (TREG), and Tumor Associated Macrophage (CD68).

The University of Minnesota's Genomic Center will prepare the RNAlater tissue samples for whole transcriptome gene analysis at the Oklahoma Medical Research Foundation (OMRF).

The Cancer Pharmacology (CP) Laboratory at the University of Wisconsin will perform analysis of pioglitazone concentration in plasma.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Participant has a newly diagnosed, histologically confirmed, stage I-IV squamous cell carcinoma or squamous cell carcinoma in situ of the oral cavity or oropharynx and will be undergoing definitive surgical, radiotherapy, or chemoradiation treatment. Patients who are NOT candidates for localized treatment (surgery, radiation or chemoradiation) with curative intent (i.e. patients with distant metastasis or contra-indication to localized treatment) are not eligible.

OR

Participant has a lesion in the oral cavity or oropharynx that is not yet biopsied but is highly suspicious for cancer. (Randomization will be placed on hold until the presence of cancer is histologically confirmed, and a treatment plan is established. If the presence of cancer is not confirmed, the participant will be considered a screen failure.)

4.1.2 The participant's primary tumor is accessible for the collection of 4 mm samples of tumor and adjacent visually normal appearing tissue for biomarker analysis and the participant is willing to have these samples collected at baseline and at the end of study visit. (The protocol requires the collection of fresh tissue for biomarker analysis)

Patients who have not yet had a diagnostic biopsy:

- The tissue samples for biomarker analysis may be collected in conjunction with the patient's standard of care diagnostic biopsy but not until after the patient has signed informed consent and it has been determined that they meet all of the eligibility criteria for this protocol with the exception of 4.1.9 (normal organ and marrow function as defined by the clinical laboratory test results listed for that criterion). In this situation, because the patient would be having a biopsy regardless of whether or not they were participating in this study, it is not required to obtain these results prior to conducting the biopsy. It is however, required to confirm normal organ and marrow function as defined in 4.1.9 prior to randomization.

- Patients who are scheduled for a direct operative laryngoscopy with biopsy (DL biopsy) for diagnostic purposes may be candidates for this study provided the following criteria are met:

    - The lesion to be biopsied is within the anatomic confines of the oropharynx (i.e. above the epiglottis).
    - Tissue samples for biomarker analysis of the required 4 mm size are able to be obtained from both the lesion and an area of visually normal appearing tissue adjacent to but 1 cm distant from the lesion.

  In this situation, randomization will be placed on hold until the following criteria are met:

    - Normal organ and marrow function as defined in 4.1.9 is confirmed.
    - There is histologic confirmation of squamous cell carcinoma.
    - It has been determined that surgical excision will be the first line standard of care treatment and the end of study tissue samples will be obtained in conjunction with that surgery.

  Because these patient's lesions are not accessible to end of study tissue sample collection in the outpatient clinic setting, the only way to obtain those samples is in conjunction with standard of care surgical excision of the lesion. If the first line of treatment will be non-surgical, the patient will be considered a screen failure. Under no circumstances will DL biopsy be used for the sole purpose of collecting tissue samples for biomarker analysis.

Patients who have already had a diagnostic biopsy:

- The baseline tissue samples for biomarker analysis will be collected in the outpatient clinic setting as a "for research purposes only" procedure. The samples may not be collected until it has been determined that the participant meets all eligibility criteria for this protocol including 4.1.9.

End of study tissue sample collection:

- If surgical excision will be the patient's first line treatment, the end of study tissue samples for biomarker analysis will be collected in conjunction with that surgery. If, for any reason, the patient's surgery is delayed beyond Day 26, the end of study tissue samples may be collected in the outpatient clinic setting.

- If the patient's first line of treatment will not be surgical excision, the end of study tissue samples for biomarker analysis will be collected in the outpatient clinic setting prior to initiation of the non-surgical treatment.

4.1.3 Participant is able to complete a minimum of 10 days of study agent dosing prior to initiation of definitive treatment for their cancer.

4.1.4 Participant is scheduled for an end of study biopsy within 22 days of starting study agent and within 52 days of their study screening visit. (If the participant is scheduled for surgical excision of the tumor and the surgery is delayed for any reason after the participant has started taking the study agent, study agent dosing may be extended up to a maximum of 25 days without compromising the evaluability of the end of study biomarkers).

4.1.5 Age ≥18 years (ACTOplus Met® XR is not recommended for use in pediatric patients)

4.1.6 ECOG performance status = 0 or 1.

4.1.7 Life expectancy is > 6 months.

4.1.8 Body mass index (BMI) is ≥ 18.5.

4.1.9 Participant has normal organ and marrow function as defined below:

Hemoglobin	≥10 g/dl
White blood cells	≥3,000/microliter
Platelets	≥100,000/microliter
Total bilirubin	≤ 1.2 x institutional upper limit of normal *
AST (SGOT)	≤ 1.2 x institutional upper limit of normal
ALT (SGPT)	≤ 1.2 x institutional upper limit of normal
Glucose, serum	< 200 mg/dL
eGFR	>45 mL/min (If eGFR is not included on the clinical lab report, the following calculator may be used: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr. Select the equation: CKD-EPI Creatinine. The participant's gender, age, race, and serum creatinine are required to complete the calculation.)

* With the exception of candidates with a diagnosis of Gilbert's disease in which case the total bilirubin may extend up to 1.5 x institutional upper limit of normal.

4.1.10 Participant is able to swallow a tablet whole.

4.1.11 Participant is willing and able to participate for the duration of the study.

4.1.12 Participant of childbearing potential agrees to use adequate contraception (a hormonal method that has been in continual use for a minimum of 3 months prior to the study screening visit, a barrier method, or abstinence) for the duration of their study participation. (Therapy with pioglitazone may result in ovulation in some premenopausal anovulatory women. In addition, the effects of ACTOplus Met® XR on the developing human fetus at the recommended therapeutic dose are unknown. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.)

Note: Due to the risks associated with hormonal methods of birth control, participants should not start hormonal therapy for the purpose of meeting the eligibility criteria for this protocol.

4.1.13 Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

4.2.1 Participant has received or will receive some form of treatment for their cancer prior to completing a minimum of 10 days of study agent dosing. (A biopsy is not considered a form of treatment.)

4.2.2 Participant has a concurrent diagnosis of Type I or Type II diabetes that is being treated with insulin or an antidiabetic agent. (Participants whose Type II diabetes is controlled with diet and/or exercise alone are eligible provided they meet all other eligibility criteria).

4.2.3 Participant has taken any of the following medications within the past 3 months:

4.2.3.1 a thiazolidinedione [e.g. pioglitazone (Actos) or rosiglitazone (Avandia)],

4.2.3.2 a biguanide [e.g. metformin (Glucophage, Glumetza, Fortamet, Riomet) or proguanil (Paludrine)]

4.2.3.3 a combination drug containing one of the agents above (Brand names include: ACTOplus Met, Avandamet, Avandaryl, Duetact, Glucovance, Invokamet, Janumet, Jentadueto, Komboglyze, Metaglip, PrandiMet, Synjardy, Xigudo).

4.2.4 Participant is currently taking a strong CYP2C8 inhibitor [e.g. gemfibrozil (Lopid)].

4.2.5 Participant is currently taking an enzyme inducer of CYP2C8 [carbamazepine (Carbatrol, Epitol, Equetro. Tegretol) cortisol (Hydrocortisone); dexamethasone (Decadron); phenobarbital (Luminal Sodium): phenytoin (Dilantin, Phenytek, Novaplus Phenytoin Sodium); primidone (Mysoline); rifampin (Rifadin, Rimactane); rifapentine (Priftin); secobarbitol (Seconol)].

4.2.6 Participant is currently taking topiramate (Topamax) commonly used in epilepsy or to prevent migraines or other carbonic anhydrase inhibitors [e.g. zonisamide (Zonegran); acetazolaminde (Diamox Sequels); or dichlorphenamide (Keveyis, Daranide)].

4.2.7 Participant is currently taking a cationic drug or multidrug and toxin extrusion [MATE] inhibitor [e.g. amiloride (Midamor); cimetidine (Tagamet); digoxin (Lanoxin, Digitek, Digox); dolutegravir (Tivicay); morphine (Roxanol, Duramorph, Kadian, MS Contin); procainamide (Pronestyl, Procanbid); quinidine (Quinidex, Cardioquin, Quin-G, Quinora); quinine (Qualaquin, Quinamm, Quiphile); ranitidine (Zantac, Deprizine, Gabitidine); ranolazine (Ranexa); triamterene (Dyrenium); trimethoprim (Proloprim, Trimpex, Primsol); vancomycin (Vancocin, Vancoled); or vandetanib (Calpresa).]

4.2.8 Participant is taking another investigational agent.

4.2.9 Participant has a history of allergic reactions attributed to compounds of similar chemical or biologic composition to ACTOplus Met® XR.

4.2.10 Participant has a contraindication to biopsy.

4.2.11 Thiazolidinediones, such as pioglitazone can cause or exacerbate congestive heart failure in some patients, therefore, participants with a history of congestive heart failure or New York Heart Association (NYHA) Class III or IV functional status are excluded. (Class III = marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea. Class IV = Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased. [53])

4.2.12 Participant has a history of liver disease.

4.2.13 Participant has > CTCAE Grade 1 limb edema (5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection).

4.2.14 Participant has a history of hypoglycemia.

4.2.15 Participant is an active alcoholic or consumes excessive amounts of alcohol per the following definitions:

Female: More than 3 drinks on any day or a total of more than seven drinks in a week.
Male: More than 4 drinks on any day or a total of more than 14 drinks in a week.

1 drink = Beer: 12 oz. (1 standard size can or bottle)
Wine: 5 oz. (one standard glass)
Spirits: 6 oz. (one mixed drink or one 1.5 fluid oz. shot)

4.2.16 Participant has a history of macular edema.

4.2.17 Participant has a history of bladder cancer (including *in situ* bladder cancer).

4.2.18 Participant has a history of invasive cancer (other than non-melanoma skin cancer or cervical cancer *in situ*) active within 18 months prior to the baseline study visit. (Participants who have a history of cancer that was curatively treated without evidence of recurrence in the 18 months prior to the baseline study visit are considered eligible).

4.2.19 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.20 Participant is pregnant, breast feeding or planning to become pregnant. (All participants of childbearing potential regardless of method of birth control must have a negative pregnancy test at baseline. A woman is considered not to be of childbearing potential if she has had a hysterectomy, bilateral oophorectomy, or if she is > 55 years of age with ≥ 2 years of amenorrhea.)

ACTOplus Met® XR is a thiazolidinedione and biguanide combination product, Pregnancy Category C. There are no adequate and well-controlled studies of ACTOplus Met® XR or its individual components in pregnant women therefore pregnant women and women planning to become pregnant are excluded from this study. Animal studies using pioglitazone show increased rates of post-implantation loss, delayed development, reduced fetal weights, and delayed parturition at doses 10 to 40 times the maximum recommended human dose.

No studies have been conducted with the combined components of ACTOplus Met® XR in nursing mothers. In studies performed with the individual components, both pioglitazone and metformin are secreted in the milk of lactating rats. It is not known whether pioglitazone and/or metformin are secreted in human milk. Because many drugs are excreted in human milk and because of the potential for ACTOplus Met® XR to cause serious adverse reactions in nursing infants, breastfeeding should be discontinued if the mother is treated with ACTOplus Met® XR.

4.3 Inclusion of Women and Minorities

Both men and women (as applicable) and members of all races and ethnic groups are eligible for this trial.

4.4 Recruitment and Retention Plan

Participants will be accrued from the investigator's clinic populations. Each of the participating organizations has a large ENT specialty clinic that receives referrals from a broad regional catchment area.

The principal investigator at each participating organization is an otolaryngologist with a team of other otolaryngologists helping to recruit participants for this study. Each of the organizations also has a lead study coordinator to assist with the identification of study candidates and the completion of study procedures.

Clinic and/or study staff at each participating institution will review clinic schedules to identify potential study candidates. Study staff may review the patient's medical record to determine if they appear to meet the study's inclusion criteria and if they have any evident exclusionary criteria. Review of medical records is not a procedure for which written consent is normally required outside of the research context and the risk of harm to the potential study candidate is very minimal.

When a potential candidate is identified:

Candidates with a histologically confirmed squamous cell carcinoma of the oral cavity or oropharynx (including those with squamous cell carcinoma in situ):

- If there is clear documentation in the medical record that the patient has been informed of their diagnosis, the patient may be contacted by phone by a member of the study team in advance of their clinic appointment to present the study and to offer to send a copy of the informed consent form for their review (time permitting).

- If it is unclear whether or not the patient is aware of their diagnosis, no contacts will be made in advance of the clinic visit. The patient's clinic care team will be notified that the patient is a potential study candidate and will be asked to obtain patient assent to have the study presented. If the clinic care team determines that the patient is not eligible for the study or if the patient declines to have the study presented, the care team will be asked to provide the reason the patient was ineligible or the reason the patient did not want to hear about the study.

Candidates with an undiagnosed suspicious lesion:

- It is not typically readily apparent from a patient's medical record how suspicious their oral/oropharyngeal lesion is. These patients will not be approached about the study in advance of their clinic visit, instead, the patient's clinical care team will be alerted that the patient may be a candidate. If, upon visual inspection by the care team, the lesion does appear to be a squamous cell carcinoma and a diagnostic biopsy is indicated, the clinical care team will be asked, upon assent of the patient, to notify a member of the study team to present the study prior to the collection of the biopsy.

Recruitment efforts will be documented on the NCI Division of Cancer Prevention's Accrual Quality Improvement Program (AQuIP) website. An entry will be made for each clinic patient who meets the primary eligibility criterion for the study (i.e. each patient with a newly diagnosed, histologically confirmed, stage 0-IV squamous cell carcinoma of the oral cavity or oropharynx who will be undergoing definitive surgical, radiotherapy, or chemoradiation treatment or with a lesion in the oral cavity or oropharynx that is not yet biopsied but is highly suspicious for cancer. AQuIP data is submitted monthly by the CLO. Participating organizations must have their monthly data entered prior to the 5th of the following month (i.e. January data must be entered by February 5th).

Patients diagnosed with, or suspected of having, oral or oropharynx cancers are highly motivated to explore prevention options. Because patients often travel some distance for treatment at these centers, the baseline visit and randomization process has been streamlined so that all procedures can be completed in a single visit if need be. An interim phone contact will be made in lieu of an additional study visit. Participants will be offered adequate remuneration to cover their travel costs. Participants who had a standard of care staging PET/CT prior to starting study intervention and are scheduled for an end of study follow-up PET/CT will be reimbursed for overnight accommodations if the PET/CT is unable to be scheduled on the same day as the rest of their end of study procedures and they travel from a distance . The protocol intervention is very short term with minimal study visits so we do not anticipate participant retention will be an issue.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

Participants will be randomized in a 2:1(active agent: placebo) ratio to one of the two following treatment groups:

- Group 1: ACTOplus met® XR (30 mg pioglitazone/1000 mg metformin HCl):
  - One (1) tablet, taken daily by mouth with a meal for 10 to 21 days.

- Group 2: Placebo:
  - One (1) tablet, taken daily by mouth with a meal for 10 to 21 days.

If the end of treatment biopsy/surgical treatment is delayed beyond Day 22, participants may continue taking study agent for a maximum of 25 days. If biopsy/surgery cannot be rescheduled on or before Day 26, the participant will be unevaluable.

5.2 Study Agent Administration

5.2.1 Study agent will be dispensed by a pharmacist or member of the study team to be self-administered by the participant.

5.2.2 One bottle of study agent containing 25 tablets will be dispensed to a participant after their eligibility has been confirmed by the CLO and they are randomized.

5.2.3 The participant will be instructed to take one (1) tablet of study agent by mouth daily with a meal at about the same time each day. The tablet must be taken whole and should not be chewed, cut, opened or crushed.

5.2.4 If the participant is having an end of study follow-up PET-CT scan, they should be instructed to take their dose of agent with the last full meal allowed prior to the scan.

5.2.5 The final dose of study agent will be taken on the day prior to the participant's day 11-22 surgery or pre-non-surgical treatment biopsy.

5.3 Run-in Procedures

There is no run-in phase for this protocol

5.4 Contraindications

5.4.1 Do not take on an empty stomach.

5.4.2 Participants should not consume excessive amounts of alcohol as this may potentiate the effect of metformin on lactate metabolism. For females, this is more than 3 drinks on any day or a total of more than seven drinks in a week. For males, it is more than 4 drinks on any day or a total of more than 14 drinks in a week.

5.4.3 Do not combine with any exclusionary medications listed in section 4.2.

5.4.4 If a dose is missed, do not make up for the dose by double dosing the following day.

5.4.5 Administration of iodinated contrast agent in patients taking metformin can lead to an acute decrease in renal function and lactic acidosis. Medical tests involving the use of iodinated contrast agent include CT scan, angiography, venography, cystourethrography, hysterosalpingogram, and intravenous urography.

Participants will be instructed to inform study staff prior to undergoing any imaging studies (other than an FDG PET-CT scan which does not use iodinated contrast).

Participants who have recently had a CT scan with iodinated contrast (commonly used to stage oral/oropharyngeal cancers) must not start study agent until their eGFR has been assessed/re-assessed ≥ 48 hours after the scan and is found to be within normal limits. If it is not within normal limits, the study agent must be held until the eGFR is found to be within normal limits.

If the participant has not completed clinical staging at the time of the screening visit and a staging scan(s) is/are planned, study agent should not be started until the participant has completed any scans that will use iodinated contrast agent, and their eGFR has been re-assessed ≥ 48 hours after the scan. If it is not within normal limits, the study agent must be held until the eGFR returns to normal limits

Participants will be told to notify study staff if they are scheduled for a test using contrast agent after they have started study agent. The participant will be instructed to hold their dose of study agent on the day of the test and continue to hold study agent dosing until their eGFR is reassessed ≥ 48 hours after the scan and is found to be within normal limits. If it is not within normal limits, the study agent must be held until the eGFR is found to be within normal limits.

Consult with the institution performing the imaging study regarding any additional precautions they have in place.

5.4.6 Temporarily discontinue if participant will be undergoing any medical procedures requiring restricted intake of food or fluids.

5.4.7 Do not open, cut, crush or chew the tablets.

5.4.8 Keep the tablets tightly closed in their original container to keep them dry and protected from light exposure.

5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication worksheet and will include: start and stop date, dose and route of administration, and indication. Medications taken for a procedure (*e.g.*, biopsy) should also be included.

Use of any exclusionary medications is prohibited while the participant is taking study agent. Participants will be instructed to inform a member of the study staff of any new medications they are prescribed while on study prior to taking the medication.

5.6 Dose Modification

<table>
<tr><th rowspan="2">CTCAE v4 Grade</th><th colspan="2">Attribution to Study Agent</th></tr>
<tr><th>Unlikely/Unrelated</th><th>Possibly/Probably/Definitely Related</th></tr>
<tr><td>1</td><td colspan="2">• No modification unless the A.E. is unacceptable to the participant or the physician feels it is in the participant's best interest medically.
• If the A.E. may be related to dose timing, asses how the participant is dosing their study agent and if taking it at a different time of day or with a more substantial meal might help.
• If dose modification is necessary because taking the agent with a more substantial meal did not improve the event, the participant finds it unacceptable, or the physician feels it is in the participant's best interest medically, the participant may be instructed to take the study agent every other day.
• If none of these measures is successful and the A.E. is unacceptable to the participant or the physician feels it is in the participant's best interest medically, study agent should be discontinued. However, the participant, if willing, should still be followed per the protocol schedule of events and have all study procedures conducted.</td></tr>
<tr><td>2</td><td>• No modification unless the A.E. is unacceptable to the participant or the physician feels it is in the participant's best interest medically.
• If the A.E. may be related to dose timing, asses how the participant is dosing their study agent and if taking it at a different time of day or with a more substantial meal might help.
• If dose modification is necessary because taking the agent with a more substantial meal did not improved the event and the participant finds it unacceptable or the physician feels it is in the participant's best interest medically, the participant may be instructed to take the study agent every other day.
• If none of these measures is successful and the A.E. is unacceptable to the participant or the physician feels it is in the participant's best interest medically, study agent should be discontinued. However, the participant, if willing, should still be followed per the protocol schedule of events and have all study procedures conducted</td><td>• If the A.E. may be related to dose timing, asses how the participant is dosing their study agent and if taking it at a different time of day or with a more substantial meal might help.

• If the AE is unlikely to be related to dose timing or did not respond to taking the study agent at a different time of day or with a more substantial meal, instruct the participant to hold study agent until the AE resolves to ≤ Grade 1 then re-start on an every-other-day dosing regimen.

• If the AE recurs, discontinue study agent and do not re-start. However, the participant, if willing, should still be followed per the protocol schedule of events and have all study procedures conducted.</td></tr>
<tr><td>3</td><td rowspan="2">Hold study agent until consulting with the protocol's medical monitor and study chair. The medical monitor and study chair will advise whether study agent may or may not be restarted and whether a dose modification is indicated.</td><td rowspan="2">Discontinue study agent. Do not re-start. However, the participant, if willing, should still be followed per the protocol schedule of events and have all study procedures conducted.</td></tr>
<tr><td>4</td></tr>
</table>

<table>
<tr><td colspan="3">Hypoglycemia (The symptoms include):</td></tr>
<tr><td>Sweating, chills and clamminess</td><td>Nervousness/shakiness/anxiety</td><td>Hunger and nausea</td></tr>
<tr><td>Irritability/impatience/confusion</td><td>Weakness/fatigue</td><td>Rapid/fast heartbeat</td></tr>
<tr><td>Numbness/tingling in the lips or tongue</td><td>Blurred/impaired vision</td><td>Sleepiness</td></tr>
<tr><td>Anger/stubbornness/sadness</td><td>Lightheaded/dizziness</td><td>Headaches</td></tr>
<tr><td>Nightmares/crying out during sleep</td><td>Lack of coordination</td><td>Seizures/ Unconsciousness</td></tr>
<tr><td colspan="3">If a participant reports symptoms of hypoglycemia, instruct them to have their blood glucose level checked if possible:
If the blood glucose level is less than the lower limit of normal but ≥ 55mg/dL (grade 1 hypoglycemia), instruct the participant to switch to every other day dosing of the study agent. If this does not alleviate the participant's symptoms, instruct the participant to stop taking the study agent.
If the blood glucose level is <55-40 mg/dL (grade 2 hypoglycemia), instruct the participant to stop taking the study agent.
If the participant is unable to have their blood glucose checked, base the dose modification on the severity of their symptoms.
If the participant is experiencing grade 1 symptoms, and taking the study agent with a more substantial meal has not improved the symptom(s), instruct the participant to switch to every other day dosing. If this does not alleviate the symptom(s), instruct the participant to stop taking the study agent.
If the participant is experiencing grade 2 symptoms, instruct the participant to stop taking the study agent.</td></tr>
<tr><td colspan="3">*For immediate, short term management of hypoglycemic symptoms, instruct the participant to try one or more of the following:
Eat a handful of raisins or candy
Drink a glass of juice, milk, or a regular (non-diet) soda
Eat a small snack</td></tr>
<tr><td colspan="3">Jaundice: Discontinue study agent. Do not re-start. Perform liver function tests ASAP.</td></tr>
</table>

5.7 Adherence/Compliance

5.7.1 Participants will be considered compliant for purposes of evaluability of study end points if they have taken ≥ 80% of the prescribed doses of study agent.

5.7.2 The following 4 methods will be employed to monitor participants' compliance.

5.7.2.1 Pill Diary (Appendix B):
Upon randomization, participants will be provided with, and instructed on the use of, a pill diary. Participants will document daily dosing of the study agent on the pill diary, noting the date and time of day that the agent was taken. A "comments" column will be included in the table for participants to make a note of any missed doses, symptoms or adverse events they experience, as well as any changes to their concomitant medications. The pill diary will also include dosing instructions and important reminders about taking the study agent. Participants will be instructed to return the Pill Diary at their end of study visit. The study coordinator or designee will review the Pill Diary with the participant and both the reviewer and the participant will sign a verification of review of the Pill Diary.

5.7.2.2 Pill count:

Note: Due to a size discrepancy between the placebo and the active study agent, in order to preserve the study blind, pill counts should not be performed by a member of the study team. The count of returned tablets should be performed by the pharmacy or by an independent third party and reported to a member of the study team for documentation in the Visit Guide and compliance calculation.

Each participant will be provided with a single bottle of study agent containing 25 doses of study agent. Participants will be instructed to bring this study agent bottle and any unused tablets back with them to their end of study visit. The number of returned doses of study agent will be subtracted from the number of doses dispensed to calculate the number of tablets that were taken during the dosing period (Day 1 – end of study dose). This number will be divided by the number of doses of study agent expected to be taken had the participant taken the study agent daily as prescribed. The resulting number x 100 will equal the % compliance.

# of tablets taken ÷ # tablets prescribed for the dosing period = ___ x 100 = % compliance

5.7.2.3 Phone contact:

Each participant will receive an interim phone contact between their baseline and end of study visits to assess for adverse events, changes to concomitant medications and compliance with taking study agent and completion of the Pill Diary

5.7.2.4 Pioglitazone analysis:

Blood samples will be collected at the baseline and end of study visits to measure pioglitazone concentration.

6. PHARMACEUTICAL INFORMATION

6.1 ACTOplus met® XR IND Exempt (132630)

ACTOplus met® XR (Takeda Pharmaceuticals America, Inc., Deerfield, IL) is a fixed-dose combination (FDC) drug of pioglitazone immediate-release combined with metformin extended-release. This FDC is approved as an adjunct to diet and exercise to improve glycemic control for patients with type 2 diabetes mellitus. Pioglitazone is an agonist of peroxisome proliferator-activated receptor γ (PPARγ), a ligand-activated nuclear transcription factor belonging to the steroid receptor superfamily that is a key regulator of insulin-responsive genes involved in the control of glucose and lipid metabolism as well as adipogenic differentiation. While originally believed to be adipocyte-specific, accumulating data show that PPARγ is also expressed in normal liver and skeletal muscle and in neoplastic tissue, including breast, colon, prostate, and lung. PPARγ activation by pioglitazone in breast, colon, and lung cancer cell lines leads to differentiation and/or apoptosis [16-18; 21]. Consistent with the cell observations, mouse xenograft studies using breast and colon cancer cell lines have shown significant reduction in tumor size after treatment with pioglitazone compared with vehicle controls, with induction of apoptosis in the breast tumors [17; 18]. Pioglitazone was also effective in multiple different carcinogen-induced cancer models, such as colon, lung, and oral squamous cell carcinoma [22; 23; 25; 54].

Metformin, a first-line drug commonly used to treat diabetes mellitus, also inhibits cell growth. Besides inhibiting gluconeogenesis, this biguanide derivative indirectly activates adenosine monophosphate-activated protein kinase (AMPK) in cells by a liver kinase B1 (LKB1)-dependent mechanism. AMPK appears to be a key molecular target for cancers associated with diabetes mellitus and obesity since it is activated under conditions of decreased energy, such as low glucose, hypoxia, or ischemia [28; 29]. Activation of AMPK inhibits mammalian target of rapamycin (mTOR) via tuberous sclerosis complex 2/1. Exposure of breast cancer cells to metformin decreases phosphorylated AKT and activation of

mTOR, resulting in inhibition of cell proliferation and an increase in apoptosis [30]. Metformin also has indirect anti-proliferative effects related to lower systemic levels of insulin.

An NCI, DCP-sponsored nonclinical study evaluated the combination of metformin and pioglitazone for synergistic or additive effects in cancer prevention. In a benzo[*a*]pyrene-induced lung carcinogenesis model, mice were administered metformin (850 mg/kg-bw/day), pioglitazone (15 mg/kg-bw/day), or the combination (same doses) for nine weeks after the last carcinogen dose, with animal sacrifice seven weeks later. Metformin alone caused a 37% reduction ($p<0.01$) in tumor multiplicity compared with control treatment, whereas pioglitazone alone resulted in a 17% reduction (non-significant) [52]. The metformin plus pioglitazone combination reduced tumor multiplicity by 44% compared with control treatment, suggesting that the two agents work together to reduce tumor multiplicity.

The formulated drug product, ACTOplus met® XR, contains 30 mg pioglitazone and 1000 mg metformin hydrochloride, along with the following inactive excipients: candelilla wax, cellulose acetate, povidone, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycols (PEG 400, PEG 8000), sodium lauryl sulfate, titanium dioxide, and triacetin. The tablet consists of an extended-release, osmotically-active core of metformin surrounded by a semipermeable membrane and coated with a pioglitazone drug layer. Two laser-drilled exit ports exist in the membrane, one on either side of the tablet. The semipermeable membrane is permeable to water but not to higher molecular weight components of biological fluids. Upon ingestion, the pioglitazone layer is dissolved; water is then taken up through the membrane, which in turn dissolves the metformin core and excipients, which exit through the laser-drilled ports in the membrane. The rate of drug delivery is constant and dependent upon the maintenance of a constant osmotic gradient across the membrane. The membrane coating remains intact during the transit of the dosage form through the gastrointestinal tract, and is excreted in the feces.

Matching placebo tablets will be manufactured containing lactose monohydrate, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

6.2 Reported Adverse Events and Potential Risks

According to the US prescribing information (PI) for ACTOplus met® XR, there have been no clinical efficacy studies conducted with the single-tablet drug product, only pharmacokinetic bioequivalence studies have been conducted. However, two clinical studies have been conducted of co-administration of separate tablets of pioglitazone (pio) *vs*. placebo (pcb) as an add-on to metformin (met). The most common adverse events (AEs) seen in pio/met more commonly than pcb/met were edema (6.0% *vs*. 2.5% of patients) and headache (6.0% *vs*. 1.9%). In an uncontrolled trial comparing two different dose levels of pioglitazone, the most common AEs that were increased in 45 mg pio/met compared with 30 mg pio/met were: edema (13.9% *vs*. 5.8%), upper respiratory tract infection (13.5% *vs*. 12.4%), increased weight (6.7% *vs*. 2.9%), and headache (5.8% *vs*. 5.4%). One AE of congestive heart failure (CHF) resulting in hospitalization was observed for both doses of pio co-administered with met (1/168 on 30 mg pio/met; 1/416 on 45 mg pio/met), whereas no patients on pcb/met developed CHF. Modest weight gain was seen with both doses of pio/met (+0.9 kg 30 mg pio/met, +1.8 kg 45 mg pio/met) compared with weight loss on pcb/met (–1.4 kg).

Common AEs observed for pioglitazone monotherapy *vs*. placebo from two pooled studies of 16 and 26 weeks' duration were: upper respiratory tract infection (13.2% *vs*. 8.5%), headache (9.1% *vs*. 6.9%), sinusitis (6.3% *vs*. 4.6%), myalgia (5.4% *vs*. 2.7%), and pharyngitis (5.1% *vs*. 0.8%). For a longer pioglitazone monotherapy study (mean duration of follow-up 34.5 months) the most common AEs compared with placebo were: hypoglycemia (27.3% *vs*. 18.8%), edema (26.7% *vs*. 15.3%; reversible upon drug discontinuation), cardiac failure (8.1% *vs*. 6.1%), pain in extremity (6.4% *vs*. 5.7%), back pain (5.5% *vs*. 5.1%), and chest pain (5.1% *vs*. 5.0%). Additionally, pioglitazone monotherapy results in

significant weight gain compared with placebo, after a median of 2.7 years, pioglitazone resulted in a median +3.6 kg *vs*. –0.5 kg for placebo. An elevated incidence of bone fractures was observed only for women on pioglitazone compared with placebo (5.1% vs. 2.5%) after a mean follow-up of three years. Finally, post-marketing reports of macular edema (uncovered due to blurred vision or by ophthalmologic exam) in some patients has been reported.

In a meta-analysis comparing safety and effectiveness of diabetes drug therapies, Bennett *et al*, [55] analyzed hypoglycemia risk by pooling data from randomized, active-controlled studies. For combination treatment of metformin with either pioglitazone or rosiglitazone, in comparison with metformin alone, the combination of metformin with a thiazolidinedione barely increased the low hypoglycemia event frequency, 3.3%, (51/1530 patients) compared with metformin monotherapy, 2.2% (34/1543 patients). In a different set of pooled studies, a similar low hypoglycemia frequency was seen for the same combination metformin plus thiazolidinedione arm, 3.8% (32/853 patients) in comparison with the combination of metformin plus a sulphonylurea, 24.3% (198/816). When all patients treated with the combination of metformin plus thiazolidinedione in the two different set of studies were combined, the cumulative frequency of hypoglycemia remained very low, 3.5% (83/2383).

The most common AEs observed for metformin monotherapy *vs*. placebo were: diarrhea—most common AE drop reason (53.2% *vs*. 11.7%), nausea/vomiting (25.5% *vs*. 8.3%), flatulence (12.1% *vs*. 5.5%), asthenia (9.2% *vs*. 5.5%), indigestion (7.1% *vs*. 4.1%), abdominal discomfort (6.4% *vs*. 4.8%), and headache (5.7% *vs*. 4.8%). Serum vitamin B12 concentrations have been found to be lower with long-term metformin monotherapy. Pioglitazone treatment led to an increased incidence of bladder cancer in two-year carcinogenicity studies compared with placebo treatment. However, in human clinical studies the incidence of bladder cancer is slightly elevated with pioglitazone monotherapy compared with placebo, though wording on the PI indicates that there are too few events of bladder cancer to establish causality to pioglitazone.

Two serious, rare AEs are highlighted in the PI boxed warning. The first is congestive heart failure, which may be caused or exacerbated by pioglitazone. The second is lactic acidosis due to metformin accumulation in the context of another co-morbidity such as sepsis, dehydration, excess alcohol intake, hepatic or renal impairment, and acute congestive heart failure. Participants should be carefully monitored for and encouraged to report immediately any signs and symptoms of congestive heart failure or lactic acidosis after initiating study treatment. These symptoms of congestive heart failure include: excessive, rapid weight gain, dyspnea, and/or edema. Symptoms of lactic acidosis include malaise, myalgia, respiratory distress somnolence and abdominal pain. Upon report or finding of any of these symptoms, the participant should be instructed to discontinue taking the study agent immediately and brought in for evaluation. Suspected lactic acidosis should be managed in a hospital setting.

Based on the safety profile of pioglitazone and metformin as monotherapy and as a drug combination, ACTOplus met® XR should not be used in patients with heart failure, renal impairment, liver disease, or history of or active bladder cancer. Additionally, metformin may lower vitamin B12 levels, and pioglitazone may reduce hemoglobin and/or hematocrit; thus, these should be monitored annually.

6.3 Availability

Blinded ACTOplus met® XR (pioglitazone and metformin hydrochloride extended-release) tablets (Takeda Pharmaceuticals America, Inc., Deerfield, IL) with 30 mg and 1000 mg of agents, respectively, is an investigational agent supplied by NCI, DCP. Blinded matching placebo tablets will also be supplied by NCI, DCP. These agents will be distributed through the DCP Repository, MRIGlobal.

6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents). These Essential Documents should be submitted to the CLO for processing. When a site has submitted all of the required documents, the DCP's Regulatory Contractor will issue Drug Shipment Authorization for that site. No study agent will be shipped to a site until the Drug Shipment Authorization has been issued and a study initiation visit or teleconference has been completed.

The request for study agent to be shipped to each site will be generated by the CLO using the DCP Clinical Drug Request form (NIH-986). At the time of study initiation, the CLO will request complete shipping contact information for the site's investigational pharmacy. If the site does not have an investigational pharmacy, the complete shipping contact information for the person responsible for study agent accountability at the site will be requested. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). The CLO will submit study agent requests to:

John Cookinham
MRIGlobal
DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800

Participants in this study are randomized on a 2:1 ratio of ACTOplus met® XR:placebo using permuted blocks of 3. Prior to study activation, study statisticians will provide MRIGlobal with a sequential list of 5-digit randomization numbers divided into blocks of 3. Each randomization number will be linked to a treatment assignment - active study agent (ACTOplus met® XR) or placebo. Within each block of 3 randomization numbers, two of the numbers will be assigned to active study agent and one will be assigned to placebo. The CLO will be provided with the list of randomization numbers in blocks of 3 but will not receive the treatment assignment information. Only MRIGlobal and the study statisticians will have access to the treatment assignment information.

When a site is issued Drug Shipment Authorization and has completed study initiation, the CLO will submit a request to MRIGlobal for a block of 3 bottles of study agent to be shipped to the site. Each study participant is dispensed one bottle of study agent containing 25 tablets. Each block consists of study agent supply for 3 participants (3 bottles). The CLO will provide the site with the randomization number for a study participant after the CLO verifies the participant's eligibility. The site will then request the bottle bearing that randomization number from their pharmacy.

When a site has dispensed two of the 3 bottles in the block, the CLO will discuss shipment of another block of 3. Shipment of subsequent blocks will be determined by the number of accruals allotted to the site in their sub-award and the rate at which the site is able to accrue participants.

6.5 Agent Accountability

The Investigator at each site, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug

Accountability Record Form (DARF) or equivalent form. The Investigator is required to maintain adequate records of receipt, dispensing, and final disposition of study agent. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity, and randomization. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

Blinded ACTOplus met® XR/Placebo will be packaged by NCI, DCP and supplied in bottles of 25 tablets.

A two (2)-part label will be attached to each bottle of study agent. The fixed part of the label will remain attached to the bottle and will have the following identifying study specific information:

Study title: Phase IIB Randomized, Placebo-Controlled Trial of ACTOplus met® XR in Subjects with Stage I-IV Squamous Cell Carcinoma of the Oral Cavity or Oropharynx Prior to Definitive Treatment
DCP protocol number: UWI2016-07-01
Dosing Instructions: Take one (1) tablet once a day with a meal. Do not chew, cut or crush the tablets.
Recommended storage conditions: Room temperature 20–25ºC (68–77ºF)
Pre-generated randomization number:
Space for Participant ID number:
Space for Dispensing Date:
Caution statement: The agent is limited by United States law to investigational use only. The agent should be kept out of the reach of children.

The tear-off portion of the label will contain a scratch off area with study agent unblinding information. This portion of the label will be removed from the bottle at the time of dispensing and kept in a central location while a participant is active on the study. Upon a participant's completion of the study, if the unblinding labels were not previously stored in the participant's study binder, they should be transferred there and affixed to a source document that will be provided by the CLO in the study Visit Guides.

The tear-off portion of the label will display the following information:

Drug: Placebo or ACTOplus met® XR
Dose: 0 or pioglitazone 30 mg and metformin 1000 mg
Pre-generated randomization number:
Space for Participant ID number:
Space for Dispensing Date:

6.7 Storage

ACTOplus met® XR tablets should be stored at 20–25ºC (68–77ºF) in a secure, locked area of the research facility, with excursions permitted to 15–30ºC (59–86ºF). It will be dispensed in light-resistant containers.

6.8 Registration/Randomization

6.8.1 Registration:
Each participating organization (PO) will be issued a sequential list of unique participant identification (PID) numbers for this protocol. Each potential study participant will be assigned the next available PID

number from the list immediately upon signing the informed consent form (ICF) for the protocol. By signing the ICF, the candidate is considered registered to the study. The University of Wisconsin is the Consortium Lead Organization (CLO) for this protocol. The CLO must be notified of registration of a study participant within 24 hours of the participant signing the ICF.

6.8.2 Randomization:
Participants who meet the eligibility criterial for the protocol will be randomized by the CLO. The PO will request randomization of a study participant by submitting (via fax or e-mail) the following documents to the CLO:

Informed Consent Form
Eligibility Questionnaire
Clinical safety/Eligibility lab report
Pre-study diagnostic biopsy report
Medical/Surgical History Worksheet

(Note: all documents submitted to the CLO must have personally identifying information deleted or completely obscured and be re-identified with the participant's PID number. Documents with visible personally identifying information will not be accepted.)

A CLO coordinator will review these documents and confirm that the participant meets the eligibility criteria and that the correct version of the ICF was signed. If eligibility is confirmed, the CLO coordinator will assign the next randomization (bottle) number in sequence for that site from a randomization list that will be pre-generated by the Statistical Center at UWCCC, as described in Section 6.4. The CLO will notify the site of the randomization number assigned to the participant. This number will correspond to the randomization number of one of the bottles of study agent issued to the site. That bottle will be requested from the site's pharmacy or other entity delegated the responsibility of study agent accountability following the site's institutional policy for requesting and dispensing study agent.

Study agent should not be started within 48 hours following administration of an iodinated contrast agent (commonly used in a staging CT scan). The participant's eGFR must be assessed ≥ 48 hours after the scan and the result must be within normal limits (see section 5.4.5) before starting study agent. To avoid missing doses of study agent (which could potentially render the participant unevaluable) if a staging test using iodinated contrast agent is planned, do not start the participant on study agent until the scan has been completed and their ≥ 48 hour post scan eGFR is confirmed to be within normal limits.

6.9 Blinding and Unblinding Methods

To ensure this trial is conducted in a double-blinded manner, the randomization code will be maintained in a password-protected database by the Statistical Center at UWCCC. Unblinding will not occur until all participants have completed the study and study data collection and analysis has been completed.

If a participant experiences a medical issue that requires knowledge of the intervention assignment for appropriate medical management, the assignment may be determined by removing the scratch-off label on the tear-off portion of the study agent bottle label. The following process should be followed:

6.9.1 The treating physician contacts the Protocol Principal Investigator, Frank Ondrey, M.D. with the request to unblind.

Frank Ondrey, M.D., PhD
Associate Professor of Otolaryngology, University of Minnesota

MMC 396
420 Delaware ST SE
Minneapolis, MN 55455
612-625-3200
Fax 612-626-9871
E-mail address: ondre002@umn.edu

6.9.2 The request will be approved upon the agreement of the NCI medical monitor for the protocol.

Please note: If the PI or medical monitor is unavailable to provide consent to unblind in a timely fashion, and it is in the participant's best interest not delay unblinding, the blind may be broken without waiting for PI or medical monitor consent. The following steps will still be followed:

6.9.3 The requesting site will notify the CLO (prevention@uwcarbone.wisc.edu) immediately of the unblinding.

6.9.4 The unblinding process will be documented in the participant's study chart.

6.9.5 The participant will be removed from the study.

6.9.6 The CLO will submit formal notification that the blind has been broken to the NCI Medical Monitor.

Eva Szabo, MD
Chief, Lung & Upper Aerodigestive Cancer Research Group
NCI/Division of Cancer Prevention
9609 Medical Center Drive, Room 5E-102, MSC 9781
Bethesda, MD 20892-9781 (For FedEx, use Rockville, MD 20850)
Phone: (240) 276-7011
FAX: (240) 276-7848
email: szaboe@mail.nih.gov

6.10 Agent Destruction/Disposal

DCP-supplied agents: at the completion of investigation, all unused study agent will be returned to NCI, DCP Repository according to the DCP "Guidelines for AGENT RETURNS" and using the DCP form "Return Drug List".

The Guidelines and form are available on the DCP website.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Evaluation/ Procedure	Registration	Screening /Baseline Visit[1]	Randomization	Day 1	Day 5-7 Interim Phone Contact	Final Dose Reminder Call 12-72 hrs. prior to final dose time	End of Study (Day 11-22[2]) or Early Termination
Informed Consent	X						
Assess Eligibility		X					
Medical/Surgical History		X					
Baseline Symptom Assessment		X					
ECOG performance status		X					
Physical Exam		X					X
Height		X					
Weight		X					X
Vital Signs (T,P,R, BP)		X					X
Clinical Safety/ Eligibility Laboratory Tests (CBC with differential, CMP, Urine Pregnancy Test[3])		X					X
Blood for Pioglitazone Analysis		X					X
Tobacco and Alcohol Use Assessment		X					X
Biopsies for Tissue Biomarkers[4]		X[5]					X[6]
Concomitant Medications		X			X		X
Adverse Events					X		X
Dispense Study Agent			X				
Dose Study Agent				X[7]		X[8]	
Collect Study Agent							X
Review Agent Diary/Record			X				X
FDG-PET/CT scan[9]							X
Telephone Contact					X[10]	X[11]	

1. Within 30 days prior to Day 1 of study agent dosing.
2. May be extended up to Day 26 if participant is scheduled for surgical excision of their cancer and surgery is delayed.
3. For women of childbearing potential only.
4. Tissue Biomarkers: Tumor and normal appearing tissue samples: Proliferation index: Ki-67 expression and Cleaved Caspase 3 Immunohistochemical analyses (tumor tissue only): Cyclin D1 (ISO83), p21 (P21 Waf1/Cip1), p AKT, p AMPK, p s6, PPARγ, PD1, PD-L1, T helper (CD4), T suppressor (CD8), Fox p3 (TREG), Tumor Associated Macrophage (CD68), and p16. (HPV testing via p16 will be performed only on the baseline sample.)
5. Biopsy(baseline): 4 mm biopsy of lesion and adjacent visually normal appearing tissue
6. End of study surgery or biopsy: If participant is having a resection, collect a 4 mm biopsy of the visually normal appearing tissue adjacent to the tumor and 2 mm of tissue from the tumor. If participant will NOT be having surgical treatment, collect a 4 mm biopsy of tumor tissue as well as a 4 mm biopsy of the adjacent visually normal appearing tissue in clinic.
7. The date the first dose of study agent is taken is considered Day 1.
8. The final dose of study agent will be timed to allow for collection of a PK trough level. The participant will be instructed to take their final dose of study agent as close to 24 hours (no more than 26 hours) prior to the collection of their end-of-study PK sample as possible.
9. FDG-PET/CT: Skull base to thigh. To be performed only on those participants who have had a standard of care staging FDG-PET/CT performed prior to starting study intervention. The participant must have completed a minimum of 10 days of study agent dosing prior to conducting the end of study FDG-PET/CT scan. The scan will be scheduled as close as possible to the date the end of study tissue biopsies are collected.
10. At this contact, the participant will be reminded that their final dose of study agent will be timed against the anticipated time of the End of Study Visit blood draw.
11. This contact will be made 2-72 hours prior to the participant's final day of study agent dosing to remind the participant what time they should take their final dose so that it occurs as close as possible to 24 hours (without going over 26 hours) prior to anticipated time of their End of Study Visit blood draw.

7.2 Baseline Testing/Prestudy Evaluation

7.2.1 Informed Consent

Written informed consent will be obtained for all potential study participants prior to conducting any research procedures. The date and time the informed consent was obtained will be documented in the participant's study records. The participant will be provided with a copy of their signed informed consent form.

7.2.2 Registration

Upon signing informed consent, the participant is assigned the next available PID number from the sequence of PID numbers provided by the CLO at the time of study initiation and is considered registered to the study. The CLO will be notified by fax (608-265-3287) or e-mail (prevention@uwcarbone.wisc.edu) within 24 hours of registration of a potential candidate to ensure accurate and timely tracking of accrual. Participating Organizations will not be reimbursed for a participant screening/baseline visit if the number of participants screened exceeds the number of screening units allotted to the site.

Participant registrations will be entered into the OnCore database by CLO staff.

If a consented study candidate is deemed ineligible (i.e. a screen failure), the following documents (to be provided to the PO at study initiation) will be submitted to the CLO:

- The Screening/Baseline Visit Guide
- Eligibility Questionnaire
- De-identified copy of the participant's informed consent form
- Off Study form
- Verification form
- Adverse Event Tracking Worksheet (If the participant has not experienced an adverse event during the screening process or as a result of the screening/baseline visit procedures, check the "none" box at the top of the Worksheet)

In addition, any blood and tissue samples collected for research purposes only will be destroyed and the destruction of the samples will be documented on the Eligibility Questionnaire.

7.2.3 Medical/Surgical History

The participant's medical/surgical history will be obtained and documented on the Medical Surgical History Worksheet.

7.2.4 Physical Exam and Vital Signs

The physical exam will consist of an evaluation of the participant's general state of health and will include at minimum an ENT exam and evaluation of the chest, heart abdomen, and extremities. The presence/absence of edema and signs/symptoms of congestive heart failure will be noted. ECOG performance status (see appendix A) will also be assessed and noted. Vital sign assessment will include temperature and resting (measured after participant has been seated for at least 5 minutes) pulse, respiratory rate and blood pressure. Height and weight will also be measured.

NOTE: If the participant had a physical exam/vital sign assessment as part of their standard medical care within 30 days of the anticipated study agent start date, and a copy of the clinic note can be obtained for the study chart, the physical exam/vital signs do not need to be repeated unless there is reason to expect the findings may have changed in the interim. Do note however, that it is unlikely that a standard of care physical assessment would address all of the additional elements required for eligibility for this protocol. Any of the following that are not specifically addressed in the clinic note, must be assessed during screening to determine eligibility:

- ECOG performance status
- Edema
- Signs/symptoms of congestive heart failure
- HEENT, Chest, Heart and Abdomen exam
- Temperature, pulse, respirations, blood pressure (after sitting 5 minutes), height and weight

7.2.5 Collection of Blood Samples for Clinical Safety/Eligibility and Pioglitazone Analysis;

- CBC with differential, comprehensive metabolic panel, and urine pregnancy test (for women of childbearing potential) - using the institution's clinical lab supplies and policies/procedures for obtaining these samples).

  NOTE: Request STAT processing if the clinical lab results are needed ASAP to confirm eligibility prior to tissue sample collection. (Study candidates who have already had a diagnostic biopsy require full confirmation of eligibility before tissue samples are collected for biomarker analysis. Study candidates with a suspicious lesion who will have their tissue samples collected in conjunction with a diagnostic biopsy do not require clinical eligibility lab results prior to the collection of tissue samples.)

- Blood for pioglitazone analysis: Supplies for the collection and storage of research blood samples will be provided by the University of Wisconsin's CP Lab. Instructions for the collection, processing, storage and shipping of research blood and tissue samples are in sections 10.2 and 10.3 of this protocol.

NOTE: If the participant had blood tests as part of their standard medical care within 30 days of the anticipated study agent start date, and a copy of the laboratory report [including the reference (normal) range for the test can be obtained for the study chart], those tests do not need to be repeated. If the testing is incomplete (i.e. some, but not all of the required blood tests were obtained) only the missing tests need to be performed. Blood samples for research will also need to be collected at the time of screening.

7.2.6 Concomitant Medications

The participant's use of prescription and over-the-counter medications; herbal remedies; vitamins and supplements will be documented on the Concomitant Medications Worksheet provided by the CLO at study initiation. The medication name, date reported, dosing regimen, indication, start date (at minimum the estimated start year), and stop date, will be recorded. Participants will be instructed to report any new medications they are prescribed while on study before they start taking them to ensure they are not contra-indicted. Medications taken for a procedure during study participation will be documented as well.

7.2.7 Baseline Symptoms

Any current/active signs and symptoms experienced by the participant will be documented as Baseline Symptoms. This will include any abnormal laboratory values at baseline that are deemed clinically

significant. A baseline symptom that increases in grade during the course of the study will be documented as an adverse event at the increased grade level. The AE onset date is the date on which the increase in severity occurred. A baseline symptom that resolves during the course of the study then recurs will be documented as an adverse event starting on the date of recurrence.

7.2.8 Eligibility Assessment

The Eligibility Questionnaire, provided by the CLO as part of the Visit Guides for this protocol, will be completed and signed by the person administering the Questionnaire. It will then be reviewed and verified by a site investigator. In the case of a candidate with a suspicious lesion that is not yet histologically confirmed, the Eligibility Questionnaire will remain pending until there is histologic confirmation of cancer. In the case of a candidate whose baseline tissue samples for biomarker assay were obtained in conjunction with a diagnostic DL biopsy, the Eligibility Questionnaire will remain pending until there is histologic confirmation of cancer AND it has been determined that the patient's first line treatment will be surgical.

7.2.9 Administer baseline tobacco and alcohol use assessments (Appendix D).

7.2.10 Tissue Biopsy

Note: To avoid subjecting study candidates to an additional invasive procedure, tissue samples for research will not be collected from a study candidate who has already had a diagnostic biopsy until it has been verified that the candidate meets all of the eligibility criteria for the study including the clinical eligibility labs.

Candidates with a lesion suspicious for cancer who have not yet had a diagnostic biopsy, may have tissue samples for research collected in conjunction with their diagnostic biopsy prior to the collection and resulting of the clinical eligibility labs provided it has been verified that they meet all other eligibility criteria. These candidates will not be randomized until the following criteria are met:

- The protocol required clinical labs have been resulted and the eligibility labs are within the required range.
- The clinical diagnostic biopsy confirms the presence of squamous cell carcinoma or squamous cell carcinoma in situ.

Two (2) four (4) mm biopsies will be obtained, one from the primary lesion and one from an area of visually normal appearing tissue adjacent to the primary lesion.

Refer to section 7.6.1 Tissue biopsy procedures, for instructions on obtaining these samples.

7.2.11 When a candidate is found to be eligible, follow the instructions in section 6.8 *Registration/ Randomization* to request randomization.

7.2.12 Drug Dispensing and Compliance Instructions

Participants will be instructed on the importance of compliance with the study agent dosing instructions and (refer to section 5. Agent Administration). Participants will be given a pill diary (Appendix B) and instructed to document each day the date and time they took their study agent. If a dose is missed or a tablet is lost, the participant should be instructed to note the reason in the "Comments" section for that day. The participant should also be instructed to use the "Comments" section to document any side effects, symptoms, or health events experienced and any new medications taken. The participant will be

instructed to initial each day's entry.

The bottle of study agent dispensed to the participant must be accounted for by the PO. The participant will be instructed to return their bottle of study agent (whether it is empty, partially full, or full) and all unused tablets of study agent at their end of study visit. **Note: Due to a size discrepancy between the placebo and the active study agent, in order to preserve the study blind, pill counts should not be performed by a member of the study team. The count of returned tablets should be performed by the pharmacy or by an independent third party and reported to a member of the study team for documentation in the Visit Guide and compliance calculation.**

Study agent may be shipped to the participant via overnight courier if the participant is unable to return for in-person dispensing. The participant's receipt of the study agent will be verified. A copy of the shipping receipt and verification of delivery will placed in the participant's study record.

7.3 Evaluation During Study Intervention

7.3.1 Interim Phone Contact

The participant will be contacted on day 5-7 to assess for adverse events and study agent dosing compliance. Adverse Events will be documented on the Adverse Event Worksheet (provided by the CLO at study initiation). The participant will be asked if they have experienced any symptoms or events since the date they signed informed consent for the study. For each event reported document the participant's verbatim description of the event, date reported, onset and end dates, CTCAE v4 term and severity grade, the action taken, outcome, whether the event was a Serious Adverse Event or not, whether the participant dropped from the study due to the event, and the MD's assessment of attribution of the event to the study agent. At this contact, the Concomitant Medication Worksheet will also be reviewed and updated. The participant will be reminded to report any new medications prior to taking them to ensure they are not contraindicated.

7.3.2 Final Dosing Reminder Call

There are several criteria to be taken into account when determining when the participant should take their final dose of study agent.

- The participant must take study agent for a minimum of 10 days.
- The participant must not take a dose of study agent on the day their end-of-study tissue samples are collected.
- The end-of-study PK sample must be drawn approximately 24 hours but no more than 26 hours after the participant takes their final dose of study agent.
- The study agent must be taken with a meal. However, participants are instructed not to eat or drink anything for 6 or more hours prior to their PET/CT scan.

Therefore, depending on whether or not the participant is having and end of study PET/CT scan and when that scan is will occur, in some cases the final dose of study agent will need to be taken and the end-of-study blood samples will need to be collected prior to the PET-CT unless there is sufficient time for the participant to take a dose of study agent after their PET-CT but 24 hours prior to collecting the PK sample on the day of the end-of-study biopsy or surgery. The date and time the participant takes their final dose of study agent will be documented.

7.4 Evaluation at Completion of Study Intervention

7.4.1 PET/CT

Prior to the end of study tissue collection, a skull base to thigh PET/CT using FDG will be conducted if the participant has a standard of care staging FDG-PET/CT prior to starting study intervention. When possible, both procedures may be scheduled on the same day. In many cases there may not be sufficient time to allow this, particularly in the case of participants who are scheduled for surgical excision of their tumor. The PET/CT should be performed as close to the date of the collection of the tissue samples as possible, but at a minimum, the participant must have completed at least 10 days of study agent dosing prior to the scan. The study budget includes funds to cover lodging if a participant needs to stay overnight because the PET-CT and end of study visits are scheduled on separate days. Note that the PET/CT must be performed before the end of study tissue samples are collected.

Refer to section 7.6.2 for the reporting methods for this procedure.

7.4.2 Physical Exam and Vital Signs

The physical exam will consist of an evaluation of the participant's general state of health and will include at minimum an ENT exam and evaluation of the chest, heart abdomen, and extremities. The presence/absence of edema and signs/symptoms of congestive heart failure will be noted. Vital sign assessment will include temperature and resting (measured after participant has been seated for at least 5 minutes) pulse, respiratory rate and blood pressure. Weight will also be measured. The participant's weight at this visit will be compared to their weight at the baseline visit. If the participant has gained more than 5 pounds since the baseline visit, a more thorough evaluation for signs and symptoms of congestive heart failure should be performed.

7.4.3 Collection of Blood Samples for Clinical Safety and Research

The following end of study blood samples will be collected:

- A CBC with differential and comprehensive metabolic panel (using the institution's clinical lab supplies and policies/procedures for obtaining these samples).

- Blood for pioglitazone trough levels: Supplies for the collection and storage of plasma for pioglitazone analysis will be provided by the University of Wisconsin's CP Lab. To obtain an accurate pioglitazone trough level, the participant should be instructed to take their final dose of study agent approximately 24 hours (but no more than 26 hours) prior to when this blood sample will be obtained. It is imperative that the date and time of the last dose of study agent is accurately documented in the Visit Guide for this study visit. Instructions for the collection, processing, storage and shipping of research blood and tissue samples are in sections 10.2 and 10.3 of this protocol.

7.4.4 Concomitant Medications

The Concomitant Medications Worksheet will be reviewed with the participant and updated if any medication doses have changed, the participant stopped taking a medication, or a new medication was taken. Medications taken for a procedure [e.g. the dose of fluorodeoxyglucose (FDG) and any medications given prior to the end of study tissue biopsy or surgery] will be included on the worksheet as well as stop dates for any medications the participant is instructed to stop taking prior to the end of study tissue biopsy or surgery. Tracking of concomitant medications will end at the conclusion of the end-of-study visit. If the participant is having surgical excision of their lesion at the end of the study, tracking of

concomitant medications ends after the end-of-study procedures are completed and the participant is admitted to surgery.

7.4.5 Adverse Events Assessment

The Adverse Events worksheet will be reviewed with the participant and updated. The participant will be asked if they have experienced any symptoms or events since the date they signed informed consent for the study. For each event reported, document the participant's verbatim description of the event, date reported, onset and end dates, CTCAE v4 term and severity grade, the action taken, outcome, whether the event was a Serious Adverse Event or not, whether the participant dropped from the study due to the event, and the MD's assessment of attribution of the event to the study agent.

7.4.6 Administer follow-up tobacco and alcohol use assessments (Appendix D).

7.4.7 Tissue Biopsy

Obtain two, 4 mm tissue samples: one from the primary tumor and one from an area of visually normal appearing tissue adjacent to, but 1 cm away from, the primary tumor. If the participant is having surgical excision of their tumor, obtain the tissue samples for research during surgery.

If the surgical excision will be delayed beyond day 26 after the first dose of study agent, the tissue samples may be obtained in the clinic within the study window if the participant is willing. Ideally, the biopsies would be obtained between days 11 and 22 but may be obtained up to day 26 and still be evaluable provided the participant continues to take study agent up until the day prior to obtaining the samples.

7.5 Post-intervention Follow-up Period

There is no post-intervention follow-up period for this protocol.

7.6 Methods for Clinical Procedures

7.6.1 Tissue biopsy procedures

At baseline, two (2) four (4) mm biopsies, one of the primary oral/oropharyngeal tumor and one of visually normal appearing mucosa adjacent to, but at least 1cm away from the tumor, will be obtained.

Half of each sample will be processed for RNA-seq analysis. The other half will be formalin-fixed and paraffin-embedded.

Have available:

- A 4 mm biopsy punch (If the lesion is not accessible by biopsy punch, alternative tools sufficient to yield a 4 mm piece of tissue with the epithelium intact may be used.)
- Two, 2 mL cryovials containing 0.5cc of RNAlater (see section 10.2.2 Collection and Handling Procedures: Biopsy for instruction on the preparation and processing of the cryovials).
    - One labeled "Normal (Baseline)"
    - One labeled "Tumor (Baseline)"

- Two clinical specimen containers of 10% formalin.
    - One labeled "Normal (Baseline)"
    - One labeled "Tumor (Baseline)" – If this sample will be used for diagnostic purposes, (i.e. the candidate has not yet had a diagnostic biopsy), submit this sample for clinical histopathology following institutional standard practice.

Please note that the Consortium is unable to supply RNAlater or formalin filled specimen containers in the lab kits for this study. Each participating organization will need to order or find a source for RNAlater and use formalin filled specimen containers from the clinical supply.

Also, note that clinical histopathology is not required for the visually normal appearing tissue biopsies and the tumor tissue sample that is collected for research purposes only in participants who have already had a diagnostic biopsy. The study budget does not include funds to cover the cost of clinical histopathology.

Obtain the tissue samples:

- Using a 4 mm biopsy punch or alternative method, remove a 4 mm piece of visually normal appearing mucosa adjacent to, but at least 1 cm away from, the tumor/suspicious lesion.
- Using a 4 mm biopsy punch or alternative method, remove a 4 mm piece of the tumor/suspicious lesion.

Using great care not to mix up the two tissue types, place each tissue sample, mucosa side up, on a clean hard surface.

Visually Normal Appearing Tissue:

Using a scalpel, carefully separate the epithelium from the subcutaneous tissue (the amount of subcutaneous tissue included in the sample should be minimized). Cut the epithelium in half. Place one of the halves in the RNAlater cryovial labeled "Normal (Baseline)". Place the other half in a container of 10% formalin.

Tumor tissue from a histologically diagnosed lesion:

Using a scalpel, carefully separate the epithelium from the subcutaneous tissue (the amount of subcutaneous tissue included in the sample should be minimized). Cut the epithelium in half. Place one of the halves in the RNAlater cryovial labeled "Tumor (Baseline)". Place the other half in a container of 10% formalin.

Tissue sample from an undiagnosed suspicious lesion:

Using a scalpel, bisect the tissue sample first, then carefully separate the epithelium from the subcutaneous tissue on one of the halves and place it in the RNAlater cryovial labeled "Tumor (Baseline)". Place the other half in a container of 10% formalin and submit for clinical histopathology per standard of care guidelines.

Process the RNAlater samples in accordance with the instructions in section 10.2.2

Samples in formalin will be paraffin-embedded and stored en bloc until the request for slides to be cut is issued.

At the End of Study Visit: Two 4 mm tissue samples will again be obtained:

- One of visually normal appearing mucosa
- One of the oral/oropharyngeal tumor

Half of each sample will be processed for RNA-seq analysis. The other half will be formalin-fixed and paraffin-embedded.

The process for obtaining these samples will depend on whether or not the samples are obtained during surgical excision of the tumor

Have available:

- A 4 mm biopsy punch (if the lesion is not accessible by biopsy punch, alternative tools sufficient to yield a 4 mm piece of tissue with the epithelium intact may be used.)
- Two, 2 mL cryovials containing 0.5cc of RNAlater (see section 10.2.2 Collection and Handling Procedures: Biopsy for instruction on the preparation and processing of the cryovials).
    - One labeled "Normal (EOS)"
    - One labeled "Tumor (EOS)"
- Two containers of 10% formalin.
    - One labeled "Normal (EOS)"
    - One labeled "Tumor (EOS)"

Samples obtained during surgery: (The participant's pre-surgical instructions, procedure preparation and recovery will be in accordance with the PO's standard clinical practice.)

- Using a 4 mm biopsy punch or alternative method, remove a 4 mm piece of visually normal appearing mucosa adjacent to, but at least 1 cm away from, the tumor/suspicious lesion.
- Excise the tumor in accordance with normal clinical practice.

Visually Normal Appearing Tissue: Place mucosa side up, on a clean hard surface. Bisect into two equal size pieces with a scalpel being careful to separate the epithelium from the subcutaneous tissue. The amount of subcutaneous tissue included in the sample should be minimized.

Place one of the halves in the RNAlater cryovial labeled "Normal (EOS)". Place the other half in a container of 10% formalin.

Tumor Tissue: After excision, remove a 2 mm piece of tumor for RNA-seq analysis, being careful to separate the epithelium from the subcutaneous tissue. The amount of subcutaneous tissue included in the sample should be minimized. Place this piece in the cryovial of RNAlater labeled "Tumor (EOS)". A full 4 mm piece does not need removed as it is preferable that the remainder of the tumor be sent intact to pathology for paraffin embedding and routine clinical histopathology.

Submit the remainder of the surgically excised tissue to pathology in accordance with normal clinical practice.

Process the RNAlater samples in accordance with the instructions in section 10.2.2

Samples in formalin will be paraffin-embedded and stored en bloc until the request for slides to be cut is issued by the CLO.

Samples obtained in the clinic (because definitive treatment will be radiation or chemoradiation without surgical excision of the primary tumor or because surgical excision of the primary tumor has been delayed):

Obtain the tissue samples:

- Using a 4 mm biopsy punch or alternative method, remove a 4 mm piece of visually normal appearing mucosa adjacent to, but at least 1 cm away from, the tumor/suspicious lesion.
- Using a 4 mm biopsy punch or alternative method, remove a 4 mm piece of the tumor/suspicious lesion.

Using great care not to mix up the two tissue types, place each tissue sample, mucosa side up, on a clean hard surface.

Visually Normal Appearing Tissue: Using a scalpel, carefully separate the epithelium from the subcutaneous tissue (the amount of subcutaneous tissue included in the sample should be minimized). Cut the epithelium in half. Place one of the halves in the RNAlater cryovial labeled "Normal (EOS)". Place the other half in a container of 10% formalin.

Tumor Tissue: Using a scalpel, carefully separate the epithelium from the subcutaneous tissue (the amount of subcutaneous tissue included in the sample should be minimized). Cut the epithelium in half. Place one of the halves in the RNAlater cryovial labeled "Tumor (EOS)". Place the other half in a container of 10% formalin.

Process the RNAlater samples in accordance with the instructions in section 10.2.2

Samples in formalin will be paraffin-embedded and stored en bloc until the request for slides to be cut is issued.

7.6.2 PET-CT

If the participant had a staging FDG-PET/CT as part of their standard clinical care upon diagnosis, they are asked to have the scan repeated for research purposes. This will be a skull base to thigh FDG-PET/CT performed prior to the collection of the end of study tissue biopsies. The scan will be performed as close to the day of tissue sample collection as possible (ideally the same day or one day before) but if the scan must be performed earlier than this due to scheduling constraints, the participant must have completed a minimum of 10 days of study agent dosing prior to the scan. The preparation for, performance of, and post-procedure participant instructions will be in accordance with the institution's standard clinical practice.

The request will be made that the tumor burden be assessed using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. [56] Tumor lesions will be measured in at least one dimension – the longest diameter in the plane of measurement. Any lymph nodes ≥ 15 mm in the short axis will be measured bi-dimensionally and reported. If the participant's standard of care staging FDG-PET/CT to be used as the baseline scan was performed at an outside institution, a copy of that scan will be obtained and provided to the radiologist performing the end of study scan. If the baseline scan results were not reported using RECIST, the radiologist will be requested to re-read the baseline scan using RECIST criteria.

For the exploratory endpoint analysis, a maximum of 5 target lesions will be identified on the baseline scan using RECIST criteria. Target lesions will be identified by type (primary lesion or secondary lesion) and anatomic location (oral cavity, oropharynx, other body organ, lymph node etc.).

Primary lesion: the primary tumor from which the baseline tumor tissue sample was collected.

Secondary lesions: may be a tumor lesion (i.e. a lesion in a body organ) or a malignant lymph node.

- To meet target criteria, a secondary tumor lesion must be ≥ 10 mm in size. No more than 2 target lesions may be identified per organ. For example, if there is more than one lesion appearing in the oral cavity/ oropharynx, the primary lesion and the next largest lesion will be the only two identified as "target" lesions.
- To meet target criteria, a lymph node must have a short axis ≥ 15 mm.

The following will be reported and documented on each of the "target" lesions identified:

- SUV (Standardized Uptake Value) of FDG
- Tumor burden:
  - For tumor lesions, document the length (in mm) of the longest diameter in the plane of measurement.
  - For lymph nodes, document the length (in mm) of the short axis. For example, a lymph node measuring 17 mm x 24 mm would be documented as 17 mm.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoint

8.1.1 Immunohistochemistry (IHC) Ki-67 in tumor tissue:

Ki-67 immunohistochemistry evaluations will be performed on pre- and post-treated oral cavity/oropharyngeal tumor tissue. One-half of the tissue will be fixed in 10% neutral buffered formalin and processed into paraffin blocks. This tissue will remain stored in blocks at each participating organization until a request is sent for slides to be cut and submitted in batch from each participating organization. Tissue samples will be cut in four (4) μm sections onto positively charged slides and submitted to the University of Minnesota's formalin-fixed, paraffin-embedded tissue sections will be deparaffinized and rehydrated, followed by antigen retrieval using Tris EDTA buffer pH 9.0 in a steamer. After blocking endogenous peroxidase and application of a protein block (Dako), immunohistochemistry for Ki-67 will be performed on a Dako Autostainer. An EnVision™+ HRP-polymer kit (Dako # K4010) will be used for detection with diaminobenzidine as the chromogen. Mayer's Hematoxylin (Dako) will be used as the counterstain. Primary antibodies will be substituted with appropriate negative control IgG for negative control slides. Digital images will be collected via a Spot Insight 4 MP CCD Scientific Color Digital camera (Diagnostic Instruments) mounted on a Nikon E-800 microscope (Nikon Plan Apo 20×/0.95 lens). Image pro plus (Media Sybernetics) will be used for quantitation via pixel counting. Data will be obtained from two tissue sections per marker.

8.2 Secondary Endpoints

8.2.1 Immunohistochemistry (IHC) Ki-67 in visually normal appearing tissue:

Analysis will be performed on pre- and post-study treatment tissue samples as described in section 8.1.1

8.2.2 Immunohistochemistry Biomarkers in tumor tissue:

Using the staining technique described in section 8.1.1, the following biomarkers, all of which are commercially available, will be assessed: Cyclin D1 (ISO83), cleaved caspase 3, p21 (P21 Waf1/Cip1), p AKT, p AMPK, p s6, p16 and PPARγ.

The following immune markers will be analyzed via IHC at Johns Hopkins University: PD1, PD-L1, T helper (CD4), T suppressor (CD8), Fox p3 (TREG), and Tumor Associated Macrophage (CD68).

Paraffin embedded tissue will be cut into four (4) μm sections onto positively charged slides at the participating organization then transferred to the JHU lab where the sections are dewaxed in xylene, followed by solvent removal in 100% ethanol. Sections are then rehydrated by immersion in a graded ethanol series, followed by distilled water, then a 60-second immersion in water with 1% Tween 20 detergent. Tissue sections then undergo heat induced epitope retrieval by immersion and incubation at 100 degrees Celsius in retrieval buffer previously determined to be the optimal buffer for proper performance of each specific antibody (Antigen Unmasking buffer (Citrate), Vector Laboratories# H-3300, incubation time 25 minutes for: anti-CD8 (Dako# M7103) and anti-PD1 (Abcam# 52587) antibodies; Target Retrieval Solution, Dako# S170084-2, incubation time 50 minutes for: anti-CD4 (SinoBiological# 10400-R113), anti-CD68 (Dako# M0814), anti-FoxP3 (Cell Signaling# 12653) and anti-PDL-1 (Cell Signaling# 13684). All subsequent wash steps will be done using Phosphate Buffered Saline w/Tween (Sigma Chemicals# P-3563; TBST). After cooling to room temperature, slides will be blocked using Dual Endogenous Enzyme Block (Dako# S2003), and primary antibodies added using appropriate dilutions in ChemMate Antibody Dilution Buffer (ChemMate# ADB250) Antibody dilutions are as follows: anti-CD8, 1:100; anti-PD1, 1:50; anti-CD4,1:200; anti-CD68, 1: 5,000; anti-FoxP3, 1:50; and anti-PDL-1, 1:100. Antibody incubations will proceed at room temperature for 45 minutes at room temperature (anti-PD1, anti-CD4, anti-CD68 and anti-PDL-1) or overnight at 4 degrees Centigrade (anti-CD8 and anti-FoxP3), and bound primary detected using Power Vision Poly-HRP anti- Rabbit IgG or anti-mouse IgG (Leica), as appropriate for the species of origin of each primary antibody, incubated 30 minutes at room temperature. Diaminobenzidine (DAB) chromogen solution (Sigma Fast DAB tablets; Sigma Chemicals# D4293) will be added and incubated for 20 minutes at room temperature, followed by nuclear counter-staining with Mayers Haematoxylin (Dako# S330930-2). Slides will then be dehydrated, cleared, and coverslips mounted.

Immunostained slides will be scanned (20x objective; 0.49 mm per pixel) with an Aperio ScanScope® CS linear-array scanner (Leica Biosystems). Afterwards, images will be segmented into individual (JPEG) images using TMALab in eSlideManager (Leica Biosystems). The saved digital images will be used for image analysis using FrIDA (FRamework for Image Dataset Analysis), a custom open source image analysis software package (available at http://sourceforge.net/projects/fridajhu/ Ref: Cornish T, De Marzo AM, Gurel B, et al. FRIDA an Open Source Framework for Image Dataset Analysis. Advancing Practice, Instruction and Innovation Through Informatics: Pittsburgh, PA, 2007.) for the analysis of RGB color image datasets, including those generated from scanning of tissue slides. Data will be obtained from two tissue sections per marker. IHC evaluations will be done on CD4, CD8, CD68, FoxP3, PD1 and PD-L1 light microscopy based on the extent and intensity of immunolabelling for the marker of interest in any given tumor.

8.2.3 Transcriptional Genomics in tumor and visually normal appearing tissue pre- and post-study treatment:

Additional tissue biopsies will be taken from participants, stored in RNAlater at 4^{O}C for a minimum of 12 to a maximum of 72 hours, and then transferred to a -70/-80^{O}C freezer until shipped to the University of Minnesota for RNA extraction. Ondrey and colleagues published the Index manuscript in head and neck cancer Gene Profiling and infrastructure and procedures will be adhered to for this study [54].

Total RNA will be isolated from individual frozen tissue samples using the Qiagen RNeasy Kit by the University of Minnesota Health Sciences Genomics Center. Samples will be analyzed separately, but will be multiplexed into groups of 8 barcoded samples per lane on the sequencer. Samples are separated after sequencing by a genetic barcode that is added to the sequence during the library preparation.

Prior to RNA-seq analysis quality control measures will be implemented. Concentration of RNA will be ascertained via fluorometric analysis on a Thermo Fisher Qubit fluorometer. Overall quality of RNA will be verified using an Agilent Tapestation instrument. Any sample providing an RNA Integrity Number (RIN) of less than 6 will be removed from the study and replaced with a newly extracted sample. Following initial QC steps sequencing libraries will be generated using the Illumina Truseq Stranded mRNA library prep kit according to the manufacturer's protocol. Briefly, mature mRNA will be enriched for via pull down with beads coated with oligo-dT homopolymers. The mRNA molecules will then be chemically fragmented and the first strand of cDNA will be generated using random primers. Following RNase digestion, the second strand of cDNA will be generated replacing dTTP in the reaction mix with dUTP. Double stranded cDNA will then undergo adenylation of 3' ends following ligation of Illumina-specific adapter sequences. Subsequent PCR enrichment of ligated products will further select for those strands not incorporating dUTP, leading to strand-specific sequencing libraries. Final libraries for each sample will be assayed on the Agilent Tapestation for appropriate size and quantity. These libraries will then be pooled in equimolar amounts as ascertained via fluorometric analyses. Final pools will be absolutely quantified using qPCR on a Roche LightCycler 480 instrument with Kapa Biosystems Illumina Library Quantification reagents. Sequencing will be performed on an Illumina Hiseq 3000 instrument with paired-end 75bp reads. Samples will be sequenced to an overall depth of 30 million reads per sample.

8.2.4 Analysis of microarray data:

RNA-Seq reads will be trimmed using the paired-end-aware program Trimmomatic [57] to remove any low-quality bases at the beginning or end of reads as well as any adapter sequences. Reads trimmed below a threshold length of 40 bases will be discarded. Trimmed reads will be compared to the human reference genome using the k-mer-based pseudoaligner Kallisto [58; 59]. Per-transcript estimated read counts provided by Kallisto are then adjusted for technical and biological variation by the generalized linear model (GLM)-based R package sleuth [60]. These models are then used to perform differential expression analysis between treatment and control conditions at the transcript and gene levels. We will specifically examine the RNA-Seq data of both the tumor and normal appearing adjacent tissue for biguanide and thiazolidinedione-specific mechanistic pathways. These will include but will not be limited to; PI3K/AMPK/mTOR signaling axes, nuclear receptor mediated differentiation pathways, nuclear receptor mediated anti-inflammatory pathways, and biguanide or thiazolidinedione specific cell stress associated pathways e.g. mitochondrial energy utilization (MCC1).

8.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, AE or serious adverse event (SAE), inadequate agent supply, noncompliance, concomitant medications, medical contraindication, or a delay in the end of study surgical excision would place the participant out of the 25-day maximum agent dosing window. In this case, if the participant is agreeable, punch biopsies of the tumor and visually normal appearing tissue adjacent to the tumor may be obtained

in the clinic setting in lieu of during surgery. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events.

8.4 Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility (including screen failure), pregnancy, or delay of surgical excision of the cancer beyond 26 days from the first dose of study agent. In the advent of such a delay, the participant will be asked if they would be willing to have punch biopsies of the tumor and visually normal appearing tissue adjacent to the tumor obtained in the clinic setting in lieu of during surgery.

8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Rationale for Methodology Selection

9.1.1 Immune Histochemistry:

Ki-67, Cyclin D1 (ISO83), Cleaved Caspase 3, p21 (P21 Waf1/Cip1), p AKT, p AMPK, p s6, p16, PPARγ, PD1, PD-L1, T helper (CD4), T suppressor (CD8), Fox p3 (TREG), Tumor Associated Macrophage (CD68). The p16 assessment for Human Papilloma Virus will be performed at baseline only.

These tissue markers are typically analyzed by immune histochemistry. In both rodent and human models, this is the standard method of analysis for treated tissue. Tissue samples from both tumor and visually normal appearing mucosa adjacent to the tumor before and after treatment with study agent will be analyzed for Ki-67 and Cleaved Caspase 3. The remaining tests will be conducted only on pre- and post-treatment tumor tissue. Commercially available human antibodies considered to be the gold standard for these markers will be utilized.

Tumor and visually normal appearing tissue samples will be studied by RNA-seq analysis pre- and post-study treatment in all participants. These analyses are more exploratory. The expression data may be able to allow for confirmation of the data obtained by IHC analysis. RNA-seq represents an emerging gold standard that allows for more comprehensive and accurate analyses compared to the expression array data that has been used for the past 10-15 years. Recently, the cost for RNA-seq has dropped dramatically allowing for more inexpensive robust analyses than those performed on affymetrix or similar platforms.

9.1.2 Pioglitazone analysis:
Pioglitazone concentration will serve as a surrogate measure of ACTOplus met® XR levels in blood. The CP lab at the University of Wisconsin has a validated assay to measure pioglitazone concentrations in plasma. Briefly, analysis is performed with reverse-phase high-performance liquid chromatography interfaced with a mass spectrometry detector using ESI in the positive mode. All standard curves have an R2 greater than 0.998. The lower limit of quantitation is 15.62 ng/mL. Pioglitazone inter-day variability over one month was 4.6% for high standard (n=6) and 6.4% for low standard (n=7). Recovery of pioglitazone from plasma was >80% based on comparison with H2O standards.

9.2 Comparable Methods

For the IHC analyses, experiments used to be conducted by western blotting and PCR, but commercially available diagnostic IHC easily surpasses those methods. Positive and negative control tissues ensure accuracy of the IHC and automated staining allows for consistency of results. For the RNA-seq analysis, the comparative methodology would be high throughput RNA expression arrays that are now considered limited in both accuracy and comprehension. The RNA-seq data can be analyzed via all of the standard bioinformatic software for detailed analyses of upregulation and downregulation of pathways associated with ACTOplus met® treatment in aerodigestive cancer. An additional benefit is that data derived from RNA-seq can utilized to confirm the IHC data.

10. SPECIMEN MANAGEMENT

Please note: To insure that antigenicity remains intact in tissue samples, no slides will be cut until they are requested by the CLO. Slides of pre- and post-study treatment tissue samples will be requested at the following two time points in the study:

1. After the 18th participant has completed the study.
2. After the final participant has completed the study.

Slides will be processed immediately upon receipt by the lab that is performing the analysis.

10.1 Laboratories

10.1.1 Paraffin-embedded Tissue Samples

10.1.1.1 Sectioning (not to be performed until directed by the CLO):
Pathology staff at each institution will prepare the following number of slides containing 2 (two), 4 μm sections per slide from the following tissue samples:

Block type	H&E stained	Unstained
Pre-study treatment tumor	1	15
Pre-study treatment normal	1	4
Post-study treatment tumor	1	15
Post-study treatment normal	1	4

10.1.1.2 IHC:
Nine slides each from the tumor pre- and post-study treatment biopsies and four slides each from the normal appearing adjacent tissue pre- and post-study treatment biopsies and the H&E stained slides will be sent to:

Gerry O'Sullivan, M.V.B., Ph. D
Director, Comparative Pathology Shared Resource
Animal Science/Veterinary Medicine Building, Room 224
1988 Fitch Ave.
St. Paul, MN 55108

Six slides each from tumor pre-and post-study treatment biopsies will be sent to:

Alan Meeker, PhD
Director, Immunohistochemistry Lab
Oncology Tissue Services

Johns Hopkins Medicine
411 N Caroline St.
Bone Street Annex Building
Room 305 Basement
Baltimore, MD 21231

10.1.2 RNAlater- preserved Tissue Samples

Frozen tissue (both lesion and normal appearing adjacent tissue samples) will be shipped to:

Beverly Wuertz,
Molecular Oncology Group,
Department of Otolaryngology,
University of Minnesota,
270 Lions Research Building,
2001 6th Street SE,
Minneapolis, MN 55455
Office: 612-625-3090
Lab: 612-624-5573
Fax: 612-626-9871

These samples will be transferred to the University of Minnesota Genomics Center for RNA extraction prior to transfer to the ORMF for RNA-seq.

10.1.3 Blood

10.1.2.1 Clinical Safety/Eligibility labs (CBC with differential, Comprehensive Metabolic Panel and urine pregnancy test) will be sent to the clinical laboratory at each institution for processing.

10.1.2.2 Plasma for Pioglitazone concentration will be batch shipped to

UWCCC Cancer Pharmacology Lab
University of Wisconsin Hospital and Clinics
Room K4/559
600 Highland Ave.
Madison, WI 53792-5669

10.2 Collection and Handling Procedures

10.2.1 Blood

10.2.1.1 Clinical Laboratory Tests
At screening/baseline and the end of study (Day 11-26) or Early Termination visit, blood for CBC with differential and comprehensive metabolic panel will be collected and sent to the institution's clinical laboratory for processing. Supplies for the collection of these samples will not be provided. These clinical labs will be collected and processed in accordance with the clinical laboratory protocols at the institution.

10.2.1.2 Pioglitazone concentration
In addition, at the screening baseline and end of study (Day 11-26) or Early Termination visit, blood for pioglitazone concentration will be collected using a 10 mL EDTA (lavender top)

vacutainer. The supplies for obtaining, labeling and storing these samples will be provided by the CP laboratory at the University of Wisconsin in research lab kits. These samples will be processed as follows:

- Immediately after collecting, invert the 10 mL EDTA vacutainer 8 times
- Centrifuge the 10 mL EDTA vacutainer at 1500g for 10 minutes at 4°C to separate the plasma
- Aliquot up to 1.8 mL of plasma into two, 2 mL cryovials
- Using the designated label from the lab kit, label the cryovial with the participant's PID number, initials, and date and time of collection.
- Store the cryovials immediately in a -70/-80°C freezer
- The samples will be batch shipped to the CP lab at two time points during the protocol. The first shipment will occur after the 18th participant has completed the study. The final shipment will occur after the last participant enrolled has completed the study.

10.2.2 Biopsy

At the baseline and Day 11-22 (end of study) visits, a 4 mm biopsy will be taken from the tumor and normal appearing tissue adjacent to, but at least 1cm away from, the target lesion. Biopsy samples will be bisected.

10.2.2.1 Formalin fixed tissue: Paraffin-embed and store until request is made by the CLO for slides to be cut.

10.2.2.2 RNAlater samples:

- Prior to obtaining the samples, prepare 2 cryovials as follows:
  - Using the graduated pipette supplied in the research lab kit, draw up 1.0 cc of RNAlater
    - Place ½ (0.5 cc) in each of the 2 cryovials
  - Pull the "Tumor" and "Normal" labels for the appropriate time point (Baseline or End of Study) from the research lab kit
- After the "Tumor" and "Normal" tissue samples have been obtained and cut in half:
  - Place a 2 mm piece of tumor tissue in one of the cryovials and complete and apply the "Tumor" label.
  - Place a 2 mm piece of visually normal appearing tissue in the other cryovial and complete and apply the "Normal" label.
- Let stand at 4°C for a minimum of 12 hours and no longer than 72 hours.
- After standing for the required period of time, remove the RNAlater with a pipette leaving only the tissue sample in the cryovial. A small amount of residual RNAlater in the cryovial is acceptable.
- Transfer the cryovials to a -70/-80°C freezer for storage. Frozen specimens will be batch shipped to the University of Minnesota's Genomics Center for RNA extraction when all participants have completed the study. The Genomics Center will then transfer the Extracted RNA to OMRF for RNA-Seq analysis.

10.3 Shipping Instructions

The following describes packaging, carrier requirements, when specimens may be shipped, and name, address, and telephone number of the person to whom the specimens are being sent. All specimens will be shipped in accordance with the International Air Transport Association (IATA) Dangerous Goods Regulations. A shipping box and mailing labels are provided with the research lab kits.

Procedure	Laboratory	Specimen	Packaging	Frequency	Contact
Biomarkers IHC	Comparative Pathology	Tumor: 9 slides each from pre- and post-study treatment Plus one H&E stained slide each from pre- and post-study treatment Visually normal: 2 slides each from pre- and post- study treatment Plus one H&E stained slide each from pre- and post-study treatment	In slide containers in bubble wrap	As directed by the CLO after the 18th participant has completed the study and after the final participant has completed.	Gerry O'Sullivan, M.V.B., Ph.D. Director, Comparative Pathology Shared Resource Animal Science/Veterinary Medicine Building, Room 224 1988 Fitch Ave. St. Paul, MN 55108
Biomarkers IHC	Johns Hopkins	Tumor: 6 slides each pre- and post-study treatment	In slide containers in bubble wrap	As directed by the CLO after the 18th participant has completed the study and after the final participant has completed.	Alan Meeker, PhD Director, Immunohistochemistry Lab Oncology Tissue Services Johns Hopkins Medicine 411 N Caroline St. Bone Street Annex Building Room 305 Basement Baltimore, MD 21231
RNA extraction	UMN Genomic Center	2 cryovials each (1 tumor, 1 visually appearing normal) from each time point, (pre- and post-study treatment)	On dry ice	As directed by the CLO after the final participant has completed.	Beverly Wuertz, Molecular Oncology Group, Department of Otolaryngology, University of Minnesota, 270 Lions Research Building, 2001 6th Street SE,

					Minneapolis, MN 55455 Office: 612-625-3090 Lab: 612-624-5573 Fax: 612-626-9871 Email: knier003@umn.edu
RNA-seq	ORMF	Extracted RNA from UMN Genomic Center	On dry ice	After the final participant has completed.	Dr. Pat Gaffney MD Arthritis & Clinical Immunology Research Program, MS 57 Oklahoma Medical Research Foundation 825 N.E. 13th Street Oklahoma City, OK 73104 Phone: (405) 271-2572
Pioglitazone Concentration	3P Lab	2 cryovials each of frozen plasma from screening/ baseline and end of study	On dry ice	As directed by the CLO after the 18th participant has completed the study and after the final participant has completed.	CP Laboratory University of Wisconsin Hospital and Clinics, Room K4/559, 600 Highland Ave. Madison, WI 53792-5669

10.4 Tissue Banking

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

PO's will ensure that participants have responded to the section of the informed consent form that asks for their consent to allow left over blood and tissue samples to be transferred to the NCI-specified repository/laboratory. The CLO will document in the OnCore Database which participants have consented to tissue banking and which have not.

11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as in the Investigator Brochure or package insert.

11.1 Adverse Events

11.1.1 Reportable AEs:

All AEs that occur after the informed consent is signed and baseline assessments are completed (including run-in) must be recorded on the AE Worksheet and entered into the OnCore database whether or not related to study agent.

11.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will be assessed according to the grade associated with the CTCAE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

CTCAE v4.0 general severity guidelines:

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

ADL
*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the AE is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form found at http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by phone or email within 24 hours of knowledge of the event.

Eva Szabo, MD
Chief, Lung & Upper Aerodigestive Cancer Research Group
NCI/Division of Cancer Prevention
9609 Medical Center Drive, Room 5E-102, MSC 9781
Bethesda, MD 20892-9781 (For FedEx, use Rockville, MD 20850)
Phone: (240) 276-7011
FAX: (240) 276-7848
email: szaboe@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug

11.2.2.3 The Lead Organization and all Participating Organizations will email written SAE reports to the medical monitor and to DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com within 48 hours of learning of the event using the fillable PDF SAE Report Form.

11.2.2.4 The DCP Medical Monitor and CCSA regulatory and safety staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. An SAE will be followed until resolution. The follow-up plan will be documented in the participant's study records.

12. STUDY MONITORING

12.1 Data Management

All of the procedures outlined in the University of Wisconsin Chemoprevention Consortium standardized Data Management Plan (version dated 05/25/2018) will be followed in this protocol. Please refer to this document for additional details on data management procedures. The University of Wisconsin Carbone Cancer Center's OnCore database will be the database of record for the protocol and subject to NCI and FDA audit. OnCore is a web-based clinical trials database. Data entry will be performed by the CLO where staff is trained in OnCore and applicable regulatory requirements such as 21 CFR; Part 11. Data from the OnCore database will be transferred to Federal Security Compliant formats for transmission to DCP according to pre-established DCP standards and procedures.

12.2 Case Report Forms

In lieu of a CRF set, a System Variable Attribute Report (SVAR) will be used to document all questions and data elements to be collected in the database for this protocol. The NCI/DCP approved SVAR will be used to create the electronic data entry pages in the OnCore database. Amendments to the SVAR will be submitted to the DCP Protocol Information Office for review and approval. Data will be extracted from source documents submitted by the PO.

12.3 Source Documents

To standardize the collection of study data, the CLO will provide the PO's with protocol specific Visit Guides and Source Document Worksheets to insure that all required data elements are captured. These documents will be used to supplement data collected on primary clinical source documents. All data reported must be documented either on a separate source document found in the participant's medical record or on the Visit Guides and Source Document Worksheets. All source documents must be signed by the study team member that collected or elicited the information in the source documents. Source documents will be submitted to the CLO (by fax or e-mail) for entry into the OnCore database within 10 business days of each study contact. Primary clinical source documents will be de-identified and relabeled with the participant's PID number prior to submission. Documents containing participant personally identifiable information that has not been completely obscured cannot be accepted and will be returned to the site.

12.4 Data and Safety Monitoring Plan

All of the procedures outlined in the University of Wisconsin Chemoprevention Consortium standardized Data and Safety Monitoring Plan (approved 03/20/2018). The UW Chemoprevention Consortium Data and Safety Monitoring Committee meets every 6-12 months to review all data from ongoing consortium studies. Members review pooled, unblinded safety data to assess ongoing human subject safety.

12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidance, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description:

This is a randomized, placebo-controlled, phase IIB oral cavity/oropharynx window of opportunity cancer chemoprevention study of ACTOplus met® XR (pioglitazone 30 mg and metformin extended release

1000 mg) daily for 10-21 days in subjects undergoing planned surgery or definitive radio/chemotherapy. The study population consists of newly diagnosed subjects ≥ 18 years of age with biopsy proven, stage I-IV squamous cell carcinoma, or squamous cell carcinoma in situ of the oral cavity or oropharynx who will be undergoing surgical, radiation or combined modality treatment.

The primary endpoint of the study is the absolute change in proliferation index (Ki67) expression in oral cavity cancer cells from baseline to post-exposure. We will evaluate the difference between the treated and control arms in absolute change in Ki67 using two-sample Student's t-test or Wilcoxon rank-sum test, as appropriate.

13.2 Randomization/Stratification:

Subjects will be randomized in a 2:1 ratio between ACTOplus met® XR and placebo using permuted blocks of size 3. Each block will have a random permutation of two subjects with ACTOplus met® XR and one with placebo. To facilitate timely dispensing of the study agent, each site will receive a block of 3 bottles of study agent upon receipt of drug shipment authorization. When the site has dispensed their last kit from the block of 3, another block of three bottles will be sent until the site has reached the accrual limit assigned in their sub-award. If a site cannot complete a block in accordance with the accrual goals for the study, the site's sub-award will be amended and their remaining accrual slots will be transferred to another site. To preserve the permutation, the site must continue to make every effort to complete a block once they have received it. Due to the small sample size, there will be no stratification analysis per site.

13.3 Accrual and Feasibility:

The sample size for each arm is based on comparing the absolute change in Ki67 between the ACTOplus met® XR arm and the placebo arm. The goal will be to bring to study completion a total of 36 subjects, or 24 subjects in the ACTOplus met® XR arm and 12 subjects in the placebo arm. Since our sample size is fixed at N=36, and we are randomizing at a ratio of 2:1 between ACTOplus met® XR and Placebo, our sample size/arm for the purpose of power calculations (if we had even sample sizes) would be n = $1/\{[1/n\_E+1/n\_C]/2\} = 16$. For the power calculation, $n =[(z_{1-\alpha/2}+Z_{\beta})^2 2\sigma^2]/\Delta^2$.

The table below shows detectable effect sizes (defined as the mean difference in the change divided by the standard deviation of the change) for various significance level α and power 1-β combinations for the primary endpoint. Based on the literature, a mean difference in the change of around 30-40% and a standard deviation of 20-30% may be reasonable to expect [61]. Given those estimates, and the sample size of 36, the minimum effect size we would expect would be at least 1.00; we would be able to detect the effect size of 1.00-1.15 with power 0.80-0.90 for a two-sided level 0.05 Student's t-test.

α \ 1-β	**0.80**	**0.85**	**0.90**
0.05	**1.00**	**1.06**	**1.15**
0.10	**0.88**	**0.95**	**1.04**

Detectable Effect Size

To account for the anticipated dilution of treatment effect due to 8% of the subjects being noncompliant with treatment, dropping out of the study or experiencing an unanticipated delay of surgery beyond 21 days, the sample size estimate is inflated to 39 subjects in total (26 subjects on the ACTOplus met® XR arm and 13 subjects on the placebo arm). Because of a short duration of treatment, we do not expect any random loss to follow-up.

The anticipated accrual rate is 1-2 subjects/month; therefore, our planned enrollment of 39 subjects should occur over 12-18 months.

Protocol accrual will be monitored through the NCI Division of Cancer Prevention's Accrual Quality Improvement Program (AQuIP). DCP will create an Accrual Zone Monitoring Plan for this protocol with milestones established based on the target enrollment, the projected monthly accrual rate and the projected duration of accrual. The CLO will submit accrual reports monthly to the Division of Cancer Prevention. If accrual falls below 90% of the projected goal, a corrective action plan will be required to ensure full enrollment within the stated accrual period. If accrual falls below 75% of the projected goal, an analysis of recruitment barriers and corrective recruitment action plan will be required. If accrual is falling short of the projected goal by > 75%, i.e. below 25% of the projected goal, at the quarter or half way marks, study continuation will require approval by DCP leadership.

For information regarding the study population (including gender and minority considerations), please see Section 4.3 Inclusion of Women and Minorities.

13.4 Primary Objective, Endpoint(s), Analysis Plan:

The primary objective of this protocol is to determine whether 10-21 days of treatment with ACTOplus met® XR will result in a decrease in proliferation index (Ki-67) expression in oral cavity/oropharyngeal tumor tissue in the aerodigestive tract as compared to placebo. The primary endpoint of the study is the absolute change in proliferation index (Ki67) expression in oral cavity cancer cells from baseline to post-exposure. Baseline, post-exposure, absolute change in Ki-67, and difference in absolute change between the ACTOplus met® XR and placebo subjects will all be summarized with descriptive statistics. The primary analysis will compare the difference in absolute change in Ki-67 between the ACTOplus met® XR and placebo arms using a two-sided two-sample Student's t-test or Wilcoxon rank-sum test, as appropriate, at a significance level of 0.05.

13.5 Secondary Objectives, Endpoints, Analysis Plans

The secondary objectives as prioritized in Section 1.2 Secondary Objectives are:

13.5.1 Compare differences in proliferation index (Ki-67) expression from baseline to post-exposure in visually normal appearing oral cavity/oropharyngeal tissue. Absolute change in Ki-67 pre- to post-study treatment and difference in absolute change between the ACTOplus met® XR and placebo subjects will be summarized with descriptive statistics as for the primary endpoint.

13.5.2 Compare immunohistochemical differences from baseline to post-exposure of oral cavity/oropharyngeal adjacent visually normal appearing tissue and tumor tissue samples with regard to the apoptosis biomarker, Cleaved Caspase 3.

13.5.3 Compare immunohistochemical differences from baseline to post-exposure of oral cavity/oropharyngeal tumor tissue samples with regard to Cyclin D1, p21 and biguanide or PPARγ associated pathway biomarkers. Prospective biomarkers on the panel will include but are not limited to pAKT, pAMPK, pS6 (Metformin), and PPARγ.

13.5.4 Compare immunohistochemical differences from baseline to post-exposure of oral cavity/ tumor tissue samples with regard to immune microenvironment (TREG, T4, T8, TAM-CD68+, PD1, PD-L1).

13.5.5 Compare and correlate pre- and post-ACTOplus met® XR treatment Human HT-12 v 4 BeadChip (Illumina) whole transcriptome gene analysis on total RNA samples from oral cavity/oropharyngeal adjacent visually normal appearing tissue and tumor tissue.

13.5.6 Determine HPV status in pre-treatment tumor tissue using p16 immunohistochemistry.

Secondary endpoints will consist of changes from baseline to post-exposure in immunohistochemical markers and gene analysis. Each of these will be summarized for baseline, post-exposure, and absolute change by treatment arm using the appropriate descriptive statistics, and will be evaluated with Student's t-test or Wilcoxon rank-sum test, as with the primary endpoint. As this is an exploratory study, in general, adjustments will not me made for the endpoints tested. The exception is the whole transcriptome gene analysis. Because of the amount of data that will be generated for this, adjustments for multiplicity of comparisons will be made to control the false discovery rate using the methods of Benjamini and Hochberg when testing treatment group differences[62].

13.5.7 In those participants who have had a standard of care staging PET/CT prior to randomization, we will compare the pre- and post-study intervention: SUV (Standardized Uptake Value) of FDG and tumor burden using RECIST v 1.1 between the two treatment arms. Because only a subset of participants will have PET/CT scans performed, this will be an exploratory analysis.

13.6 Reporting and Exclusions

All participants who take any study agent, ACTOplus met® XR or placebo, will be analyzed for adverse events. Subjects that maintain 80% compliance for the time period beginning day 1 and ending on the day before surgical intervention will be considered compliant. Compliance will be measured through pill counts conducted by the pharmacy or an independent 3rd party (not a member of the study team) and reported to the study coordinator for documentation in the Visit Guide. For biomarker modulation, all participants that have evaluable pre- and post-study treatment samples will be included in the analysis. Compliance and availability of evaluable samples for biomarker studies will be included in descriptive statistics.

13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of ACTOplus met® XR or placebo.

13.8 Evaluation of Response

For the primary analysis comparing the absolute change in proliferation index (Ki-67) expression from baseline to post-exposure between treatment arms, an intent to treat analysis will be used. All of the participants who met the eligibility criteria, with the exception of those who did not receive study agent, will be included in the main analysis. Random dropouts will be excluded. Data will be examined for non-random dropouts. An appropriate sensitivity analysis will be conducted in the case of missing data.

13.9 Interim Analysis

There is no planned interim analysis of the primary endpoint of the study. Safety data will be monitored periodically by the Consortium's data monitoring committee.

13.10 Ancillary Studies

Not Applicable

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Good Clinical Practice" for all study personnel listed on the FDA Form 1572 for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of training in "Protection of Human Research Subjects" for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.6 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.7 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.8 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.9 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the NCI Cancer Prevention and Control CIRB, including Study-specific Worksheet (SSW) approval for the participating organizations. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the NCI Cancer Prevention and Control CIRB prior to implementation.

14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates, Inc.
2001 Gateway Pl, Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400
Fax: 650-691-4410

E-mail Submissions: regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to DCP's Regulatory Contractor.

14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

15. FINANCING, EXPENSES, AND/OR INSURANCE

The costs of all procedures for this protocol are paid for by the study contract with the exception of a pre-randomization standard of care staging PET/CT, a standard of care diagnostic biopsy, clinical

histopathology and the costs associated with surgical treatment of the oral/oropharyngeal for those study participants undergoing surgical treatment of their cancer at their end of study visit. If, at the time of surgery, there are added costs for the collection of the 4 mm tumor and visually appearing normal adjacent tissue during surgery, those added costs will be paid for by the study contract. In the event that a participant is physically injured as a result of participating in this research, there is no provision for compensation for medical care for the injury.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PILL DIARY

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PILL DIARY PAGE 1 of 3

Dosing Instructions:

Take one (1) tablet by mouth daily with a meal at approximately the same time each day.

Do not chew, cut or crush the tablets.

Do not take on an empty stomach.

Tablets are moisture and light sensitive. Keep the tablets tightly closed in their original container. Do not transfer to a pill organizer.

If you miss a dose, take it with your next meal on the same day. Do not make up a dose by taking two doses in one day.

Important Reminders:

Contact study staff immediately if you experience any of the following:

Nausea or Vomiting	Loss of appetite	Stomach pain	Dark urine
Slow or irregular heartbeat	Unusual weakness or tiredness	Unusual muscle pain	Dizzy or lightheaded
Trouble breathing (especially while lying down)	Swelling in the ankles or feet	Rapid weight gain	Feel generally unwell

Minimize use of alcohol:

Women:	No more than 3 drinks/day or more than 7 in a week.
Men:	No more than 4 drinks/day or more than 14 in a week.

One drink is:

Beer (12 oz.) 1 standard can or bottle	Wine (5 oz.) 1 standard glass	Spirits (6 oz.) 1 mixed drink or one 1.5 fluid oz. shot

Check with study staff before taking any new medications to be sure the medication is not excluded for use while on this study.

Notify study staff before having any scans (e.g. CT scan). The study medication should not be taken with the iodine containing dye used for some types of scans.

Instructions for Completing the Pill Diary:

Record the date and time you take your dose each day and initial each entry.
In the Comments column:

- List any side effects or symptoms noticed.
- List any new medications taken and reason for taking
- If you missed a dose indicate why.
- Make a note if you've lost any pills
- Include any additional information you would like to note.

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PILL DIARY PAGE 2 of 3

DO NOT THROW AWAY YOUR PILL BOTTLE!
BRING IT ALONG WITH THIS PILL DIARY TO YOUR NEXT STUDY VISIT.

DAY	DATE	TIME	COMMENTS	INITIALS
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				

PILL DIARY PAGE 3 of 3				
DO NOT THROW AWAY YOUR PILL BOTTLE! BRING IT ALONG WITH THIS PILL DIARY TO YOUR NEXT STUDY VISIT.				
20				
21				
22				
23				
24				
25				

I reviewed this Pill Diary with the participant	_____ __ __/__ __/__ __ __ __ (Reviewer's signature) (Date)
I verify the information on this Pill Diary is correct.	_____ __ __/__ __/__ __ __ __ (Participant's signature) (Date)

APPENDIX C: TOBACCO AND ALCOHOL RESOURCES

National and Local Resources to Help with Alcohol Abuse and Alcoholism

NIAAA's online guide ***Treatment for Alcohol Problems: Finding and Getting Help*** is written for individuals, and their family and friends, who are looking for options to address alcohol problems. It is intended as a resource to understand what treatment choices are available and what to consider when selecting among them.
https://pubs.niaaa.nih.gov/publications/treatment/treatment.htm

Other resources:

National Institute on Alcohol Abuse and Alcoholism www.niaaa.nih.gov
301–443–3860

National Institute on Drug Abuse www.nida.nih.gov
301–443–1124

National Clearinghouse for Alcohol and Drug Information www.samhsa.gov
1–800–729–6686

Substance Abuse Treatment Facility Locator www.findtreatment.samhsa.gov
1–800–662–HELP

Alcoholics Anonymous (AA) www.aa.org
212–870–3400 or check your local phone directory under "Alcoholism"

Moderation Management www.moderation.org
212–871–0974

Secular Organizations for Sobriety www.sossobriety.org
323–666–4295

SMART Recovery www.smartrecovery.org
440–951–5357

Women for Sobriety www.womenforsobriety.org
215–536–8026

Al-Anon Family Groups www.al-anon.alateen.org
1–888–425–2666 for meetings

Adult Children of Alcoholics www.adultchildren.org
310–534–1815

10/3/18

National and local resources to help with quitting smoking

NCI's Smokefree.gov offers science-driven tools, information, and support that has helped smokers quit. You will find state and national resources, free materials, and quitting advice from NCI.

Smokefree.gov was established by the Tobacco Control Research Branch of NCI, a component of the National Institutes of Health, in collaboration with the Centers for Disease Control and Prevention and other organizations.

Publications available from the Smokefree.gov Web site include the following:

- Clearing the Air: Quit Smoking Today for smokers interested in quitting.
- Clear Horizons for smokers over age 50.
- Staying Smoke-Free for Good for smokers who have recently quit.
- Smoke-free for women, including pregnant women.
- Smoke-free information in Spanish
- Pathways to Freedom: Winning the Fight Against Tobacco for African American smokers.

NCI's Smoking Quitline at **1–877–44U–QUIT (1–877–448–7848)** offers a wide range of services, including individualized counseling, printed information, referrals to other resources, and recorded messages. Smoking cessation counselors are available to answer smoking-related questions in English or Spanish, Monday through Friday, 8:00 a.m. to 8:00 p.m., Eastern time. Smoking cessation counselors are also available through LiveHelp, an online instant messaging service. LiveHelp is available Monday through Friday, 8:00 a.m. to 11:00 p.m., Eastern time.

Your state has a toll-free telephone quitline. Call **1–800–QUIT–NOW (1–800–784–8669)** to get one-on-one help with quitting, support and coping strategies, and referrals to resources and local cessation programs. The toll-free number routes callers to state-run quitlines, which provide free cessation assistance and resource information to all tobacco users in the United States. This initiative was created by the Department of Health and Human Services. For more information about quitlines, speak to an expert on the Smokefree.gov Web site.

10/3/18

APPENDIX D: TOBACCO AND ALCOHOL QUESTIONNAIRES

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TOBACCO ASSESSMENT – BASELINE

Instructions:
When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

Section A. Basic Cigarette Use Information

1. Have you smoked at least 100 cigarettes (5 packs = 100 cigarettes) in your entire life?

☐ Yes
☐ No → **Skip to Section B**
☐ Don't know/Not sure → **Skip to Section B**

2. How old were you when you first smoked a cigarette (even one or two puffs)?

_____ Years old

3. How old were you when you first began smoking cigarettes regularly?

_____ Years old
☐ Check here if you have never smoked cigarettes regularly.

4. How many total years have you smoked (or did you smoke) cigarettes? Do not count any time you may have stayed off cigarettes.

_____ Years (If you smoked less than one year, write "1.")

5. On average when you have smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

6. Do you NOW smoke cigarettes?

☐ Everyday
☐ Some days
☐ Not at all → **Skip to question 8**

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7. How soon after you wake up do you smoke your first cigarette?

☐ Within 30 minutes
☐ After 30 minutes

8. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff)
☐ 1-7 days → Number of days since last cigarette _____
☐ Less than 1 month → Number of weeks since last cigarette _____
☐ Less than 1 year → Number of months since last cigarette _____
☐ More than 1 year → Number of years since last cigarette _____
☐ Don't know/Don't remember

Section B. Use of Other Forms of Tobacco

9. Have you ever used other forms of tobacco, not including cigarettes?

☐ Yes
☐ No → **Skip to Section C**

10. How often do you/did you use other forms of tobacco?

☐ Every day → Number of times per day _____
☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

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11. Which of the following products have you ever used regularly?
Check all that apply

- ☐ Cigarettes
- ☐ E-cigarettes or other electronic nicotine delivery system
- ☐ Traditional cigars, cigarillos or filtered cigars
- ☐ Pipes
- ☐ Waterpipe
- ☐ Hookah
- ☐ Clove cigarettes or kreteks
- ☐ Bidis
- ☐ Smokeless tobacco, like dip, chew, or snuff
- ☐ Snus
- ☐ Paan with tobacco, gutka, zarda, khaini
- ☐ Other, Please specify: _____

12. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?

- ☐ Within the past month (0 to 1 month ago)
- ☐ Between 1 and 3 months (1 to 3 months ago)
- ☐ Between 3 and 6 months (3 to 6 months ago)
- ☐ Between 6 and 12 months (6 to 12 months ago)
- ☐ Between 1 and 5 years (1 to 5 years ago)
- ☐ Between 5 and 15 years (5 to 15 years ago)
- ☐ More than 15 years ago
- ☐ Don’t know/Not sure
- ☐ Never used other forms of tobacco regularly

Section C. Second-Hand Smoke Exposure

13. Are you currently living with a smoker?

- ☐ Yes
- ☐ No

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14. In the past 30 days, have you lived in a place where other people smoked cigarettes indoors?

☐ Yes
☐ No

15. In the past 30 days, have you worked in a place where other people smoked cigarettes indoors?

☐ Yes
☐ No

16. Thinking of all your childhood and adult years, have you ever lived in a place where other people smoked cigarettes indoors?

☐ Yes → In total, for about how many years? _____ If less than 1, write "1."
☐ No

17. Thinking of all the years you have worked, have you ever worked in a place where other people smoked cigarettes indoors?

☐ Yes → In total, for about how many years? _____ If less than 1, write "1."
☐ No

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)

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ALCOHOL ASSESSMENT – BASELINE

Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. In your entire life, have you had at least 12 drinks of any kind of alcoholic beverage?

   ☐ Yes
   ☐ No **(End)**
   ☐ Refused **(End)**
   ☐ Don't know/Not sure

2. In the past 12 months, on average, how often did you drink any type of alcoholic beverage?

   _____ (Enter the number of days you drank based on the timeframe checked below. Enter 0 if you never drank and skip to Question 6.)

   ☐ Week
   ☐ Month
   ☐ Year
   ☐ Refused
   ☐ Don't know/Not sure

3. In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have per day?

   _____ (Enter the average number of drinks per day)

   ☐ Refused
   ☐ Don't know/Not sure

4. In the past 12 months, on how many days did you have 5 or more drinks of any alcoholic beverage?

   _____ (Enter the number of days you had 5 or more drinks, or enter 0 if none.)

   ☐ Refused
   ☐ Don't know/Not sure

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5. Was there ever a time or times in your life when you drank 5 or more drinks of any kind of alcoholic beverage almost every day?

   ☐ Yes
   ☐ No
   ☐ Refused
   ☐ Don't know/Not sure

6. If you do not currently drink alcoholic beverages, but did in the past, how long has it been since you last drank regularly?

   ☐ Within the past month (0 to 1 month ago)
   ☐ Between 1 and 3 months (1 to 3 months ago)
   ☐ Between 3 and 6 months (3 to 6 months ago)
   ☐ Between 6 and 12 months (6 to 12 months ago)
   ☐ Between 1 and 5 years (1 to 5 years ago)
   ☐ Between 5 and 15 years (5 to 15 years ago)
   ☐ More than 15 years ago
   ☐ Don't know/Not sure
   ☐ Never drank regularly

7. At the heaviest point, either now or in the past, on the days when you drank, about how many drinks did you drink a day on the average?

   _____ (Enter the number of drinks a day)

   ☐ Refused
   ☐ Don't know/Not sure

8. How many years have you been drinking (or did drink) regularly?

   _____ years

   ☐ Refused
   ☐ Don't know/Not sure

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9. At what age did you begin drinking regularly?

_____ years of age

☐ Refused
☐ Don't know/Not sure

10. What type(s) of alcohol do you drink? (Mark ALL that apply)

☐ Wine
☐ Liquor
☐ Beer
☐ Wine cooler

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)

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TOBACCO ASSESSMENT - FOLLOW-UP

Instructions:
When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. Do you NOW smoke cigarettes?

☐ Everyday
☐ Some days
☐ Not at all → **Skip to Question 3.**
☐ Never smoked → **Skip to Question 4**

2. On average, when you smoked, about how many cigarettes do you (or did you) smoke a day? (A pack usually has 20 cigarettes in it).

_____ Number of cigarettes per day

3. How long has it been since you last smoked a cigarette (even one or two puffs)?

First check which one of the following choices applies to you. Then, if applicable, write a number on the line for how many days, weeks, months, or years it has been since your last cigarette.

☐ I smoked a cigarette today (at least one puff)
☐ 1-7 days → Number of days since last cigarette _____
☐ Less than 1 month → Number of weeks since last cigarette _____
☐ Less than 1 year → Number of months since last cigarette _____
☐ More than 1 year → Number of years since last cigarette _____
☐ Don't know/Don't remember

4. Since your last visit, have you used other forms of tobacco, not including cigarettes?

☐ Yes
☐ No (**End)**

5. How often do you/did you use other forms of tobacco?

☐ Every day → Number of times per day _____
☐ Some days → Number of days _____ per ☐ Week ☐ Month ☐ Year

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6. Since your last visit, which of the following products have you used? ***Check all that apply***

- ☐ Cigarettes
- ☐ E-cigarettes or other electronic nicotine delivery system
- ☐ Traditional cigars, cigarillos or filtered cigars
- ☐ Pipes
- ☐ Waterpipe
- ☐ Hookah
- ☐ Clove cigarettes or kreteks
- ☐ Bidis
- ☐ Smokeless tobacco, like dip, chew, or snuff
- ☐ Snus
- ☐ Paan with tobacco, gutka, zarda, khaini
- ☐ Other, Specify _____

7. If you do not currently use other forms of tobacco, but did in the past, how long has it been since you last used other forms of tobacco regularly?

- ☐ Within the past month (0 to 1 month ago)
- ☐ Between 1 and 3 months (1 to 3 months ago)
- ☐ Between 3 and 6 months (3 to 6 months ago)
- ☐ Between 6 and 12 months (6 to 12 months ago)
- ☐ Between 1 and 5 years (1 to 5 years ago)
- ☐ Between 5 and 15 years (5 to 15 years ago)
- ☐ More than 15 years ago
- ☐ Don't know/Not sure
- ☐ Never used other forms of tobacco regularly

The following instructions pertain to questions 8 - 10. During each of the following time frames, please indicate whether you smoked cigarettes every day, some days, or not at all.

8. During study treatment

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure
- ☐ Not applicable

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9. After the end of study treatment

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure
- ☐ Not applicable (I have not completed the study treatment)

10. Since your last visit to this clinic

- ☐ Smoked every day
- ☐ Smoked some days
- ☐ Did not smoke at all
- ☐ Don't know/not sure
- ☐ Not applicable (This is my first visit to this clinic)

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)

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ALCOHOL ASSESSMENT - FOLLOW-UP

Instructions:

For the following questions about drinking alcoholic beverages, a drink means a 12 oz. beer, a 5 oz. glass of wine, or one and a half ounces of liquor.

When a number is requested in the response, please enter a whole number (i.e. "4") and not a range or fraction of a number.

1. During the past 30 days, did you drink any alcoholic beverages?

   ☐ Yes
   ☐ No **(End)**
   ☐ Refused **(End)**
   ☐ Don't know/Not sure

2. During the past 30 days, how many days per week or per month did you drink any alcoholic beverages, on the average?

   _____ (Enter number of days you drank based on the timeframe checked below. Enter 0 if you did not drink.)

   ☐ Week
   ☐ Month
   ☐ Refused
   ☐ Don't know/Not sure

3. On the days when you drank, on average, about how many drinks did you have?

   _____ (Enter the average number of drinks you had per day.)

   ☐ Refused
   ☐ Don't know/Not sure

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4. In the past 30 days, on how many days did you have 5 or more drinks per day?

_____ (Enter the number of days you had 5 or more drinks, or enter 0 if none)

☐ Refused
☐ Do not know/Not sure

This assessment was completed by: ☐ Study Team Member ☐ Participant

Completed By: _____ Date __ __ / __ __ / __ __ __ __
(Signature of person completing) *(MM/DD/YYYY)*

Completed By: _____
(Printed name of person completing)