RESILIENCE: Effect of Comprehensive Celecoxib through Treatment for Advanced-Stage Head and Neck Cancer: A Randomized, Double-Blinded, Placebo-Controlled Trial

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LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450

Abbreviation or Term[1]	Definition/Explanation
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HNC	Head and Neck Cancer
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase

Abbreviation or Term[1]	Definition/Explanation
LLQ	The lower limit of quantitation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MME	Morphine Milligram Equivalent
MRI	Magnetic resonance imaging
MRSD	The maximum recommended starting dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
QD	Once-daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
$T_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time of maximum observed concentration
TID	Three times daily
TSH	Thyroid-stimulating hormone
ULN	The upper limit of normal
ULQ	The upper limit of quantitation

Abbreviation or Term[1]	Definition/Explanation
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[1] All of these abbreviations may or may not be used in the protocol.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

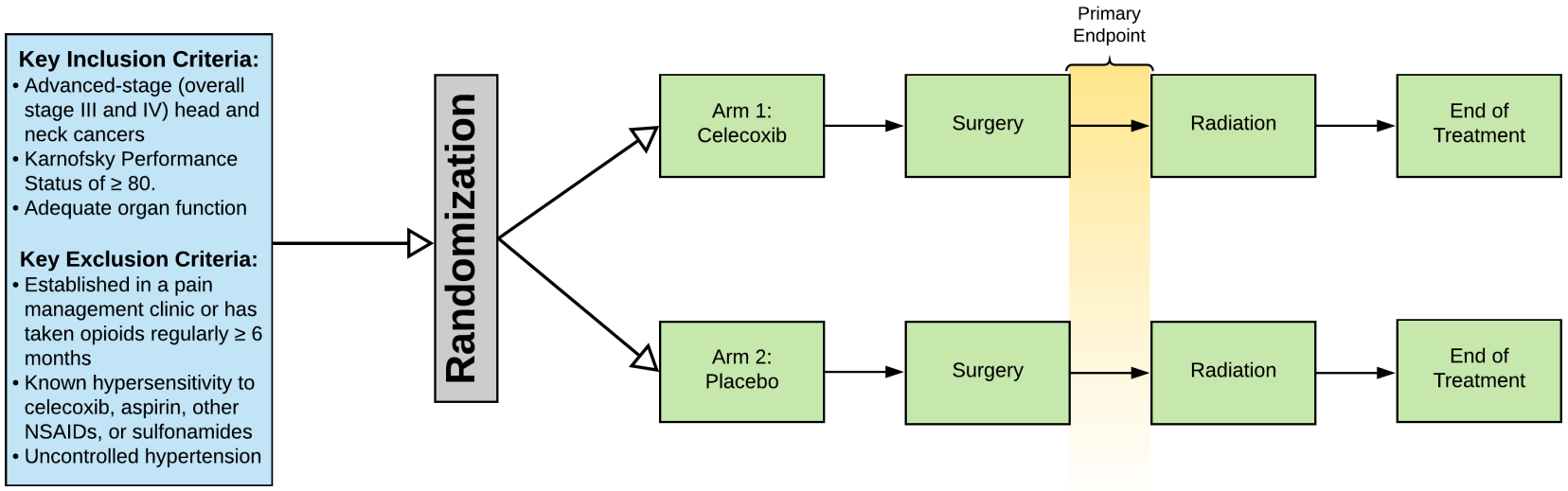
Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

STUDY SUMMARY

Title	Effect of Comprehensive Celecoxib Through Treatment for Advanced-Stage Head and Neck Cancer: A Randomized, Double-Blinded, Placebo-Controlled Trial
Short Title	RESILENCE
Protocol Identifiers (IRB – internal)	IRB # 124211
IND number	IND Exempt
Phase	Pilot
Design	Randomized, double-blinded, placebo-controlled
Study Duration	2 years
Study Center	Single Site: Huntsman Cancer Institute
Objectives	<u>Primary Objective:</u> To assess the number of days from surgery to the initiation of radiation with the addition of celecoxib compared to placebo. <u>Secondary Objectives:</u> - To assess overall pain control and management for patients on celecoxib compared to placebo. - To assess functional outcomes for patients on celecoxib compared to placebo. - To assess the effect of celecoxib therapy on Quality of Life (QoL) compared to placebo. - To assess the average number of treatment days missed during adjuvant radiation for patients on celecoxib compared to placebo.
Number of Subjects	60
Diagnosis and Main Eligibility Criteria	***Inclusion Criteria:*** - Advanced-stage (overall stage III and IV) head and neck cancers (sinonasal, oral cavity, oropharynx, larynx, and hypopharynx) undergoing surgical resection and then adjuvant radiation. - Karnofsky Performance Status of ≥ 70 - Adequate organ function. ***Exclusion Criteria*** - Metastatic disease - Exclude patients with chronic kidney disease (stage 4 and 5), prior CVA or acute MI, chronic heart failure, prior episode of GI bleed or stomach or intestinal ulcer, and liver failure.

	- Uncontrolled hypertension - Established in a pain management clinic or has taken opioids regularly for ≥ 6 months.
Study Product, Dose, Route, Regimen	Celecoxib/placebo 200mg BID oral or via a feeding tube
Duration of administration	Celecoxib/placebo will be taken 1 to 7 days prior to surgery until the completion of adjuvant radiation, approximately 4 months total, maximum allowable time on the study is limited to 6 months.
Reference therapy	Placebo
Statistical Methodology	A mixed-effects regression model that accounts for clustering (patients nested within providers) to compare the average number of days from surgery to the initiation of radiation between treatment and control groups

SCHEMA


Key Inclusion Criteria:
• Advanced-stage (overall stage III and IV) head and neck cancers
• Karnofsky Performance Status of ≥ 80.
• Adequate organ function
Key Exclusion Criteria:
• Established in a pain management clinic or has taken opioids regularly ≥ 6 months
• Known hypersensitivity to celecoxib, aspirin, other NSAIDs, or sulfonamides
• Uncontrolled hypertension
Randomization
Arm 1: Celecoxib
Arm 2: Placebo
Surgery
Surgery
Primary Endpoint
Radiation
Radiation
End of Treatment
End of Treatment

1 OBJECTIVES

1.1 Primary Objective

Recent population-level evidence demonstrates that the number of days from surgery to initiation of adjuvant radiation for advanced-stage head and neck cancer has a strong impact on survival outcomes. Therefore, we seek to assess the number of days from surgery to initiation of radiation with the addition of celecoxib compared to placebo.

Primary Endpoint: The number of days from surgery to the initiation of radiation.

1.2 Secondary Objective

- To assess overall pain control and management for patients on celecoxib compared to placebo.

  Secondary Endpoints:

  - Subjective pain scores on the visual analog scale of pain intensity averaged over a week at rest, with a swallow, and with a cough.
  - Patient satisfaction with pain control questionnaire.
  - Narcotic consumption in daily total morphine equivalents averaged over a week.

- To assess functional outcomes for patients on celecoxib compared to placebo

  Secondary Endpoints: Current activity level and swallowing capabilities, including food and liquid variety and assessment of G tube utilization.

- To assess the effect of celecoxib therapy on Quality of Life (QoL) compared to placebo.

  Secondary Endpoint: completion of quality of life questionnaires EORTC QLQ-H&N43 and MDASI-HN as per the schedule of events.

- To assess the average number of treatment days missed during adjuvant radiation for patients on celecoxib compared to placebo.

  Secondary Endpoint: the number of treatment days missed or delayed during adjuvant radiation.

2 BACKGROUND

2.1 Hypothesis

Using celecoxib comprehensively throughout treatment starting 1 to 7 days prior to surgery to the end of adjuvant radiation, will improve pain control, reduce opioid use, and improve QOL and functional status, leading to improved compliance with adjuvant radiation which is known to correlate with improved survival outcomes.

2.2 Head and Neck Cancers

Head and neck cancers (HNC) are defined as squamous cell carcinomas originating in the mucosal surfaces of the upper aerodigestive tract: the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands.[10] In the United States, an estimated 51,540 new cases were diagnosed in 2018 with a five-year survival rate of 64.8%.[9] Successful treatment requires a multidisciplinary approach often combining surgery, radiation therapy, and chemotherapy. 30-40% of patients present with early-stage (stage I or II) disease and can undergo successful surgery and/or external beam or brachytherapy radiation therapy and experience a 70-90% overall five-year survival rate. However, patients with locoregionally advanced disease (stage III/IV) require a combined modality approach often incorporating surgery and postoperative radiation therapy with or without chemotherapy, with reduced overall five-year survival rates of 40-60%.

2.3 The Effect of Pain Control on Overall Survival and Study Objective Rational

Currently, pain control throughout therapy is a major issue for patients with advanced-stage head and neck cancers (sinonasal, oral cavity, oropharynx, larynx, and hypopharynx) undergoing primary surgical resection and then adjuvant therapy. In order to maximize survival outcomes, patients treated with surgery and then adjuvant therapy (ie: radiation or chemoradiation) need to start adjuvant therapy within 8 weeks or approximately 60 days after surgery and need to minimize delays or gaps in adjuvant treatments. A recent NCDB study in this patient population demonstrated 5-year OS differences of 67% versus 52% in these 2 cohorts (initiation of adjuvant therapy <50 days versus >50 days).[1] This has been confirmed in a systematic review and other evaluations of large aggregated national datasets.[2-5] Based on our experience and retrospective examination, we have identified that the leading culprit in these cases is pain management and functional issues. These issues contribute to increased narcotic utilization and reduced recovery after surgery with weight loss, poor oral intake, and reduced overall strength, resulting in delays in initiating adjuvant therapy. This post-surgical condition of the patient is also a significant contributor to missed treatments once adjuvant therapy has begun. Based on retrospective examination, it is estimated a significant percentage of patients do not achieve the recommended rate of compliance.

We recently demonstrated with the addition of celecoxib (a selective COX-2 inhibitor NSAID) in our immediate post-operative pain management pathway that we achieved a statistically significant and clinically meaningful decrease in the amount of opioids utilized while as an inpatient.[8] The primary outcome of compliance will be analyzed by the average number of days from surgery to the initiation of radiation and adjuvant therapy. In our historical cohort of over 100 recent patients, the mean was 72.8 days (Standard Deviation 16.2 days). Our goal with this intervention is to reduce the days from surgery to radiation to 57.2days or less because recent population-level data reaffirmed this milestone as significantly improving survival outcomes. Secondary outcomes are subjective pain scores, narcotic use, functional outcomes, and patient QOL and satisfaction with pain control throughout treatment, as well as the average number of days missed during adjuvant therapy. We will study these issues prospectively with monitoring progression through treatment, standardized pain questionnaires, pain score monitoring at each phase through treatment, patient satisfaction with pain, monitoring opioid use, and QOL and functional assessments. We strongly feel that

we can achieve a significant improvement in compliance with adjuvant radiation after surgery and will investigate this medication to achieve that end, which we hope will translate into improved disease-specific and overall survival for our cancer patients.

2.4 Disease group rationale

Patients with advanced-stage head and neck cancers have significant challenges with pain control, opioid utilization, and achieving completion of treatment in a timely fashion. A recent examination of the national cancer database of this population demonstrated that 42% of patients do not start adjuvant radiation within the recommended timeframe (<50 after surgery) and examination of our historical cohorts showed similar findings. Therefore this disease group is an ideal cohort to seek to optimize these parameters, improve pain and quality of life, improve timely cancer care, and improve survival outcomes for our patients.

2.5 Drug selection rationale

Celecoxib has been shown in randomized controlled trials and meta-analysis to improve pain control, decrease opioid use, and improve functional status in patients with chronic inflammatory conditions, such as osteoarthritis and rheumatoid arthritis, thus is a good candidate for our patients.[6] Decreasing opioid utilization after surgery is clinically significant, as the CDC has shown that dosages of opioids at 50 MME (morphine milligram equivalents) or more per day doubles the risk of overdose and other opioid-related complications.[7]

2.6 Clinical experience

A retrospective matched cohort study of 147 patients who had undergone head and neck cancer surgery with free tissue reconstruction were separated into groups based on celecoxib use in the postoperative setting. Groups were matched by stage and cancer site resulting in 102 patients included, 51 celecoxib and 51 control. Postoperative use of opioids was recorded per patient per day and group mean morphine milligram equivalent was compared. Use of celecoxib was associated with a mean decrease in oral opioid use of 9.9 mg per day (95% CI, -1.2-21.1), an IV mean difference of 3.9 mg per day (95% CI, 1.0-6.8), and a total mean difference of 14 mg per day. The 51 patients who received celecoxib after surgery had a significant decrease in opioid requirements compared to the control group. This is a clinically meaningful difference in decreasing opioid utilization after surgery because the CDC has shown that dosages of opioids at 50 MME (morphine milligram equivalents) or more per day doubles the risk of overdose and other opioid-related complications.[7]

3 DRUG INFORMATION

3.1 Celecoxib

3.1.1 Pharmacology

Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of

cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

3.1.2 Physical and Chemical Properties

Celecoxib is chemically designated as 4-[5-(4 methylphenyl)- 3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The empirical formula is C17H14F3N3O2S, and the molecular weight is 381.38.

Peak plasma levels are reached 3 hours after fasted oral celecoxib dosing with a half-life of 11 hours. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose-proportional up to 200 mg BID; at higher doses there are less than proportional increases in Cmax and AUC. With multiple dosing, steady-state conditions are reached by day five with extensive distribution into tissues and about 97% of the drug protein bound.

Celecoxib metabolism is primarily mediated via CYP2C9 ultimately leading to hepatic elimination. Three metabolites, a primary alcohol, the corresponding carboxylic acid, and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

3.1.3 Pharmaceutical Properties and Formulation

Celecoxib will be compounded by Investigational Drug Services at Huntsman Cancer Institute into an oral suspension containing either 100 mg or 200 mg of celecoxib, together with inactive ingredients including croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, and sodium lauryl sulfate.

Placebo will be identical in appearance to match active counterparts.

3.1.4 Clinical Safety

Celecoxib has been shown to be safe and efficacious in many patient populations and has demonstrated acceptable tolerance. Celecoxib use is contraindicated in patients with renal and hepatic impairment. Celecoxib use can increase the risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines and older patients with a history of peptic ulcer disease and/or GI bleeding are at higher risk for developing serious GI events. Adverse reactions occurring in ≥ 2% of patients receiving celecoxib from 12 controlled studies in patients with osteoarthritis and rheumatoid arthritis are included in Table 1.

Table 1: Adverse events in ≥ 2% of osteoarthritis and rheumatoid arthritis patients

Adverse Event	Frequency
Gastrointestinal:	
Abdominal Pain	4.1%
Diarrhea	5.6%
Dyspepsia	8.8%

Flatulence	2.2%
Nausea	3.5%
Body as a whole:	
Back Pain	2.8%
Peripheral Edema	2.1%
Injury-Accidental	2.9%
Central, Peripheral Nervous system:	
Dizziness	2.0%
Headache	15.8%
Psychiatric:	
Insomnia	2.3%
Respiratory:	
Pharyngitis	2.3%
Rhinitis	2.0%
Sinusitis	5.0%
Upper Respiratory Infection	8.1%
Skin:	
Rash	2.2%

4 STUDY DESIGN

4.1 Description

This study is a randomized, double-blind, placebo-controlled, pilot study in which patients will be randomized to receive comprehensive treatment with placebo or celecoxib 200mg twice daily.

4.2 Randomization and Blinding

Patients who meet all criteria for enrollment will be randomly assigned to receive celecoxib (Arm 1) or placebo (Arm 2). Patients will be randomized through the OnCore system in a 1:1 ratio between Arm 1 and Arm 2 and stratified by treating provider.

To preserve the blind, only the Investigational Drug Services Pharmacy personnel at Huntsman Cancer Institute will know treatment assignments. Access to unblinded data/documents will be controlled by the pharmacy to ensure the blind is maintained. Every effort will be made to blind both the patient and the investigator to the treatment assignment, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel, or patient is inadvertently unblinded, the unblinding will not be sufficient cause for the patient to be discontinued from study treatment or excluded from study analyses.

In the case of an emergency, the investigator has the sole responsibility for determining if the unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the treating investigator decides that unblinding is warranted, the investigator should contact the investigational pharmacy for treatment assignment.

4.3 Number of Patients

A total of 40 evaluable patients will be enrolled in this study with 20 patients randomized to each arm: 20 patients will receive celecoxib and 20 patients will receive placebo. It is expected that 25% of patients who start study therapy and undergo surgery will not start adjuvant radiation. Patients who do not start adjuvant radiation will be replaced. Taking this into account, it is estimated that 53 patients will be randomized to result in 40 evaluable patients.

4.4 Number of Study Centers

This will be a single-center trial run at the Huntsman Cancer Institute at the University of Utah.

4.5 Study Duration

Based on current volumes, it is proposed that this study can be completed within 2 years of initiation.

5 ELIGIBILITY CRITERIA

This eligibility checklist is used to determine patient eligibility and filed with the enrolling investigator's signature in the patient research chart.

Patient No. _____

Patient's Initials: (L,F,M) _____

5.1 Inclusion Criteria

Yes/No (Response of "no" = patient ineligible)

5.1.1 _____ Male or female subject aged ≥ 18 years.

5.1.2 _____ Advanced-stage (overall stage III and IV) head and neck cancers (sinonasal oral cavity, oropharynx, larynx, and hypopharynx) undergoing surgical resection and then adjuvant radiation. Primary and recurrence cases are acceptable.

5.1.3 _____ Karnofsky Performance Status of ≥ 70.

5.1.4 _____ Adequate organ function demonstrated on labs drawn during the screening window and defined as:

- Hematologic:
  - Hemoglobin ≥ 10 g/dL
- Hepatic:
  - Total Bilirubin ≤ 2 mg/dL
  - AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN
  - Albumin > 3.5 g/dL
- Renal:
  - eGFR ≥ 30 mL/min/1.73m2 or creatinine clearance ≥ 30 mL/min by Cockcroft-Gault:
    - Males: $\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}$
    - Females: $\left(\frac{(140-age)\times weight[kg]}{serum\ creatinine\left[\frac{mg}{dL}\right]\times 72}\right)\times 0.85$
  - Serum potassium within normal limits.

5.1.5 _____ Negative serum or urine pregnancy test at screening for women of childbearing potential.

5.1.6 _____ Highly effective contraception for female subjects throughout the study and for at least 5 days after the last dose of study therapy if the risk of conception exists (see section 8.6).

5.1.7 _____ Recovery to baseline or ≤ Grade 1 CTCAE v5.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

5.1.8 _____ Willing to maintain a diary of all opioids used during the trial for the treatment of pain.

5.1.9 _____ Able to provide informed consent and willing to sign an approved consent form that conforms to federal and institutional guidelines.

5.1.10 _____ Subject has verbally confirmed they are willing to complete adjuvant radiation therapy if recommended after surgery per protocol.

5.1.11 _____ Adjuvant radiation has been recommended by the institutional treatment planning conference with the best available data, but will be confirmed based on final surgical pathology.

5.2 Exclusion Criteria

Yes/No (Response of "yes" = patient ineligible)

5.2.1 _____ Known distant metastatic disease or the tumor is deemed not surgically resectable.

5.2.2 _____ Established in a pain management clinic or has taken opioids regularly for ≥ 6 months.

5.2.3 _____ Known or suspected to be poor CYP2C9 metabolizers based on previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin).

5.2.4 _____ Known hypersensitivity to celecoxib, aspirin, other NSAIDs, or sulfonamides.

5.2.5 _____ Uncontrolled hypertension defined as blood pressure (BP) > 150 mmHg systolic or > 90 mmHg diastolic on three consecutive reads, taken in one sitting, despite optimal antihypertensive treatment.

5.2.6 _____ Patients with a known history of the following:

- Cerebrovascular accident (CVA), stroke, or cardiovascular thrombotic events (e.g. acute myocardial infarction).
- Chronic heart failure.
- Gastrointestinal bleeding, ulceration, peptic ulcer disease, or perforation of the stomach or intestines.
- Aspirin-sensitive asthma**.**
- Chronic kidney disease, stage 4 or 5.

5.2.7 _____ Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen

5.2.8 _____ The subject has an uncontrolled, significant intercurrent or recent illness requiring systemic therapy, would preclude safe study participation, or is deemed clinically significant by the investigator.

5.2.9 _____ Known HIV infection with a detectable viral load within 6 months of the anticipated start of treatment.

Note: Patients on effective antiretroviral therapy with an undetectable viral load within 6 months of the anticipated start of treatment are eligible for this trial.

5.2.10 _____ Known chronic hepatitis B virus (HBV) or hepatitis C virus infection with a detectable viral load.

Note: Patients with an undetectable HBV viral load on appropriate suppressive therapy are eligible. Patients with an undetectable HCV viral load on appropriate treatment are eligible.

5.2.11 _____ Subjects taking prohibited medications as described in Section 7.3.2. A washout period of prohibited medications for a period of at least 5 half-lives or as clinically indicated should occur prior to the start of treatment.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Recruitment Strategies

Potential patients will be identified by Head and Neck Investigators in the setting of their outpatient clinics.

6 STRATIFICATION FACTORS

At the time of randomization, patients will be stratified by the treating provider.

7 TREATMENT PLAN

7.1 Administration Schedule

Celecoxib 200 mg/20 mL or placebo will be taken orally or by feeding tube twice daily (every 12 hours ± 2 hours) without regard to food. Patients will complete 1 to 7 day(s) of study therapy prior to surgery and continue regular dosing until the completion of radiation therapy.

7.2 Celecoxib/ Placebo

7.2.1 How Supplied, Stored, Packaged and Labeled

Celecoxib/placebo will be compounded by Investigational Drug Services at Huntsman Cancer Institute into an oral suspension. The content of celecoxib will be suspended with Ora-Blend, a suspending and flavoring agent, as described by Donnelly et al to a final concentration of 10 mg/mL. [11] The suspension will be stored and dispensed in amber PVC bottles.

Placebo will be provided as assigned and will be identical in appearance to match their active counterparts.

Celecoxib/placebo will be kept at the Huntsman Cancer Institute Investigational Pharmacy in accordance with Good Clinical Practice (GCP) and GMP requirements and will be inaccessible to unauthorized personnel. Celecoxib/placebo suspension is stable for 93 days when refrigerated or stored at room temperature. The suspension should be stored in a well-ventilated area at 5-25°C. Investigators or designated personnel should check the temperature of the storage room daily and ensure that temperature monitoring devices are working correctly.

7.2.2 Preparation and Administration

Subjects will be provided enough celecoxib to last until their next scheduled visit. Celecoxib 200 mg/20mL should be administered orally or by feeding tube without regard to food twice daily (every 12 hours ± 2 hours). It should not be coadministered with aluminum or magnesium-containing antacids. Subjects should not take extra medication for any reason nor should they re-administer in the case of vomiting after administration. If a dose is missed outside of the dosing window, it should not be made up.

7.2.3 Accountability and Compliance

Drug compliance will be recorded by patients on the drug diary (see Appendix 2). A member of the study team will review patient drug compliance at the end of treatment for each cycle and provide patient re-education as required. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with study visits or study drug.

Excess or unused study drug should be returned to the investigative site, for accounting and destroyed in accordance with GCP after drug accountability has been performed.

7.3 Concomitant Medications and Therapies

7.3.1 Allowed Therapy

Any medication which is considered necessary for a subject's welfare is permitted and may be given at the discretion of the investigator. Medications for the treatment of underlying disease and symptomatic treatment of adverse events are permitted. Exceptions are listed in the section below.

7.3.2 Prohibited Therapy

Prohibited therapies that are necessary for patient health and wellbeing may be allowed only after discussion with and approval from the principal investigator and the medical monitor (and the DSMC when applicable).

Celecoxib is primarily metabolized by CYP2C9 in the liver. Co-administration of celecoxib with drugs that are known to inhibit CYP2C9 should be done with caution. Significant interactions may occur when celecoxib is administered together with drugs that inhibit CYP2C9. In vitro studies also indicate that celecoxib is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6.

In addition to cautionary use of CYP2C9 inhibitory drugs and those metabolized by CYP2D6, the following medications are prohibited while on study therapy unless prior approval is obtained:

- Other NSAIDs (e.g. ibuprofen, naproxen, etc.)
  - Aspirin may be administered post-surgery but should be administered with caution.
- Anticoagulants (e.g., warfarin)
- Known inhibitors of CYP2C9 (e.g., fluconazole)
- Warfarin
- Lithium
- Thiazides, loop diuretics, ACE-inhibitors, or angiotensin II antagonists

Celecoxib should not be coadministered with aluminum- or magnesium-containing antacids, but such antacids may be taken two hours after celecoxib dosing.

7.3.3 Duration of Therapy

Subjects will receive twice-daily dosing of 200 mg celecoxib three to seven days prior to surgery and continue twice-daily dosing until the completion of adjuvant radiation. The total duration of treatment should be approximately four to six months.

Subjects will receive celecoxib treatment until intolerable toxicity, completion of adjuvant radiation, or six months.

7.3.4 Criteria for discontinuation of study treatment

Patients may withdraw from treatment or the study overall at any time at their own request, or they may be withdrawn at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures. In addition to the drug-specific discontinuation criteria listed in Dose Modification Section and the Dose Limiting Toxicity Section, the following will result in treatment discontinuation:

- Disease progression
- Unacceptable Toxicity
- Subject withdraws consent from the study treatment and/or study procedures.
- Non-compliance as defined as having missed > 40% of required celecoxib doses.
- Dose hold ≥ 14 days unless resuming treatment is judged by the Investigator to be in the best interest of the patient.
- Does not require adjuvant radiation.
- Pregnancy
- Significant protocol violation
- The patient refused further treatment
- Study terminated by investigator sponsor
- Lost to follow-up
- Death

7.3.5 Criteria for withdrawal from the study

Subjects will be taken off study for the following:

- Completed study follow-up period
- Disease progression as assessed by the treating investigator.
- The necessity for prohibited treatment (as defined in section 6.4) of sufficient dose and duration to confound the study results as assessed by the treating investigator.

- If, in the investigator's opinion, the continuation of the trial would be harmful to the subject's well-being.
- Development of intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Participant requests to be withdrawn from the study
- Death
- Screen failure

8 TOXICITIES AND DOSE MODIFICATION

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for adverse event and serious adverse event reporting.

8.1 Dose Modifications

Every effort should be made to administer each investigational product at the planned dose and schedule. In the event of study treatment toxicity, dosing may be interrupted, delayed and/or reduced, only as described in the dose modifications section. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed (CTCAE v5.0) and/or the most conservative recommendation for any given toxicity. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

All dose modifications must be clearly documented in the patient's medical chart and in the CRF. Appropriate follow-up assessments should be done until adequate recovery occurs as assessed by the Investigator.

8.2 Dose Interruptions

Dose interruptions for study treatment-related AEs are allowed as per the recommendations provided in Section 8.4. Doses of celecoxib/placebo that were not administered due to toxicity will not be replaced. In addition to dose interruption, the need for a dose reduction at the time of treatment resumption should also be considered based on recommendations provided in Section 8.4.

Dose interruptions of more than 14 days will result in permanent discontinuation unless resuming treatment is judged by the Investigator to be in the best interest of the patient.

8.3 Dose Reductions

Following dosing interruption due to toxicity, the celecoxib dose may need to be resumed at a reduced dose as per the recommendations provided in Section 8.4. Dose reduction should proceed by decreasing the administered dose by one dose level per table 2.

Once the study treatment has been reduced for a given patient, all subsequent cycles should be administered at that dose level. Intra-patient dose re-escalation is not allowed.

Table 2: Dose Level Reduction

Agent	Initial Dose	Level -1
Celecoxib/placebo	200 mg twice daily	100 mg twice daily

8.4 Adverse Event Management

General treatment modifications for study therapy are provided in table 3 for adverse events that are deemed definitely, probably or possibly related to study therapy. Study therapy should be discontinued upon the second occurrence of an adverse event requiring a dose hold and reduction.

Table 3: Adverse Event Management Guidelines

Adverse Event	Grade	First Occurrence
Hematology		
Hemoglobin	Grade ≥ 3	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.
Hepato-Biliary		
AST or ALT increase or bilirubin increase	Grade ≥ 3	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.
Renal		
Serum creatinine	Grade ≥ 2	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.
Hyperkalemia	Grade ≥ 2	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.
Skin Reactions		
Rash	Grade ≥ 2	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.
Stevens-Johnson syndrome or toxic epidermal necrolysis	Any	Discontinue study therapy

Gastro-intestinal		
Nausea or vomiting lasting ≥ 7 days despite optimal anti-emetic therapy	Grade ≥ 2	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.
Diarrhea	Grade ≤ 2	Continue study therapy at the current dose level and initiate appropriate antidiarrheal treatment, hydration, and attention to diet. Maintain close monitoring.
	Grade ≥ 3	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.
GI Ulceration, Bleeding or Perforation	Any	Discontinue study therapy
Cardiovascular		
Hypertension	Grade ≥ 3	Hold until resolution and start appropriate antihypertensive therapy. Once hypertension has resolved to baseline or grade ≤ 1, reinitiate celecoxib at one dose reduction.
Cardiovascular thrombotic event (e.g. myocardial infarction with elevated troponin or stroke)	Any	Discontinue study therapy
Other		
Clinically significant, non-hematological adverse events attributed to the study drug.	Grade ≥ 3	Hold study therapy until recovery to grade 1 and reinitiate at a dose level reduction.

8.5 Supportive Care

All supportive measures consistent with optimal patient care may be given throughout the study.

8.6 Contraception

Women of childbearing potential are required to use one method of appropriate contraception during trial participation and 5 days after the last dose of study therapy. Childbearing potential is defined as those who have not been surgically sterilized or have not been free from menses for at least 1 year. Appropriate methods of birth controls for women include oral or implanted contraceptives, intrauterine device (IUD), diaphragm with spermicide, cervical cap, abstinence, use of a condom by the sexual partner or sterile sexual partner and also based on the judgment of the investigator.

Acceptable methods of contraception are:

- Single method (one of the following is acceptable):
  - intrauterine device (IUD)
  - contraceptive rod implanted into the skin
- Combination method (requires the use of two of the following):
  - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - male condom or female condom (cannot be used together)
  - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

9 SCHEDULE OF EVENTS

The Schedule of Events table provides an overview of the protocol visits and procedures. Refer to the Study Procedures section of the protocol for detailed information on each assessment required for compliance with the protocol. The Investigator may schedule visits (unplanned visits) in addition to those listed in the Schedule of Events table in order to conduct evaluations or assessments required to protect the wellbeing of the patient. This Schedule of Events will be followed for the entire study.

Table 4: Schedule of Events

Examination	Screening[1]	Pre-Operation[2]	Surgery[3]	Post-Operation[4]	5 Weeks Post-Operation	Mid Radiation[5]	End of Treatment[6]
Informed Consent	X						
Medical History	X						
Eligibility Criteria	X						
Vital Signs	X			X		X	X
Physical Exam[7]	X			X		X	X
Karnofsky Performance Status[8]	X	X		X		X	X
Functional Oral Intake Score	X	X		X		X	X
Hematology[9]	X			X		X	X
Chemistry[10]	X			X		X	X
Pregnancy Test[11]		X					
HIV and Hepatitis Serologies[12]	X						
Radiation Oncology Consultation	X[13]						
Surgery			X[14]				
Celecoxib/placebo[15]		X					
Questionnaires[16]		X		X		X	X
Pre-treatment Questionnaire[17]		X					
Analgesic Use Record[18]		X		X		X	X
Adverse Events		X					
Concomitant Medications	X	X		X		X	X
Telephone Call or Email[19]					X		

[1] All screening procedures must be completed ≤ 28 days prior to surgery.
[2] This visit may be combined with Screening if all Pre-Operation visit procedures occur ≤ 14 days prior to surgery. All pre-operation activities must be completed prior to starting study therapy.
[3] All procedures must be completed prior to surgery.
[4] Post-operation visit will occur 5 to 30 days after surgery.
[5] Mid-radiation visit will occur 5-35 days after initiation of radiation therapy.
[6] End of treatment visit will occur 1 to 30days after the last treatment of radiation.
[7] Appendix 8: Treating Investigator Patient Assessment Guidance to be filled out by the treating investigator at the time of physical exam.
[8] See Appendix 8: Treating Investigator Patient Assessment Guidance
[9] Hematology to include CBC with platelets and differential.
[10] Chemistry to include a complete metabolic panel (CMP).
[11] All women of child-bearing potential must have a negative pregnancy test 7 days prior to surgery.
[12] Only required if there is a known history of HIV, hepatitis B, or hepatitis C to confirm eligibility.
[13] The radiation oncology consultation should be completed prior to registration if possible. This will include a discussion of the indications for adjuvant radiation treatment, a typical treatment course, and the anticipated/possible side effects so the subjects know what to expect if enrolled on trial.
[14] Prior to surgery, the surgical team (physicians, nursing staff, pharmacy, etc.) will be notified about the patients involvement in the trial to ensure standard of care celecoxib and other prohibited therapies are not inadvertently administered.
[15] Patients will complete 1 to 7 days of study therapy prior to surgery and continue twice daily dosing until the last radiation session.
[16] Appendix 3: MDASI Head and Neck Cancer, Appendix 4: EORTC QLQ-H&N43, Appendix 5: Pain Satisfaction Questionnaire, and Appendix 7: Visual Analog Scale for Pain to be completed within 1 month of the scheduled time-points.
[17] Appendix 6: Pre-treatment Questionnaire to be completed at the pre-operation visit.
[18] Patients will be required to record all opioids taken for pain management on Appendix 4: Pain Management Diary while at home. Diary does not need to be maintained during admission post-surgery but should be started when study therapy is started and continue until completion of study therapy.
[19] 5 weeks (±7 days) post-operation the study team will contact the patient to review their medication diary, adverse events, and analgesic use record. If not returning to the study site at this time point, patients will be asked to fax or scan and email their Patient Dosing Diary and Pain Management Diary use records for the study team for review to ensure timely review of study drug compliance.

10 STUDY PROCEDURES

10.1 Screening

For screening procedures see the Schedule of Events and the Assessments Section. Screening activities may only begin after a subject has signed consent. All screening activities must take place within 28 days prior to surgery unless otherwise noted.

10.2 Treatment Period

Once a subject has completed screening, has been found to be eligible, and has been registered, treatment procedures may begin. At the pre-operation visit baseline, questionnaires will be completed and study medication will be dispensed. Patients will be instructed not be begin study medication until 6 days prior to the date of surgery to ensure 5 full days of twice-daily dosing. All pre-operation visit procedures must take place within 14 days prior to surgery unless otherwise noted.

Upon completion of 1 to 7 days of study therapy dosing, patients will undergo head and neck surgery as deemed appropriate by the treating investigator. 14 days (± 7 days) after surgery patients will return to the clinic and begin arrangements for adjuvant radiation therapy.

Five to thirty days post-operation every effort should be made to contact the patient to assess study drug compliance and adverse events. For patients not returning to the study site during this time frame, this contact may occur by phone or email. During this contact the study team will check the patient's Dosing Diary, Pain Management Diary, and adverse events. The patient will be asked to scan and email or fax their Dosing Diary and Pain Management Diary for assessment of adherence to the study regimen. However, if the patient does not have access to equipment to do this or is unwilling, failure to obtain the diaries will not be considered a deviation.

During adjuvant radiation, patients will return to clinic for evaluation (Mid-Radiation visit) 5 to 30 days after initiating radiation therapy. Patients will be instructed to continue study therapy twice-daily dosing until completion of their last radiation treatment.

See the Schedule of Events and the Assessments Section for treatment period procedures.

10.3 End of Treatment

Upon discontinuation of study treatment, an End of Treatment visit will occur. The end of treatment visit will occur 1 to 30 days after the last radiation treatment or after patient discontinues treatment. For End of Treatment procedures see the Schedule of Events and the Assessments Section.

11 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-

being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

11.1 Physical Examinations and Vital Signs

Patients will have physical examinations to include major body systems, vital signs, assessment of Karnofsky performance status (see Appendix 8), Functional Oral Intake Score (Table 5), weight and height (height will be measured at screening only) at the time points described in the Schedule of Events. If necessary to facilitate scheduling, physical exam may occur one day prior to study treatment. Appendix 8: Treating Investigator Patient Assessment Guidance is to be filled out by the treating investigator at every physical exam.

Vital signs, to include blood pressure, pulse rate, and temperature will be also recorded at the time points described in the Schedule of Events.

Table 5: Functional Oral Intake Scale

Score	Performance	Implication	Deficit
1	Aspirates saliva	Nothing by mouth	Profound
2	Tube dependent	Nothing by mouth/minimal trials	Profound
3	Tube dependent	Full trials by mouth	Severe
4	Total Oral	Single texture trials	Moderate
5	Total Oral	Multiple texture trials	Mild
6	Total Oral	By mouth/ restrictions	Minimal
7	Regular diet	By mouth/ no restrictions	Normal

11.2 Adverse Events

Adverse events experienced during trial participation will be collected per the Schedule of Events and Adverse Events Section. Each study participant will be questioned about the occurrence of adverse events in a non-leading manner. Should the treating investigator feel that the adverse event is attributed to study therapy, then dose modification guidelines in the Dose Modification Section will be followed.

11.3 Laboratory Assessments

Samples for all laboratory assessments will be drawn at the time points indicated in the Schedule of Events and when clinically indicated. Laboratory tests may be performed up to 3 days prior to the scheduled clinic visit. All safety laboratory analyses will be performed by the local laboratory for each study center. All safety laboratory assessments must be reviewed

by the treating investigator. When applicable, results from the pregnancy test must also be available for review prior to dosing.

Table 6: Laboratory Assessments

Laboratory Assessments	
CBC with Platelet Count and Differential	• White Blood Cell Count • Hemoglobin • Platelets • Absolute Neutrophil Count • Absolute Lymphocytes
Complete Metabolic Panel (Chemistry)	• Sodium • Potassium • Chloride • Carbon Dioxide • Alkaline Phosphatase • Aspartate Aminotransferase • Alanine Aminotransferase • Urea Nitrogen • Glucose • Creatinine • Calcium • Protein • Albumin • Bilirubin
Pregnancy	• Beta-hCG Qualitative Urine or Serum

11.4 Analgesic Use Record

All patients will be required to keep a diary of all opioids used for pain management during the trial. Patients should be instructed to record all opioid use from the start of study therapy to the end of study therapy. This information will be converted to Oral Morphine Equivalents (OME) and recorded in the eCRF.

12 CRITERIA FOR EVALUATION AND ENDPOINT

12.1 Primary Objective

The number of days from surgery to the initiation of adjuvant radiation will be retrospectively collected and compared between Arm 1 and Arm 2. The day of surgery will be considered day 0 and the number of days will be counted until the first dose of adjuvant radiation.

12.2 Secondary Objectives

12.2.1 Safety

Routine safety will be evaluated from the results of reported signs and symptoms during study visits. Safety will be evaluated from scheduled physical examinations, vital sign measurements, and clinical laboratory test results collected at the participant's visits

Physical Examination

Complete and symptom-directed physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner).

Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse rate, and temperature.

Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the Schedule of Events.

12.2.2 Pain Control and Management

Pain control and management will be compared between Arm 1 and Arm 2 and will be gauged through:

- Patient-reported subjective pain scores will be recorded on the visual analog scale of pain intensity averaged over a week at rest, with a swallow, and with a cough.
- Questionnaires focused on patient satisfaction with pain control.
- Narcotic consumption in daily total morphine equivalents averaged over a week collected from patient recorded opioid use throughout study therapy.

12.2.3 Functional Outcome

Functional outcomes will be compared between Arm 1 and Arm 2. Activity level will be assessed utilizing Karnofsky Performance Status and the use of G tube (yes or no) will be noted at every study visit. Patient-reported quality of life will be assessed by QLQ-H&N43 as indicated in the Schedule of Events. Swallowing capabilities, including food and liquid variety, will be captured through the use of a 7-point, Functional Oral Intake Scale as assessed by the treating investigator.

The number of days of adjuvant radiation missed or delayed will be retrospectively collected and compared between Arm 1 and Arm 2. Every day that treatment is delayed will be counted until the resumption of therapy.

12.3 Stopping Rules

While an interim analysis is not planned for this trial, continual safety monitoring will be provided by the DSMC. The study will be stopped if at any time the following *combination* of conditions occurs, which is: at least 2 patients undergoing study therapy experience grade

≥ 3 toxicities related to study drug resulting in discontinuation, *and* the proportion of patients experiencing these toxicities exceeds 15%. With this rule, if the true proportion of patients experiencing these toxicities is 2%, which is considered acceptable, the probability of stopping accrual is 0.03. If the true proportion of patients experiencing these toxicities is 20%, which is considered unacceptable, the probability of stopping accrual is 0.88.

13 STATISTICAL CONSIDERATIONS

13.1 Statistical hypothesis

We will use a mixed-effects regression model that accounts for clustering (patients nested within providers) to compare the average number of days from surgery to the initiation of radiation between treatment and control groups. We hypothesize that utilization of study therapy will significantly reduce the average number of days to initiation of adjuvant radiation.

13.2 Sample size determination

The sample size calculation was based on the current average number of days to adjuvant radiation in our patients with advanced-stage head and neck cancer, 72.8 days (Standard Deviation 16.2 days) based on the most recent 100 patients that fit criteria. Our goal is to reduce the current average number of days to adjuvant radiation down to 57.2days since this has been shown to improve survival.

Assuming Group A mean =72, Group B mean = 57.2, and the common SD =16.2, a two sample t-test with 20 patients in each group will provide 80% power with an alpha = 0.05. Note that the estimated SD = 16.2 days includes variation by provided as well as random variation and thus the estimated power is likely to be conservative as control of provider variation using a mixed-effects model should provide additional power.

13.2.1 Statistical justification for change in hypothesis

The sample size calculation was modified due to an interim review with the clinical trials team, the investigators, and the safety and monitoring committee. It was determined by expert opinion and previously established data, that a reduced group B mean was clinically reasonable based on similar studies and prior results seen in similar situations, and this results in a reduced sample size necessary to achieve 80% power.

13.3 Population for analyses

13.3.1 Evaluable for toxicity

Subjects who have taken one dose of study therapy will be evaluable for toxicity.

13.3.2 Evaluable for the primary endpoint

Subjects who have completed study therapy lead-in, undergone surgery, and received one treatment of adjuvant radiation will be evaluable for the primary endpoint. Patients who do not start adjuvant radiation will be replaced.

13.4 Statistical Analyses

Appropriate descriptive statistics will be reported for all study variables, stratified by treatment arm. These will include mean, standard deviation and 95% confidence interval for continuous study variables. For categorical study variables the descriptive statistics will include counts, proportions and 95% binomial confidence intervals.

13.4.1 Primary endpoint

The primary endpoint is the number of days from surgery to adjuvant chemotherapy. A Gaussian mixed effects regression model will be used to compare the average number of days from surgery to the initiation of radiation between treatment and control groups. The model will contain fixed effects for treatment arm and provider and a nested random effect for patient within provider. The mean difference between treatment groups, two-sided p-value and 95% confidence interval will be calculated from the model.

13.4.2 Secondary endpoint

The secondary endpoints fall into two categories for statistical analysis:

A. Opioid use, subjective pain score, functional assessment of swallow, number of treatment days missed or delayed, and quality of life questionnaire (EORTC QLQ-H&N43 and MDASI-HN) individual items and summary scales.

   Each of the endpoint variables in Category A will be analyzed using a Gaussian mixed effects regression model. The model will contain fixed effects for treatment arm and provider and a nested random effect for patient within provider. The mean difference between treatment groups and a 95% confidence interval will be calculated from the model.

B. G tube required (Y/N)

   G tube use will be analyzed using a mixed effects logistic regression model. The model will contain fixed effects for treatment arm and provider and a nested random effect for patient within provider. An odds ratio between treatment groups and a 95% confidence interval will be calculated from the model.

14 REGISTRATION GUIDELINES

Study related screening procedures can only begin once the patient has signed a consent form.

Patients must meet all of the eligibility requirements listed in Section 5 prior to registration.

Patients must be registered before receiving any study treatment and must being treatment within five working days after registration.

To register eligible patients on study, complete a Clinical Trials Office Patient Registration Form and submit to CTORegistrations@hci.utah.edu.

15 DATA SUBMISSION SCHEDULE

The Case Report Forms (CRFs) are a set of (electronic or paper) forms for each patient that provides a record of the data generated according to the protocol. CRF's should be created prior to the study being initiated and updated (if applicable) when amendments to the protocol are IRB approved. These forms will be completed on an on-going basis during the study. The medical records will be source of verification of the data. During the study, the CRFs will be monitored for completeness, accuracy, legibility and attention to detail by a member of the Research Compliance Office. The CRFs will be completed by the Investigator or a member of the study team as listed on the Delegation of Duties Log. The data will be reviewed no less than annually by the Data and Safety Monitoring Committee. The Investigator will allow the Data and Safety Monitoring Committee or Research Compliance Office personnel access to the patient source documents, clinical supplies dispensing and storage area, and study documentation for the above-mentioned purpose. The Investigator further agrees to assist the site visitors in their activities.

Data capture should be restricted to endpoints and relevant patient information required for planned manuscripts.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Human Subject Protections

The study will be conducted in accordance with the appropriate FDA, IRB, ICH GCP and other federal and local regulatory requirements, as applicable. Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version. All patients must be at least 18 years of age to participate.

16.2 Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other applicable patient-facing documents. The investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information.

The investigator or designee should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

16.3 Data and Safety Monitoring Plan

A Data and Safety Monitoring Committee (DSMC) is established at Huntsman Cancer Institute (HCI) to ensure the well-being of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. The roles and responsibilities of the DSMC are set forth in the NCI-approved Data and Safety Monitoring (DSM) plan. The activities of the committee include reviewing adverse events (including SAEs), deviations, important medical events, significant revisions or amendments to the protocol, and approving cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be

stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This is a Phase II treatment study with no IND application classified as moderate risk per the NCI-approved DSM plan.

Each moderate risk study may be assigned a physician member of the DSMC as medical monitor, or in rare cases, an external medical monitor. The medical monitor will be notified of all serious adverse events (SAEs). SAEs occurring in patients treated at HCI or its affiliates will also be reviewed by the full DSMC monthly.

Each moderate-risk study will be assigned a dedicated research compliance officer who will monitor the trial. Moderate-risk trials will be monitored by RCO personnel after the first patient is enrolled and every six months thereafter during active enrollment. The RCO monitor will review the study status and summarize enrollment, toxicities, SAEs, dose escalation, statistical endpoints (e.g., stopping rules), deviations, etc. for the full DSMC membership at the regularly scheduled meetings. Amendments that increase risk, change dosing, or impact study objectives will be reviewed by the DSMC and approved by the PRMC and IRB. Moderate-risk trials will be formally reviewed by the DSMC after the first patient is enrolled and then semi-annually thereafter.

An initial audit of moderate-risk studies will be conducted by the RCO approximately one year after enrollment begins and annually thereafter. Audits of moderate-risk studies may be conducted more frequently as requested by the DSMC, IRB, PRMC, RCO management, or the PI.

16.4 Adverse Events and Serious Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for AE and SAE reporting.

16.4.1 Adverse Events (AEs)

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. For the purposes of this study, the terms toxicity and adverse event are used interchangeably. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Collection of adverse events will begin from the first dose of study medication and until the end of treatment visit (or until a new cancer treatment is initiated).

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

As far as possible, each adverse event should be evaluated to determine:

1. The severity grade based on CTCAE v5.0 (grade 1-5)
2. Its relationship to the study drug(s) (definite, probable, possible, unlikely, not related)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes an SAE

All adverse events will be treated appropriately. Such treatment may include changes in study drug treatment as listed in the dose modification section of this protocol (see section 8 for guidance). Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about celecoxib are described in the Drug Information (section 3) and in the current product insert. This information will be included in the patient informed consent and will be discussed with the patient during the study as needed.

All adverse events will be immediately recorded in the patient research chart.

16.4.2 Serious Adverse Event (SAE)

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Causes congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug

- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Collection of serious adverse events will begin after the first dose of study medication and end at the end of treatment visit or until a new cancer treatment is initiated, whichever happens the soonest.

Any death from any cause while a patient is receiving treatment on this protocol or up to the end of treatment visit, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related, must be reported.

Toxicities which fall within the definitions listed above must be reported as an SAE regardless if they are felt to be treatment related or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be documented as AEs in the patient research chart.

16.4.3 Reporting Serious Adverse Events

All serious adverse events should be reported as soon as possible but no later than one business day after the Investigator becomes aware. All SAEs must be reported via the HCI CTMS (OnCore) and submitted to HCI-RCO@utah.edu. The HCI Clinical Site Monitor will in turn, submit the report to the Medical Monitor. The RCO will summarize and present all reported SAEs according to the Data and Safety Monitoring Plan at the monthly DSMC meeting.

At a minimum, initial SAE reports must include a description of the event, assessment of event causality, event grade, and the expectedness of the event. Although the Investigator may not know all the information at the time of the event, the available information should be reported. An SAE follow-up may be submitted at a later date once more information is known. It is required that follow-up reports be submitted until the SAE is resolved.

Follow-Up Information

It is recommended that follow-up reports be submitted as new information becomes available, however, a follow-up report should be submitted within 7 days of knowledge of event resolution. Follow-up information will be added to the SAE in OnCore and submitted to the DSMC via RCO.

16.4.4 FDA Notifications

Per 21 CRF 600.80 adverse events and serious adverse events will be reported on a MedWatch 3500A form to the FDA. Reportable events will be reported by the RCO according to the following guidelines:

16.4.4.1 MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description

- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- Expectedness of the event (i.e., expected or unexpected event).

16.4.4.2 FDA Reporting Timelines:

- 7 Calendar Day Report:

  Any event that is fatal or life-threatening, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA by telephone or fax within seven calendar days of first learning of the event.

- 15 Calendar Day Report:

  Any event that is serious, unexpected, and definitely, probably or possibly related to study medication will be reported to the FDA in an IND safety report within 15 calendar days of first learning of the event.

  In accordance with 21 CFR 312.32, an Analysis of Similar Events should be included in the IND Safety Report. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

  FDA fax number for IND Safety Reports:

  Fax: 1 (800) FDA 0178

16.4.5 IRB Notification

The University of Utah IRB requires any unanticipated problems that may increase the risk to research participants be promptly reported. All study-therapy related, unexpected adverse events whose nature, severity, or frequency is not consistent with either:

- The unknown or foreseeable risk of adverse events that are described in the protocol related-documents, such as the IRB-approved research protocol, applicable investigator brochure, the current IRB-approved informed consent document, and/or other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease or condition of the subject(s) experiencing the adverse event.

Adverse events meeting this criterion must be promptly reported to the IRB within 10 business days of awareness.

16.5 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject as an SAE. Pregnancies or

lactation that occurs during the course of the trial or with 5 days of completing the trial or starting another new anticancer therapy, whichever is earlier, must be reported to the DSMC, IRB, FDA, and the sponsor as applicable. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events.

16.6 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all subjects included in the trial.

Any amendments to the protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

16.7 Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The sponsor requires the **prompt reporting** to HCI RCO of protocol deviations which are:

- Exceptions to eligibility criteria.
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm), or
- Possible serious or continued noncompliance

16.8 FDA Annual Reporting

This study is IND exempt therefore there are no annual reporting requirements to the FDA.

16.9 Clinical Trials Data Bank

The study will be registered on **http://clinicaltrials.gov** and the NCI CTRP (Clinical Trials Reporting Program) by the Clinical Trials Office.

16.10 Record Keeping

Per 21 CFR 312.57, the Investigator records shall be maintained for a period of 2 years following the date a marketing application is approved; or, if no application is filed or the application is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

17 BIBLIOGRAPHY

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Appendix 1: Patient Dosing Diary

Subject Number: _____ Date: _____

The study therapy should be stored in a well-ventilated area at 5-25°C (41-77° F—refrigeration is recommended, particularly during the summer months). Study therapy should be taken twice a day, every 12 hours ± 2 hours, without regard to food. It should not be taken with aluminum- or magnesium-containing antacids (such as: Acid Gone, Di Gel, Milk of Magnesia, Mylanta, or Gaviscon) within two hours of taking study therapy.

Date	Time	Amount of mLs Taken	Comments:
	AM	mL	
	PM	mL	
	AM	mL	
	PM	mL	
	AM	mL	
	PM	mL	
	AM	mL	
	PM	mL	
	AM	mL	
	PM	mL	
	AM	mL	
	PM	mL	
	AM	mL	
	PM	mL	
	AM	mL	
	PM	mL	

_____ _____

Patient Signature Date

Appendix 2: Pain Management Diary

Subject Number: _____ Date: _____

Date	Medication Taken	Dose Taken (mg)

_____ _____

Patient Signature Date

Appendix 3: MDASI Head and Neck Cancer

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

M. D. Anderson Symptom Inventory - Head & Neck (MDASI-HN)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your problem with **mucus** in your mouth and throat at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **swallowing/chewing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Page 1 of 2

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
16. Your **choking/coughing** (food/ liquids going down the wrong pipe) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your difficulty with **voice/speech** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **skin pain/burning/rash** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your problem with **tasting food** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your **mouth/throat sores** at their WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your problem with your **teeth or gums** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. General activity?	○	○	○	○	○	○	○	○	○	○	○
24. Mood?	○	○	○	○	○	○	○	○	○	○	○
25. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
26. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
27. Walking?	○	○	○	○	○	○	○	○	○	○	○
28. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

Appendix 4: EORTC Q LQ-H&N43

EORTC QLQ – H&N43

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had pain in your throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems because of losing some teeth?	1	2	3	4
41.	Have you had problems opening your mouth wide?	1	2	3	4
42.	Have you had a dry mouth?	1	2	3	4
43.	Have you had sticky saliva?	1	2	3	4
44.	Have you had problems with your sense of smell?	1	2	3	4
45.	Have you had problems with your sense of taste?	1	2	3	4
46.	Have you had problems with coughing?	1	2	3	4
47.	Have you had problems with hoarseness?	1	2	3	4
48.	Have you had problems with your appearance?	1	2	3	4
49.	Have you felt less physically attractive as a result of your disease or treatment?	1	2	3	4

Please go on to the next page

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
50.	Have you felt dissatisfied with your body?	1	2	3	4
51.	Have you had problems eating?	1	2	3	4
52.	Have you had problems eating in front of your family?	1	2	3	4
53.	Have you had problems eating in front of other people?	1	2	3	4
54.	Have you had problems enjoying your meals?	1	2	3	4
55.	Have you had problems talking to other people?	1	2	3	4
56.	Have you had problems talking on the telephone?	1	2	3	4
57.	Have you had problems talking in a noisy environment?	1	2	3	4
58.	Have you had problems speaking clearly?	1	2	3	4
59.	Have you had problems going out in public?	1	2	3	4
60.	Have you felt less interest in sex?	1	2	3	4
61.	Have you felt less sexual enjoyment?	1	2	3	4
62.	Have you had problems raising your arm or moving it sideways?	1	2	3	4
63.	Have you had pain in your shoulder?	1	2	3	4
64.	Have you had swelling in your neck?	1	2	3	4
65.	Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
66.	Have you had a rash?	1	2	3	4
67.	Has your skin changed colour?	1	2	3	4
68.	Have you worried that your weight is too low?	1	2	3	4
69.	Have you worried about the results of examinations and tests?	1	2	3	4
70.	Have you worried about your health in the future?	1	2	3	4
71.	Have you had problems with wounds healing?	1	2	3	4
72.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
73.	Have you had problems chewing?	1	2	3	4

Appendix 5: Pain Satisfaction Questionnaire

Subject Number: _____ Date: _____

Please circle or mark one number per question to indicate your pain control satisfaction as it applies to the past 7 days

1. How often was your pain well controlled?
    0) Never
    1) Sometimes
    2) Usually
    3) Always

2. How often did the staff do everything they could to help you with your pain
    0) Never
    1) Sometimes
    2) Usually
    3) Always

3. How satisfied are you with your Overall pain control
    0) Very Dissatisfied
    1) Somewhat dissatisfied
    2) Neutral
    3) Somewhat satisfied
    4) Very satisfied

4. Was there anything else that we could have done to make your pain control better during you treatment?

_____ _____

Patient Signature Date

Appendix 6: Pre-treatment Questionnaire

Subject Number: _____ Date: _____

1. In the past, how effective are narcotic pain medications (such as morphine, Vicodin, Norco, Percocet, oxycodone, Dilaudid) at controlling your pain?

    0) Very ineffective
    1) Somewhat ineffective
    2) Somewhat effective
    3) Very effective

2. In the past, how has your pain tolerance been?

    0) Very poor
    1) Somewhat poor
    2) Somewhat tolerant
    3) Very tolerant

3. Do you experience a significant amount of pain on a daily basis aside from the pain due to your current head and neck condition

    0) Yes, I do.
    1) No, I do not.

_____ _____

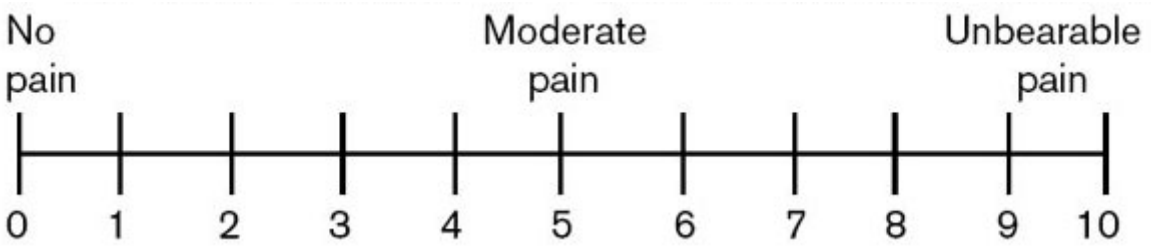
Patient Signature Date

Appendix 7: Visual Analog Scale for Pain

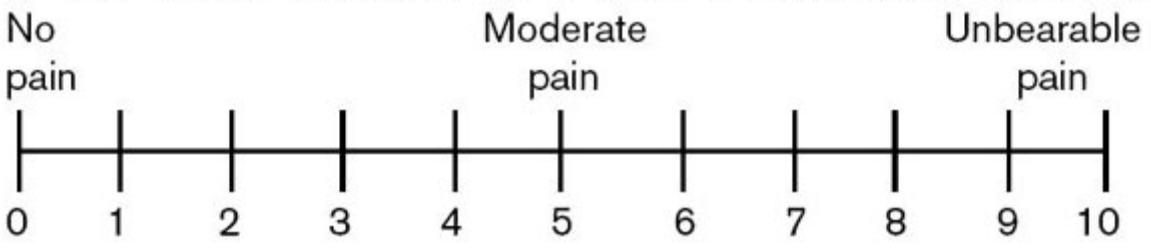
Subject Number: _____ Date: _____

Place an X on the line to indicate your pain intensity averaged as it applies to the past 7 days while at rest, with a swallow, and with a cough.

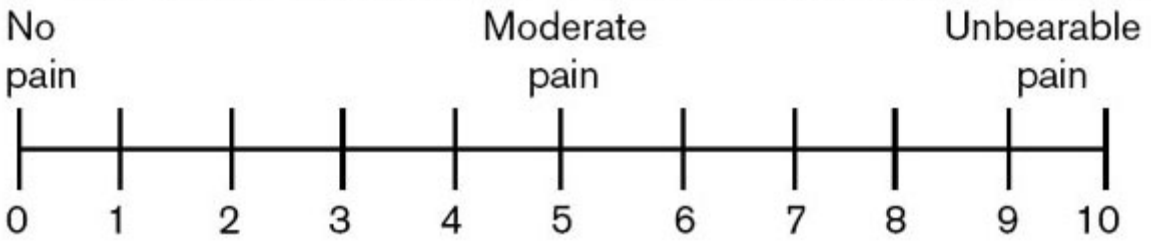
While at rest:



With a Swallow:



With a Cough



_____ _____

Patient Signature Date

Appendix 8: Treating Investigator Patient Assessment Guidance

Subject Number: _____ Date: _____

During a physical exam, complete the following questions by circling the applicable answer:

1. Karnofsky Performace Status

Score	Definition
100	Normal, no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self but unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very ill; hospitalization and active supportive care necessary
10	Moribund
0	Dead

2. Functional Oral Intake Scale

Score	Performance	Implication	Deficit
1	Aspirates saliva	Nothing by mouth	Profound
2	Tube dependent	Mothing by mouth/minimal trials	Profound
3	Tube dependent	Full trials by mouth	Severe
4	Total Oral	Single texture trials	Moderate
5	Total Oral	Multiple texture trials	Mild
6	Total Oral	By mouth/ restrictions	Minimal

7	Regular diet	By mouth/ no restrictions	normal

Appendix 8: Treating Investigator Patient Assessment Guidance

3. Does the patient use a feeding tube?

   Yes No

_____ _____

Investigator Signature Date