| | |
|---|---|
| Title: | **Celecoxib for Pain Management after Tonsillectomy** |
| Short Title | Celecoxib after Tonsillectomy |
| Drug Name: | celecoxib |
| FDA IND | N/A |
| eIRB Number | 15-011707 |
| Protocol Date: | May 12, 2015 |
| Amendment 1 Date: | May 23, 2016 |
| Amendment 2 Date: | June 8, 2016 |

Amendment 3 Date: August 29, 2016

Amendment 4 Date: October 31, 2016

Amendment 5 Date: October 23, 2017


**Principal Investigator**

John Germiller, M.D., Ph.D.
Division of Otolaryngology, First Floor, Wood Center
The Children's Hospital of Philadelphia
3401 Civic Center Blvd.
Philadelphia, PA 19104

Phone 215-590-3440
email: germiller@email.chop.edu

## TABLE OF CONTENTS

## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ACE | Angiotensin converting enzyme |
| ADR | Adverse drug reaction |
| AE | Adverse Event |
| AUC | Area under the curve (concentration over time) |
| BID | Twice daily |
| BMI | Body Mass Index |
| CBC | Complete blood count |
| CI | Confidence interval |
| $C_{max}$ | Peak plasma level of drug (maximum concentration) |
| COX-1 | Cyclooxygenase-1 |
| COX-2 | Cyclooxygenase-2 |
| CRF | Case report form |
| CYP2C9 | Cytochrome P isozyme 2C9 |
| ED | Emergency Department |
| GI | Gastrointestinal |
| JIA | Juvenile idiopathic arthritis |
| JRA | Juvenile rheumatoid arthritis |
| NOS | Not otherwise specified |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OA | osteoarthritis |
| OR | Odds ratio |
| PACU | Perioperative anesthesia care unit |
| PK | Pharmacokinetics |
| RA | Rheumatoid arthritis |
| SAE | Serious adverse event |
| SAN | Storage area network |
| SSRI | Selective serotonin reuptake inhibitor |
| $T_{1/2}$ | Half life |
| $T_{max}$ | Time to peak plasma level of drug |

## ABSTRACT

Context:

Tonsillectomy is one of the most common pediatric surgical procedures in the United States. Postoperative pain is substantial, with typical regimens employing narcotic derivatives and acetaminophen for 1-2 weeks after surgery. Recent enthusiasm for use of ibuprofen as an alternative has been tempered by equivocal data on its relative safety in regard to risk of postoperative hemorrhage. A few centers have used celecoxib, a selective inhibitor of cyclooxygenase-2, which should provide pain relief without increasing bleeding risk.

Objectives:

The primary objective is to evaluate efficacy of celecoxib for pain control after tonsillectomy in children. The secondary objective is to assess safety in regard to postoperative hemorrhage and adverse events.

Study Design:

Randomized, double-blind, placebo-controlled trial. Subjects will take acetaminophen plus either celecoxib or placebo in regular scheduled doses, and will supplement as needed with standard of care analgesic therapy (oxycodone/acetaminophen).

Setting/Participants:

Subjects are healthy children aged 3 to 11 years who undergo tonsillectomy with or without adenoidectomy at any CHOP location. Subjects with coagulation disorders are excluded. Approximately 300 subjects will be enrolled, 150 in each treatment group.

Study Interventions and Measures:

Subjects are provided celecoxib or placebo in scheduled doses every 12 hours for 5 days, then continue until they are pain-free, for a maximum of 10 days. Throughout the study, they are allowed to use oxycodone/acetaminophen as needed for additional pain control, following standard clinical care. Acetaminophen is used around the clock for the first 5 days in all subjects. For 14 days following surgery, subjects record pain levels on validated pain scale instruments, quantity of narcotic medication and acetaminophen required, and time to return to normal diet. All Emergency Department and hospital admissions during the 30 postoperative days are recorded, noting incidence of excess pain, dehydration, hemorrhage, and other complications.

Pain control efficacy is assessed by comparing groups for number of days in which narcotic medication was used, and total quantity of rescue pain medication consumed. Rates of hospital readmission and postoperative hemorrhage, and the need for operative control, are also compared between groups.

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Study Title** | **Celecoxib for Pain Management after Tonsillectomy** |
| **Funder** | Pfizer and Children's Surgical Associates |
| **Clinical Phase** | N/A |
| **Study Rationale** | Tonsillectomy is one of the most common pediatric surgical procedures in the United States. Postoperative pain is substantial, with typical regimens employing narcotic derivatives and acetaminophen for 1-2 weeks after surgery. Recent enthusiasm for use of ibuprofen as an alternative has been tempered by equivocal data on its relative safety in regard to risk of postoperative hemorrhage. A few centers have used celecoxib, a selective inhibitor of cyclooxygenase-2, which should provide pain relief without increasing bleeding risk. We aim to determine if celecoxib can reduce postoperative pain and narcotic usage in this population, without increasing risk of hemorrhage. |
| **Study Objective(s)** | **Primary**<br>To measure efficacy of celecoxib for pain control after tonsillectomy. The primary measures of pain control will be the total quantity of rescue medication consumed, and total number of days requiring rescue medication.<br><br>**Secondary**<br>• To evaluate surrogate measures of pain control, including time to return to normal diet, rates of pain-related complications and admissions (e.g., dehydration).<br>• To evaluate safety in regard to rates of postoperative hemorrhage and adverse events.<br>• To evaluate tolerability of celecoxib for short term administration in this population. |
| **Study Drug** | Celecoxib, as a suspension 100 mg/5mL. Dosing is 6 mg/kg BID (maximum 300 mg BID). |
| **Study Design** | Randomized, double-blind, placebo-controlled trial. Subjects will take acetaminophen plus either celecoxib or placebo in regular scheduled doses for 5 days, then continue until they are pain-free, for a maximum of 10 days. They will supplement as needed with standard of care analgesic therapy (oxycodone/acetaminophen). |
| **Subject Population** | **Inclusion Criteria**<br><br>1. Males and females age 3 to 11 years inclusive. |

| | |
|---|---|
| **key criteria for Inclusion and Exclusion:** | 2. Scheduled to undergo tonsillectomy (with or without adenoidectomy).<br>3. Weight ≥ 10 kg.<br>4. Girls ≥ 11 years of age must have a negative urine/serum pregnancy test on the day of surgery and must use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), Depo-Provera, or an oral contraceptive, for the duration of the study.<br>5. Parental/guardian permission (informed consent) and if appropriate, child assent.<br>**Exclusion Criteria**<br>1. Prior tonsillar surgery.<br>2. Concomitant surgical procedure that adds more than mild additional pain. Note: ear tubes are always permissible.<br>3. Coagulation disorder, or any other hematologic disorder that affects clotting or results in anemia.<br>4. Moderate to severe asthma, defined as subjects who either (1) have daily symptoms requiring daily use of short-acting bronchodilators, or (2) had an exacerbation in the last 3 months requiring admission, ED visit, or systemic corticosteroid administration.<br>5. Any degree of aspirin-sensitive asthma, or any history of asthma exacerbation caused by NSAID use.<br>6. Severe obstructive sleep apnea that requires use of CPAP or BiPAP.<br>7. Significant chronic pulmonary disease, defined as subjects requiring oxygen therapy, ventilator support, or positive pressure therapy.<br>8. Significant cardiac disease, defined as any one of the following: cardiovascular disease, structural cardiac anomalies, prior cardiac surgery, or requirement for cardiac anesthesia.<br>9. Severely obese (BMI > 99$^{th}$ percentile for age).<br>10. History of hepatic or renal disease, or condition that impairs hepatic or renal function.<br>11. Juvenile rheumatoid arthritis (JRA).<br>12. History of GI bleeding, or chronic GI condition that would increase risk of bleeding, ulceration, or perforation. |

| | |
|---|---|
| | 13. Hypertension.<br>14. Craniofacial syndromes.<br>15. Syndrome or neurologic condition that would hinder accurate assessment of postoperative pain.<br>16. Inability to feed orally or take oral pain medication.<br>17. Chronic pain disorders, or otherwise requiring pain medication more than once weekly.<br>18. Laboratory abnormalities on the preoperative CBC:<br>Hemoglobin < 9 gm/dL<br>Platelet count < 100,000/$mm^3$<br>19. Any investigational drug use within 30 days prior to enrollment.<br>20. Pregnant or lactating females.<br>21. Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.<br>22. Hypersensitivity or allergic reactions to celecoxib, aspirin, or other NSAIDs, including asthma flare ups.<br>23. Allergy to sulfonamides or calcium carbonate. |
| **Number Of Subjects** | Total 300 subjects, equally divided between celecoxib and placebo. |
| **Study Duration** | Each subject's participation will last from 1-4 months.<br>The entire study is expected to last 1 year. |
| **Study Phases** | (1) Screening: screening for eligibility and consent obtained. This is done at the pre-operative office visit.<br>(2) Study Drug Treatment: After surgery, subjects consume study medication every 12 hours for 5 days, then until pain-free, for a maximum 10 days.<br>(3) Follow-Up: Admissions to ED or hospital are recorded during the 30 postoperative days. Subjects receive telephone follow up at 3, 14, and 30 days to assess compliance and record any complications or AEs |
| **Efficacy Evaluations** | Pain control efficacy is assessed by comparing number of days in which narcotic medication was used, and total quantity of rescue pain medication consumed. Also compared are time to return to |

| | |
|---|---|
| | normal diet, and rates of ED or hospital readmission for dehydration and excessive pain. |
| **Safety Evaluations** | Recording of AEs and comparison of celecoxib to placebo groups. Rates of hospital readmission and postoperative hemorrhage, and the need for operative control, will also be compared between groups. |
| **Statistical And Analytic Plan** | Primary efficacy endpoints are number of days requiring rescue narcotic medication, and total amount of rescue narcotic consumed, expressed as morphine equivalents and normalized to body weight. Secondary efficacy endpoints are the time to return to normal diet, and rate of readmission for dehydration or excessive pain. These are compared between celecoxib and control groups using two-sample t-tests.<br>The primary safety endpoints are rates of AEs and rates of postoperative hemorrhage. These will be compared by descriptive summaries. |
| **DATA AND SAFETY MONITORING PLAN** | The P.I. will be responsible for monitoring the integrity of the data and the safety of all subjects. The PI reviews SAEs immediately, and other AEs during regular meetings with the study team approximately every 2 weeks. Data is collected for all hospital readmissions in the 30 days following surgery, and this includes the AE data. AEs are reported to the IRB as described in the protocol section AE Reporting. There is no Data Safety Monitoring Board for this study. |

## TABLE 1: SCHEDULE OF STUDY PROCEDURES

| **Study Phase** | **Screening** | **Treatment** | | | | **Follow-up** | | |
|---|---|---|---|---|---|---|---|---|
| **Visit / Activity** | **Before Surgery** | **Surgery Day** | **Treatment (home)** | **Call 1** | **Treatment (home)** | **Home Observation** | **Call 2** | **Call 3** |
| **Postoperative Day** | | **0** | **1-5** | **3(+/-1)** | **6-10** | **11-14** | **14(+/-1)** | **30 (+/-2)** |
| Informed Consent/Assent | X | | | | | | | |
| Review Inclusion/Exclusion Criteria | X | | | | | | | |
| Demographics/Medical History | X | | | | | | | |
| Physical Examination | X[1] | | | | | | | |
| Vital Signs: BP, HR, RR | | X[2] | | | | | | |
| Height and Weight | X[1] | | | | | | | |
| Pregnancy Test | | X[2] | | | | | | |
| Prior/Concomitant Medications | X[1] | X[2] | | | | | | |
| CBC with platelets | X[1] | | | | | | | |
| Randomization | X | | | | | | | |
| Dispense Study Drug | | X | | | | | | |
| Administer Study Drug | | X | X | X | X[3] | | | |
| Acetaminophen | | X | X | X | PRN | PRN | | |
| Oxycodone | | PRN | PRN | PRN | PRN | PRN | | |
| Diary- Pain, Narcotic use, diet, fluid intake, urine output | | X | X | X | X | X | | |
| Drug compliance | | | | X | | | X | |
| Drug accountability | | | | | | | X | |
| Adverse Event Assessment | | | | X[4] | | | X | X |

Notes

1- These are clinical care; they are recorded from the preoperative office visit.
2- Recorded from perioperative records. Pregnancy testing for females of childbearing potential is always done as part of clinical care before surgery in the preoperative area.
3- Duration of study drug is until child is pain-free (see text), or the maximum of 10 days has been reached.
4- Includes specific query about skin rash. If skin rash has occurred, subjects discontinue study medication.

# 1 BACKGROUND INFORMATION AND RATIONALE

## 1.1 Introduction

Tonsillectomy is one of the most common pediatric surgical procedures in the United States. Postoperative pain is substantial, with typical regimens employing narcotic derivatives and acetaminophen for 1-2 weeks after surgery. Ibuprofen has been used by some centers as an alternative to narcotics, and has proven effective for pain control. However, ibuprofen inhibits platelet function, and the possibility that it might increase risk of postoperative bleeding, combined with equivocal data regarding its safety, has limited its widespread adoption in this setting. Tonsillectomy carries a significant bleeding risk of 2-5%, and hemorrhage events are often emergent situations, since they typically occur 1-2 weeks after surgery when patients are at home. Up to half of patients who have hemorrhage require re-operation.

A few centers have used celecoxib to control post-tonsillectomy pain. Celecoxib is a newer nonsteroidal anti-inflammatory drug (NSAID) that is a selective inhibitor of cyclooxygenase-2. Because platelet inhibition is mediated via cyclooxygenase-1, celecoxib should provide pain relief without increasing bleeding risk like traditional NSAIDs. We hope to employ this drug as a key element in post-tonsillectomy management, and this study represents the first step in evaluating its efficacy and safety. Specifically, we aim to determine if celecoxib can reduce postoperative pain and narcotic usage after tonsillectomy, without increasing risk of hemorrhage.

## 1.2 Name and Description of Investigational Product or Intervention

The study drug is celecoxib. Celecoxib is a nonsteroidal anti-inflammatory drug with anti-inflammatory, analgesic, and antipyretic activities. Its mechanism of action is by 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.

Celecoxib is approved by the FDA for use in children ages 2 and older for treatment of juvenile rheumatoid arthritis. Celecoxib is on the CHOP formulary for use in (1) patients >= 2 years old for JRA, (2) patients >= 12 years old and >=40 kg who have increased risk for GI adverse effects or bleeding concerns precluding use of traditional NSAIDs, and (3) oncology patients with surface area >= 0.4 square meters for anti-angiogenesis. Celecoxib is approved by the FDA for use in adults for treatment of arthritic conditions, acute/ postoperative pain, and primary dysmenorrhea, and has been widely used since its introduction in 1998.

## 1.3 Findings from Clinical Studies

### 1.3.1 Clinical Studies

#### *1.3.1.1 Human Pharmacokinetics*

The following are adapted from the *Full Prescribing Information* for Celebrex (Pfizer, Inc).

***Absorption**:* Peak plasma levels of celecoxib occur approximately 3 hrs after an oral dose. Under fasting conditions, both peak plasma levels ($C_{max}$) 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 $C_{max}$ and AUC. Absolute bioavailability studies have not been conducted. With multiple dosing, steady-state conditions are reached on or before Day 5. The pharmacokinetic parameters of celecoxib in a group of healthy adult subjects are shown in Table 2 below.

**Table 2 : Summary of Single Dose (200 mg) Disposition Kinetics of Celecoxib in Healthy Adult Subjects**

| Mean (%CV) PK Parameter Values | | | | |
|---|---|---|---|---|
| **Cmax, ng/mL** | **Tmax, hr** | **Effective $t_{1/2}$, hr** | **Vss/F, L** | **CL/F, L/hr** |
| 705 (38) | 2.8 (37) | 11.2 (31) | 429 (34) | 27.7 (28) |

Subjects under fasting conditions (n=36, 19-52 yrs.)

Kinetics of suspension formulation and sprinkled capsules: In healthy adult volunteers, the overall systemic exposure (AUC) and $C_{max}$ of celecoxib was equivalent when celecoxib was administered as an intact capsule, as capsule contents sprinkled on applesauce, or as a 20 mg/mL oral suspension. There were no significant alterations in $C_{max}$, $T_{max}$ or $t_{1/2}$ after administration of capsule contents on applesauce [Krishnaswami et al 2012].

***Distribution**:* In healthy subjects, celecoxib is highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, $\alpha_1$-acid glycoprotein. The apparent volume of distribution at steady state ($V_{ss}/F$) is approximately 400 L, suggesting extensive distribution into the tissues.

***Metabolism**:* Celecoxib metabolism is primarily mediated via CYP2C9. 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.

***Excretion**:* Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% was excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of the glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half-life is approximately 11 hours under fasted conditions. The apparent plasma clearance (CL/F) is about 500 mL/min.

***Pediatric Pharmacokinetics***:

Single-dose and steady-state pharmacokinetics were investigated in 10 children aged 6-16 receiving celecoxib over a 1 week period for anti-angiogenesis [Stempak et al 2002]. The drug was absorbed and distributed similarly as adults, but was metabolized much faster.

Celecoxib was cleared approximately twice as fast as adults, and had a half-life approximately half as long (3.7 hours compared to 8.9 hours). These findings led the authors to conclude that higher or more frequent dosing may be needed in children, rather than simply the use of weight-adjusted adult dosing.

The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 JRA patients 2 years to 17 years of age weighing ≥10 kg with pauciarticular or polyarticular course JRA and in patients with systemic onset JRA. Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient. Based on these data, the manufacturer recommends twice-daily administration of 50 mg capsules to JRA patients weighing ≥10 to ≤25 kg and 100 mg capsules to JRA patients weighing >25 kg to achieve plasma concentrations similar to those observed in a clinical trial that demonstrated the non-inferiority of celecoxib to naproxen (*see Clinical Studies in Children, below).* Celecoxib has not been studied in JRA patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), or beyond 24 weeks duration of therapy.

***Platelet pharmacodynamics****:* In clinical trials using normal volunteers, celecoxib at single doses up to 800 mg and multiple doses of 600 mg twice daily for up to 7 days duration (higher than recommended therapeutic doses) had no effect on reduction of platelet aggregation or increase in bleeding time.

#### *1.3.1.2 Clinical Studies in Adults*

Celecoxib has been well studied in adults and is widely used in the management of rheumatoid arthritis and osteoarthritis (OA). In knee and hip OA, celecoxib was evaluated in placebo- and active-controlled clinical trials of up to 12 weeks duration. Treatment with celecoxib 100 mg twice daily or 200 mg once daily resulted in improvement in pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, celecoxib doses of 100 mg twice daily and 200 mg twice daily provided significant reduction of pain within 24-48 hours of initiation of dosing [Celebrex *Full Prescribing Information,* Pfizer Inc.]

Celecoxib has also been studied in adults for managing acute pain after surgery, and in primary dysmenorrhea. In acute analgesic models of post-oral surgery pain, post-orthopedic surgical pain, and primary dysmenorrhea, celecoxib relieved pain that was rated by patients as moderate to severe. Single doses provided pain relief within 60 minutes. [Celebrex *Full Prescribing Information,* Pfizer Inc.] Li et al [2009] studied 51 adults over 55 years of age receiving total hip replacement, randomized to diclofenac, rofecoxib, or placebo. Overall, ADRs were similar between the two NSAIDs. Rofecoxib resulted in less perioperative blood loss compared to diclofenac (7% increase over placebo with rofecoxib, vs. 32% increase over placebo with diclofenac).

Adverse drug reactions (ADRs) of celecoxib appear to be similar to other NSAIDs. Upper GI bleeding is a known risk of chronic NSAID therapy. In a large population-based, nested case-control analysis of 10,892 adults, Hippisley-Cox et al [2005] studied rates of first-ever

adverse upper GI events. The COX-2 inhibitors (rofecoxib or celecoxib) were found comparable to the traditional NSAIDs (ibuprofen, diclofenac, and naproxen). For further discussion of adverse reactions, see Section 9.4 below.

***Adverse Events from the analgesia and dysmenorrhea studies:*** Approximately 1,700 patients were treated with celecoxib in studies of post-oral surgery pain (single dose), and of analgesia and dysmenorrhea (up to 600 mg/day). The types of adverse events were similar to those reported in arthritis studies. The only additional adverse event reported was post-dental extraction alveolar osteitis (dry socket) in the post-oral surgery pain studies. For further discussion of adverse reactions, see Section 9.4 below.

#### *1.3.1.3 Clinical Studies in Children*

Celecoxib has been studied in children, mainly with juvenile rheumatoid arthritis, and was found to be effective and well tolerated. Foeldvari et al [2009] studied celecoxib at 2 dose levels in 242 children aged 2-17 years, at least 9 kg, compared to naproxen, for 12 weeks, with a 12-week open label extension. The drug was given as a suspension (10 mg/mL or 20 mg/mL for the low and high-dose groups, respectively). Celecoxib was non-inferior to naproxen for efficacy, and safety data (adverse events) were comparable between groups. This was true even with fairly high dosages in the high-dose group -- 6 mg/kg BID (maximum of 300 mg BID). The most common (>5%) adverse events were headache, fever, upper abdominal pain, cough, nasopharyngitis, abdominal pain, nausea, arthralgia, diarrhea and vomiting. Similar AEs and rates were seen in the naproxen-treated subjects. The incidence of AEs in the 12-week, open-label extension was similar during the double blind study, and this was at the higher celecoxib dose (6 mg/kg BID).

Murto et al [2015] studied celecoxib in 282 children age 2-18 who underwent tonsillectomy. This study used a loading dose of 6 mg/kg preoperatively followed by 3 mg/kg BID on postoperative days 0-2. The drug was given as a suspension (10 mg/mL). Celecoxib was effective for pain reduction and was well-tolerated, with no difference in adverse events between the celecoxib and placebo groups. The results are detailed further in Section 1.5, "Use after tonsillectomy," below.

Sobel et al [2014] compared safety of celecoxib and ibuprofen from a Phase-4 registry in 274 children 2-17 years with JIA/JRA. Again, adverse drug reactions (ADRs) were comparable; no bleeding events were reported. In a retrospective review of ADRs, Titchen et al [2005] compared several NSAIDs in 19 children who had ADR reports between 1999 and 2003. Again total AEs were comparable among celecoxib, rofecoxib, and the standard NSAIDs. Finally in a Cochrane Review, Derry et al [2013] report 1785 children and adults 15 years and older, receiving a single dose of celecoxib vs placebo for moderate to severe postoperative pain. Celecoxib was effective in pain reduction, and AEs were generally mild to moderate in severity, and were experienced by a similar proportion of participants in the celecoxib and placebo groups.

In summary, celecoxib has been shown safe and effective in children receiving short term therapy, much longer than that proposed in the present study. Its efficacy and safety however have not been studied beyond six months of treatment.

## 1.4 Selection of Drugs and Dosages

Celecoxib is available commercially only as capsules. In young children, it is typically administered by opening the capsules and sprinkling the drug on puree food such as applesauce. Older children may swallow capsules whole if they are capable.

Suspension formulations have been used in several large studies in children. The trials in children with both JRA and tonsillectomy, detailed above, used suspensions of 10 or 20 mg/mL made at the local institutions [Foeldvari et al 2009, Murto et al 2015]. The suspensions are stable at least 93 days at either room temperature or refrigerated [Donnelly et al 2009]. Pharmacokinetic analysis has been performed in both adults and children [Krishnaswami et al 2012], showing drug bioavailability in the suspensions that was equivalent to capsule or sprinkle administration.

Dosage endorsed by the FDA for children with JRA is 50 mg BID for weight 10 kg to <=25 kg, and 100 mg BID for weight >25 kg. This is approximately 3 mg/kg BID, which was the dose used in the recent pediatric tonsillectomy trial by Murto et al [2015], and was also the lower dose group in the pediatric JRA trial [Foeldvari 2009]. However, the conclusion of the Murto group was that this dose is too low to produce major relief of the acute pain after tonsillectomy. Citing the PK study by Stempak [2002] showing shorter half life and more rapid clearance in children, the authors recommended higher dosing for tonsillectomy and a longer duration of therapy.

Indeed, much higher doses have been well tolerated in children. As noted earlier, the higher dose group in the Foeldvari study (6 mg/kg BID) had rates of adverse events comparable to the lower dose group, even when given well over 12 weeks. Furthermore, the PK study by Stempak et al [2002] used even higher doses (average 8.6 mg/kg BID, range 7-12 mg/kg BID) for over one week in 10 cancer patients aged 6-16, with no reported toxicity.

Based on data from all the studies in children, our dosing for the present study is as follows. Children will receive 6 mg/kg BID (maximum 300 mg BID) for the duration of their acute pain, up to a maximum of 10 days. We will formulate study drug into a suspension following the method of Donnelly et al [2009], except with a 20 mg/mL concentration to facilitate the current dosing. The latter concentration was used effectively in the JRA trial as well. Subjects will receive their first dose just before surgery, following Murto et al [2015].

## 1.5 Relevant Literature and Data

**Background**

Pain management after pediatric adenotonsillectomy remains a significant health care problem [Baugh et al, *AAO-HNSF Clinical Practice Guideline,* 2011]. Historically, pain has been managed with opiates, but recently there has been increased interest in reducing the use of opiates in children, particularly following the recent FDA black-box warning that followed reports of deaths in children treated with codeine after tonsillectomy, who had an uncommon genetic variant causing hypermetabolism of codeine [Kuehn 2013].

Accordingly, there has been increased interest in use of non-narcotic alternatives, including NSAIDs, for postoperative tonsillectomy pain management. Many centers use NSAIDs extensively for pain management. However, because this surgery is notable for a significant risk of life-threatening airway hemorrhage of 2-5%, there has been reluctance nationally to adopt widespread use of NSAIDs for this indication, based on the tendency of traditional nonselective NSAIDs to inhibit platelet function, and thus possibly increase bleeding risk.

At this time, the literature remains equivocal about the safety of traditional NSAIDs regarding postoperative bleeding risk. In a 2011 Practice Guideline published by the American Academy of Otolaryngology-Head & Neck Surgery, conflicting evidence was presented. A Cochrane review of 13 randomized trials involving 955 children requiring surgical intervention for bleeding, and 7 trials involving 471 children not requiring surgical intervention, found that NSAIDs did not significantly increase bleeding risk [Cardwell et al 2005]. Furthermore, a meta-analysis found increased risk from use of aspirin, but not for nonaspirin NSAIDs such as diclofenac and ibuprofen [Krishna et al, 2003]. On the other hand, another systematic review found some evidence for increased risk of reoperation for bleeding in patients given NSAIDs postoperatively [Møiniche et al 2003].

Importantly, since that publication, an updated Cochrane review was published [Lewis et al, 2013]. There were 15 studies involving 1101 children in this updated review. Fourteen studies compared NSAIDs with other analgesics or placebo and reported on bleeding requiring surgical intervention. The use of NSAIDs was associated with a nonsignificant increase in the risk of bleeding requiring surgical intervention: Peto odds ratio (OR) 1.69 (95% confidence interval (CI) 0.71 to 4.01). In 10 studies involving 365 children, NSAIDs did not significantly alter the number of perioperative bleeding events requiring non-surgical intervention: Peto OR 0.99 (95% CI 0.41 to 2.40), but the confidence intervals did not exclude an increased risk. The Cochrane group concluded that "there is insufficient evidence to exclude an increased risk of bleeding when NSAIDs are used in paediatric tonsillectomy"[Lewis et al, 2013].

<u>CHOP experience with NSAIDs post-tonsillectomy</u>

For approximately 1 year, CHOP Otolaryngology used ibuprofen extensively an adjunct to pain management for tonsillectomy patients. Though primary pain management remained acetaminophen and oxycodone, patients were instructed to add the ibuprofen if they experienced breakthough pain. Ibuprofen was also commonly used in-house, in younger patients admitted postoperatively for observation. Indeed, it was quite successful as a rescue medication, with successful resolution of pain escalations requiring calls to phone triage, as well as significant reduction in pain calls overall (unpublished internal review, summer 2013). However, a possible rise in overall rates of postoperative hemorrhage was observed during the ibuprofen period, and also in rates of bleeding requiring re-operation. In a 4 month period reviewing 696 tonsillectomy cases, overall events were 33/696 = 4.7%, including 20 (3.5%) requiring re-operation (unpublished internal review, Spring 2014). These were slightly increased over historical rates in our Division of about 3-4% and 2%, respectively. Importantly, during that time ibuprofen status of each individual patient was not documented, so it is unclear how many of these cases were actually using rescue

ibuprofen at home. Nevertheless, it was clear that an increase trend toward hemorrhage was evident during the time ibuprofen was most extensively used.

More recently, in the Spring of 2014, there were 3 notable severe hemorrhage events in which ibuprofen was known to have been used. Two lost significant blood volume and were difficult to control in the operating room and required transfusions, which are rarely needed in this situation. The third child had hemorrhage severe enough to require tracheotomy. These 3 severe events prompted our Division Chief to suspend the use of ibuprofen throughout the Division. The prevailing opinion in our Division at this time is that ibuprofen slightly increases overall bleeding risk, but more importantly, it increases the severity of the events when they do occur. This has prompted our division as a group to seek a safer alternative to ibuprofen for pain management.

Current CHOP Standard of Care for Pain Management

Standard care at CHOP is oxycodone (0.075 mg/kg/dose) and acetaminophen (15 mg/kg/dose), as liquid formulations for all ages. Both are officially prescribed as every 4 hours as needed, but patients are usually instructed by the PACU nurses to use the acetaminophen and oxycodone around the clock for the first few days, until their pain becomes less intense. The number of days are not specified. Patients then switch to using both as-needed. The only patients not routinely advised to use around-the-clock dosing are the very young infants and toddlers (under age 3).

Patients are instructed to call the phone triage nurses if they experience uncontrolled pain at home. In that case, the phone triage nurse first confirms the patient is taking their acetaminophen and oxycodone. Their oxycodone dose is then increased as necessary up to 0.1 mg/kg/dose every 4 hours, with referral to the ED if pain is still not controlled. Review of phone triage logs revealed over 24% of patients called with pain issues, and 7-8% required up-dosing of oxycodone (Internal QI data, March 2013).

Celecoxib as a possibly safer alternative

Celecoxib is a selective inhibitor of cyclooxygenase-2. As such, it provides the pain control of traditional, nonselective NSAIDs, but without their side effect of platelet inhibition, which is mediated through COX-1. Celecoxib is widely used in the management of pain of rheumatoid arthritis and osteoarthritis in adults, and is FDA-approved in children 2 years and older and > 10 kg for management of juvenile rheumatoid arthritis (see *Clinical Studies,* above). It is currently on the CHOP Formulary for this indication.

Use after tonsillectomy

There is limited data on use of Cox-2 inhibitors after surgery in children, including tonsillectomy. Before it was withdrawn from the market, another Cox-2 inhibitor, rofecoxib, was administered to children successfully with no increase in bleeding rates observed [Joshi et al 2003]. Rofecoxib, which was available as a liquid formulation, was

pulled from the market in 2004 over concerns for increased risk of myocardial infarction in adults with coronary artery disease.

In adults, several small studies found celecoxib to be safe and effective after tonsillectomy. A small study of 120 adults in Finland compared celecoxib capsules to ketoprofen, a nonselective NSAID, after tonsillectomy. While ketoprofen provided a better initial pain control, after discharge, recovery with celecoxib was faster and the rate of secondary hemorrhage was lower (<1%, vs. 6% with ketoprofen) [Nikanne et al 2005]. The University of Iowa also reported a small study of celecoxib capsules after tonsillectomy in adults (N=18, randomized, placebo-controlled). In this small cohort, celecoxib reduced postoperative narcotic and acetaminophen requirements compared to placebo; no postoperative hemorrhages were noted in either group. [Van Daele et al, 2014]

Celecoxib itself has not yet been widely used for pediatric tonsillectomy, likely due to the fact that a liquid formulation is not yet commercially available. The Children's Hospital of Eastern Ontario developed their own oral suspension, which it now uses it as its primary regimen for pain control (S. Kherani MD, personal communication). The suspension is stable for 90 days and its details were published [Donnelly et al, 2009].

The CHEO group recently completed a randomized trial comparing celecoxib to placebo in 282 children after tonsillectomy [Murto et al, 2015]. Celecoxib was given as a loading dose of 6 mg/kg just prior to surgery, followed by 3 mg/kg BID for 5 more doses. They used their in-house suspension of 10 mg/mL referenced above. The 3 mg/kg dose was chosen as it closely approximates that recommended for children with JRA. Pain scores were found to be significantly lower in the celecoxib group, though the reductions were only modest (11% reduction in worst pain levels for postoperative days 0-2). Co-analgesic consumption was also modestly but significantly reduced (20% less consumption of acetaminophen and oral morphine). Notably, the dosing period was very short (2 days), after which pain scores rebounded to levels equal to or greater than placebo, for the duration of the postoperative recovery. In this trial, celecoxib was found safe and well tolerated, with rates of adverse events, including bleeding, no different from placebo.

Of interest, the group separately analyzed the data from the 7.4% of their cohort who were genetically slow metabolizers of celecoxib (CYP2C9*3 heterozygotes). Children in this subgroup receiving celecoxib showed greater relief of pain, and for a longer duration, than those with the normal genotype.

In summary, the authors found: (1) only modest pain reduction, followed by immediate rebound, when children were given standard celecoxib dosing (which was developed based on JRA patients); (2) an excellent safety profile; (3) better pain control in the slow metabolizers. These findings, combined with prior data showing celecoxib to have more rapid clearance in children compared to adults [Stempak 2002, detailed above], led the authors to conclude that different doses should be used after tonsillectomy. They recommended a higher dose of the drug, and for longer duration, to ensure more effective pain control in this setting. Finally, noting the synergy of acetaminophen with NSAIDs,

they also recommended adding supplemental acetaminophen "around the clock," as the combination may provide greater analgesic effects.

Summary of current evidence and rationale

The available evidence regarding safety of ibuprofen after tonsillectomy remains equivocal, even after several systematic reviews and meta-analyses. Additionally, CHOP Otolaryngology has clinically observed increased severity of bleeding events in patients who received ibuprofen. These observations support the search for a safer alternative for pain management. The ideal drug would decrease narcotic usage in children, while not increasing bleeding rates over traditional regimens (narcotic+ acetaminophen), be well-tolerated, and have experience in its use in children. Celecoxib satisfies these criteria, with enough preliminary data to suggest it is effective for pain control while not increasing bleeding risk. Furthermore, recent pediatric data confirm it is safe and effective after pediatric tonsillectomy, and confirm the efficacy and safety of an oral suspension. However, the fact that benefits were only modest under the current approved dosing for chronic use in JRA, suggests that higher doses are needed in children undergoing this surgical procedure. This the rationale for the doses used the present study.

### 1.6 Compliance Statement

This study will be conducted in full accordance all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 2 STUDY OBJECTIVES

The purpose of the study is to determine the efficacy and safety of celecoxib when used for pain control after tonsillectomy.

### 2.1 Primary Objective

The primary objective of this study is to determine whether celecoxib reduces pain in children 3 to 11 years after tonsillectomy. The primary measures of pain control will be total quantity of rescue pain medication used, and number of days on rescue medication.

### 2.2 Secondary Objectives

The secondary objectives are to:

- Determine whether celecoxib shortens time to return to normal diet.
- Determine whether celecoxib reduces pain-related complications and readmissions (e.g. admissions for dehydration, calls or ED admissions for excessive pain).
- Determine whether celecoxib increases rate of post-tonsillectomy hemorrhage compared to placebo.
- Evaluate the tolerability of celecoxib for short-term administration after tonsillectomy.
- Evaluate safety in terms of rates of other adverse events.

# 3 INVESTIGATIONAL PLAN

## 3.1 General Schema of Study Design

This is a randomized, double-blind, placebo-controlled trial. Subjects will take either celecoxib or placebo in regular scheduled doses, twice daily for a maximum of 10 days following tonsillectomy surgery, and will supplement as needed with standard of care analgesic therapy (oxycodone/acetaminophen). Subjects record pain scores, narcotic consumption, and type of diet daily for 14 days. Follow up telephone calls are performed by registered nurses during therapy, and by study staff the end of the recovery period (2 weeks), and at 30 days. Adverse events, admissions, and complications are recorded during follow up calls, from patient diaries, and from hospital records. The overall schema is presented in the Table of Study Procedures above.

### 3.1.1 Screening Phase

Potential subjects are identified during the pre-operative office visit by the physicians and nurse practitioners in the Division of Otolaryngology. Subjects will have been already been determined to need tonsillectomy surgery, with or without adenoidectomy, will have been consented for the surgical procedure, will have just undergone the preoperative anesthesia pre-visit process, which includes history and physical, and assessment of comorbid conditions that affect surgery. Potential subjects are screened for inclusion and exclusion criteria, then the study is explained, including the randomization scheme, risks, benefits, and alternatives, then subjects are approached for informed consent/ assent. Subjects who consent/assent to the study are randomized to either study drug or placebo prior to surgery.

Parental/guardian permission (informed consent) and, if applicable, child assent, will be obtained prior to any study-related procedures being performed. Note that blood samples (CBC with platelets) are drawn on all subjects as part of clinical care, and all females of childbearing potential undergo a preoperative urine pregnancy test on the day of surgery, also as clinical care.

### 3.1.2 Study Treatment Phase (Postop day 0 until pain-free, maximum 10 days)

This Phase includes the day of surgery (Day 0), and up to 10 postoperative days, during which time subjects receive study medication.

Subjects receive their first dose of study medication just before surgery in the preoperative holding area. After surgery, subjects undergo usual clinical care in the post-anesthesia care

unit, then are either discharged to home (Day Surgery), or are admitted for inpatient observation as per clinical care. The procedures below are identical for either pathway.

They then receive a dose of study drug that evening, then twice daily thereafter, at 12 hour intervals. Pain levels are assessed just before each dose of study medication, and as needed in between. All subjects take acetaminophen (15 mg/kg/dose) in scheduled doses every 4 hours for the first 5 days. During those 5 days, any acetaminophen dose scheduled during the early morning hours (midnight to 6 AM) will be optional if subject is asleep. After 5 days, acetaminophen is taken as needed.

Subjects supplement with standard of care oxycodone to control any breakthrough pain. Subjects record volume of oxycodone consumed throughout the 2-week recovery period, the pain scores, and time to return to normal diet. A follow up call by a study nurse occurs at Day 3 (+/- 1 day) to assess compliance with medication, pain control, compliance with symptom diaries, and adverse events.

During this phase, subjects take study medication for 5 days, then continue until the point they are pain-free, defined as follows: At the time a dose of study drug is due, the subject's pain score is now 0, and has also been 0 for the last 24 hours (total 3 consecutive '0' scores), AND the subject has not required any rescue medication in prior 24 hours. The maximum duration on study medication is 10 days. Based on clinical experience, we expect most subjects will require pain medication about 8 days [Sobol et al, 2006].

Before discharge, as per clinical care, subjects receive specific instructions to call the emergency line if they experience any hemorrhage, even in small amounts. In addition, subjects are instructed to discontinue study medication if they experience either skin rash or hemorrhage. These, or any other complications occurring during the treatment and follow up periods (e.g., dehydration), are managed according to usual clinical care pathways, including referral to the ED as appropriate. There are no changes to these pathways related to the study. However, the occurrence and outcomes of such complications are recorded for study purposes.

During the treatment period, subjects self-monitor for dehydration, and are treated and/or readmitted as per clinical judgement, which is all standard of care. This includes specific recording of fluid intake and number of voids each day in the Study Diary. Additionally, these are assessed by the nurse on the Day 3 telephone call. Subjects with low urine output (less than 1 void every 12 hours), inadequate oral intake (based on weight), or other clinical concern for dehydration are referred to the ED. Evaluation and management then follow established pathways (http://www.chop.edu/clinical-pathway/gastroenteritis-and-dehydration-clinical-pathway). Subjects judged to have significant dehydration receive IV fluid rehydration and evaluation of serum electrolytes; BUN and creatinine are also assessed per clinical judgement. All subjects whose dehydration is serious enough to require IV fluids, or who have abnormal serum creatinine (>1.5X upper limit of normal for age), will discontinue the study drug for the duration of the study. Any abnormalities of electrolytes or renal function will be reassessed as per clinical care. These results are all recorded by the study team. Subjects not requiring IV fluids or lab draws in the ED will be considered as mild dehydration and will continue the study medication, once they demonstrate adequate

oral intake. The above procedures will apply whether the subject is seen at CHOP or at an outside emergency department.

The rationale for the 5 day minimum dosing is as follows. First, all subjects are expected to have pain lasting at least 5 days. Second, while celecoxib has effects within hours, it may take up to 5 days for subjects to reach their final steady-state levels of pain control (as discussed in section 1.3.1.1). Third, by the same logic, 5 days would also be the minimum time to know the side effect profile of the drug. Fourth, a 5 day minimum would reduce the risk of pain relapse in the active drug group. If celecoxib turns out to be extremely effective for pain, subjects could become pain-free well before their tonsillectomy wounds have healed. Without a 5 day minimum, these subjects would discontinue study drug too early, and would likely relapse into an undesirable state of uncontrolled pain.

### 3.1.3 Follow-up Phase (Discontinuation of study drug to Postop day 30)

In clinical practice at CHOP and at most centers, patients do not generally return for postoperative follow up visit after tonsillectomy surgery. This will be the case for subjects in this study as well, with all routine follow up conducted by telephone contact, without any further scheduled Study Visits.

Between the day they become pain-free and Day14, subjects no longer take study medication, but continue to record pain levels, narcotic usage, and diet. Subjects receive a second follow up call by a study team member on Day 14 (+/- 1 day) to review compliance with medication, and adverse events or complications. Subjects receive a final call on Day 30 (+/- 2 days) to review final outcomes (adverse events, complications) and to ensure return of the diaries to the study team.

As noted above, any complications during this period are managed per clinical care, with their occurrence and outcomes recorded for study purposes.

## 3.2 Allocation to Treatment Groups and Blinding

Before surgery, subjects are randomized to either celecoxib or placebo. Randomization sequence will be generated and maintained by the CHOP Investigational Pharmacy. The assignment will be concealed from both subjects and investigators. This blinding will be maintained throughout the study. Breaking the blind will only occur if the information is required in an emergency situation. This is very unlikely, as the clinical management of complications such as bleeding does not depend upon on a subject's current medications.

Blinding of subjects will be further assured by providing both celecoxib and placebo in suspensions of identical appearance and taste. This should not be difficult, as celecoxib does not have a characteristic taste [Krishnaswami et al 2012].

Siblings undergoing surgery on the same day will be randomized to the same treatment group.

## 3.3 Study Duration, Enrollment and Number of Sites

### 3.3.1 Duration of Study Participation

The total study duration per subject will be up to 4 months. This includes the screening day, the lag time until surgery occurs (varies, but is typically 0-3 months), the day of surgery, and the postoperative 30 days which include treatment and follow up.

### 3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted only at CHOP.

Recruitment will stop when there are 180 subjects with evaluable data. It is expected that approximately 300 subjects will be enrolled to produce 180 evaluable subjects (those who return their Study Diary and properly log rescue medication consumption).

## 3.4 Study Population

### 3.4.1 Inclusion Criteria

1) Males and females age 3 to 11 years inclusive.
2) Scheduled to undergo tonsillectomy (with or without adenoidectomy).
3) Weight ≥ 10 kg.
4) Girls ≥ 11 years of age must have a negative urine/serum pregnancy test on the day of surgery and must use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), Depo-Provera, or an oral contraceptive, for the duration of the study.
5) Parental/guardian permission (informed consent) and if appropriate, child assent.

The inclusion age range (3-11 years) was chosen due to the demographic of the surgical population, and in order to reduce for variability in efficacy measures. First, the large majority of tonsillectomy procedures are performed in the younger age group (for example, between September 2013 thru June 2014, 1421 tonsillectomies were performed at CHOP in the age 3-11 group vs. 140 for age >=12). Second, the young patients are historically more likely to experience readmission due to pain (e.g., dehydration ) (40 readmissions vs. 9 at CHOP during the same period, respectively). Third, in clinical experience, adolescent patients experience substantially higher pain levels, and display much wider variation in intensity, narcotic consumption, and outcome measures, such as time out of school or time to return to normal diet. This may be simply due to behavioral variations in teenagers, but may also be in part due to their different indications for tonsillectomy (chronic tonsillitis, versus mainly sleep disordered breathing in the younger patients). Thus, inclusion of adolescents would add undesirable variability in efficacy measures. Fourth, bleeding risk is higher in teenagers and adults [Wei et al, 2000]. Until the bleeding risk from celecoxib is better defined from studies like this, this fact justifies postponing inclusion of this older age group until a future study.

### 3.4.2 Exclusion Criteria

1) Prior tonsillar surgery.
2) Concomitant surgical procedure that adds more than mild additional pain. Note: ear tubes are always permissible.
3) Coagulation disorder, or any other hematologic disorder that affects clotting or results in anemia.
4) Moderate to severe asthma, defined as subjects who either (1) have daily symptoms requiring daily use of short-acting bronchodilators, or (2) had an exacerbation in the last 3 months requiring admission, ED visit, or systemic corticosteroid administration.
5) Any degree of aspirin-sensitive asthma, or any history of asthma exacerbation caused by NSAID use.
6) Severe obstructive sleep apnea that requires use of CPAP or BiPAP.
7) Significant chronic pulmonary disease, defined as subjects requiring oxygen therapy, ventilator support, or positive pressure therapy.
8) Significant cardiac disease, defined as any one of the following: cardiovascular disease, structural cardiac anomalies, prior cardiac surgery, or requirement for cardiac anesthesia.
9) Severely obese (BMI > 99th percentile for age).
10) History of hepatic or renal disease, or condition that impairs hepatic or renal function.
11) Juvenile rheumatoid arthritis (JRA).
12) History of GI bleeding, or chronic GI condition that would increase risk of bleeding, ulceration, or perforation
13) Hypertension.
14) Craniofacial syndromes.
15) Syndrome or neurologic condition that would hinder accurate assessment of postoperative pain.
16) Inability to feed orally or take oral pain medication.
17) Chronic pain disorders, or otherwise requiring pain medication more than once weekly.
18) Laboratory abnormalities on the preoperative CBC:
    - Hemoglobin < 9 gm/dL
    - Platelet count < 100,000/mm3
19) Any investigational drug use within 30 days prior to enrollment.
20) Pregnant or lactating females.
21) Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.
22) Hypersensitivity or allergic reactions to celecoxib, aspirin, or other NSAIDs, including asthma flare ups
23) Allergy to sulfonamides or calcium carbonate.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

# 4 STUDY PROCEDURES

Please see also the Table of Procedures.

## 4.1 Pre-op Phase

- Informed Consent / Assent
- Review Inclusion/Exclusion Criteria
- Medical Record Review
- Record data from clinical care: Demographics, Medical History, Physical Exam, height, weight, laboratory test (CBC with platelet count), prior/concomitant medications
- Randomization – performed prior to surgery day.

## 4.2 Study Treatment Phase (Postop day 0 until pain-free, maximum 10 days)

This Phase includes the day of surgery (Day 0), and the postoperative days (maximum 10), during which subjects receive study medication.

### 4.2.1 Day of Surgery (Day 0)

- Clinical Care: Surgery and General Anesthesia, Vital Signs, Pregnancy Test, Medications, preoperative CBC with platelet count (if not already reviewed), give prescription for oxycodone and acetaminophen
- Dispense study drug, provide instructions
- Start study medication
- Dispense Study Diary
- Medical Record Review
- This visit including the surgery may be either at the CHOP Perioperative Complex or at one of the CHOP Ambulatory Surgery Centers.

### 4.2.2 Telephone Call 1 (Day 3 +/- 1)

- Assess pain control and any problems or questions with medications or diary
- Assess possible adverse events. Includes specific query about the occurrence of skin rash and review of oral fluid intake and urine output to assess for dehydration.
- If volume depleted, referral to ED.

- If dehydration serious enough to require IV fluids, or elevation of serum creatinine as specified above, discontinue study medication.
- Subjects reminded to call for inadequate fluid intake or urine output.
- Assess compliance with study drug and diary
- Medical Record Review

## 4.3 Follow-up Phase (Discontinuation of study drug to Postop day 30)

This Phase begins after the last dose of study medication.

### 4.3.1 Telephone Call 2 (Day 14 +/- 1)

- Assess pain control and any problems or questions with medications or diary
- Assess possible adverse events
- Assess compliance with study drug and diary
- Drug accountability calculation
- Medical Record Review

### 4.3.2 Telephone Call 3 (Day 30 +/- 2)

- Assess possible adverse events
- Arrange return of Study Diary.

## 4.4 Unscheduled Visits

Complications are common during the 2-week postoperative recovery after any tonsillectomy, with hospital readmission rates currently ranging between 5-10% at our institution. These complications include hemorrhage, refractory pain, refractory nausea/vomiting, and dehydration, and will be managed according to usual clinical care pathways, which include referral to the ED as appropriate. There are no changes in these pathways related to this study. However, the occurrence and outcomes of such visits will be recorded for study purposes.

In the event that there are problems related to study procedures that are outside the usual pathways for post-tonsillectomy clinical care, subjects will be triaged by our phone nurses, and brought into the Otolaryngology Clinic or ED as appropriate, for evaluation by one of our attending surgeons.

## 4.5 Concomitant Medications

All prior and concomitant medications used from Days 0-14 will be recorded. The dates of administration, dosage, and reason for use will be included.

The following concomitant medications are prohibited while receiving study drug:

- Other NSAIDs including aspirin
- Antiplatelet agents, anticoagulants (bleeding risk)
- ACE inhibitors or Angiotensin II receptor blockers
- Antibiotics (systemic only): Aminoglycosides, fluconazole, fluoroquinolones
- CYP2D6 substrates: Aripiprazole, codeine
- CYP2C8 substrates
- CYP2C9 inducers or inhibitors
- Corticosteroids (systemic only)
- Cyclosporine
- Digoxin, Lithium, Desmopressin, Mifepristone, Nitric Oxide agents
- Certain antihypertensives – Beta blockers, eplerenone, hydralazine
- Chemotherapy agents: Doxorubicin
- Hormones: estrogen derivatives (thrombogenic enhancement)
- Loop or thiazide diuretics, tramadol, SSRIs, tamoxifen, prostaglandins, tenofovir

## 4.6 Rescue Medication Administration

All subjects are prescribed oxycodone and acetaminophen as clinical care. There is no difference in dosing compared to their use outside the research. However, there is a slight modification to the usual clinical instructions as follows. In current clinical care, patients are instructed by the PACU nurses to use the acetaminophen and oxycodone around the clock for the first few days, until their pain becomes less intense. The number of days are not specified. Patients then switch to using both as-needed. In this study, all subjects will take their acetaminophen around the clock for 5 days, with oxycodone reserved for breakthrough pain (but still up to every 4 hours as needed). After 5 days, both rescue medications are taken as needed.

Up-dosing of oxycodone is common, especially within the first week, and we expect this will be true for study subjects as well. These are usually managed by the phone triage nurse practitioners, who are permitted to increase oxycodone dose up to 0.1 mg/kg/dose every 4 hours if necessary, with referral to the ED if pain is still not controlled. Throughout the study, subjects will record the quantity they consume, as this is a key outcome variable. We expect that subjects receiving placebo will consume similar quantities as children outside the research, and that subjects on celecoxib will consume a lower quantity.

## 4.7 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or if it is felt by the Investigator that continuing the study would in any way endanger their health. Any subject who withdraws will continue to have appropriate pain control, since they were already prescribed standard of care analgesics.

Postoperative hemorrhage is not rare after tonsillectomy (typical rates 2-5%), and so is expected to occur to some subjects in this study. Subjects who experience postoperative

hemorrhage will be instructed to immediately discontinue the use of study medication, in addition to the usual instructions for management of this complication. However, these subjects will not be withdrawn from the study, but rather will continue in the follow-up phase of the study. This includes recording pain diaries and receiving follow up calls per the schedule described. This will allow assessment of final outcomes for these subjects, and maintain the blinding needed for scientific validity of the study.

Subjects who develop a rash while taking study medication will be instructed to immediately discontinue the study drug, but to continue to use their rescue medication as per clinical care. As was the case for hemorrhage, these subjects will not be withdrawn from the study, but rather will continue in the follow-up phase of the study. This includes recording pain diaries and receiving follow up calls per the schedule described. This will allow assessment of final outcomes for these subjects, and maintain the blinding needed for scientific validity.

As described previously (section 3.1.2), subjects who develop significant dehydration will be assessed in the ED. Those who require IV fluids, or have abnormalities in laboratory assessment (creatinine), immediately discontinue the study drug, but continue to use their rescue medication as per clinical care. As was the case for hemorrhage, these subjects will not be withdrawn from the study, but rather will continue in the follow-up phase of the study. This includes recording pain diaries and receiving follow up calls per the schedule described. The study team will also follow up with the subject's PCP to ensure resolution of any abnormalities of lab values or renal function.

The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

#### 4.7.1 Early Termination Study Visit

Subjects who withdraw from the study will have an exit phone call follow up that includes all elements outlined in Call 2 and Call 3 in the Visit Table.

## STUDY EVALUATIONS AND MEASUREMENTS

### 4.8 Screening and Monitoring Evaluations and Measurements

#### 4.8.1 Medical Record Review

The following will be recorded from the medical record, which includes surgical office visit notes completed just prior to screening, operative notes from the tonsillectomy procedure, and perioperative nursing and anesthesia notes: Date of birth, date of surgery, operating surgeon. Height, weight. Other comorbid medical conditions. Prior/concomitant medications. Prior surgical procedures. Diagnosis necessitating surgery (e.g. sleep-disordered breathing, chronic tonsillitis). Data from preoperative polysomnogram, if performed. Tonsil size from operative note. Surgical details (method of tonsil removal, cautery wattage/mode, complications, procedure time). Analgesics given during procedure and in PACU, including doses. Corticosteroids and their doses given intraoperatively.

### 4.8.2 Laboratory Evaluations

Values are recorded from certain laboratory studies done routinely for clinical care. These are listed below. There are no research-only laboratory studies.

#### *4.8.2.1 Hematology Tests*

As part of clinical care, all patients without a recent hemoglobin and platelet count (within the prior 6 months) undergo a preoperative blood draw (CBC with platelet count). Results are recorded for this study. If any preoperative coagulation studies are performed for clinical care, these data are also recorded.

#### *4.8.2.2 Pregnancy Testing*

As part of clinical care prior to administering general anesthesia, a urine pregnancy test is always performed for female subjects ≥ 11 years of age and girls <11 years who are physically capable of becoming pregnant. Results are recorded for this study. If the test is positive, subjects will be withdrawn from the study.

## 4.9 Efficacy Evaluations

### 4.9.1 Days receiving narcotic medication

Following Sobol et al [2006], the day a subject is considered "off" narcotic medication is defined as the day they received either 0 or only 1 dose of narcotic. This number is recorded from the number of doses of oxycodone subjects record each day in their Study Diary.

### 4.9.2 Pain Scales (See Appendix)

The subject's pain level is recorded on the study Diary in the recovery room, then twice daily, just before receiving each dose of study medication. The 10-point Wong-Baker FACES pain scale is used for all ages (scale is validated for ages 3 and above) [Wong and Baker 1988]. Alternatively, children 10 and older may mark their pain on the customary 10-point pain scale shown.

### 4.9.3 Measurement of Oxycodone and Acetaminophen Usage

Oxycodone and acetaminophen dosages are prescribed by the surgeon after the procedure, and are most commonly oxycodone suspension 0.075 mg/kg/dose every 4 hours as needed, and acetaminophen syrup 15 mg/kg/dose every 4 hours as needed. There will be no change in these prescribed doses, except that subjects will take the acetaminophen around the clock for the first 5 days. Quantity administered in the PACU is recorded from flowsheets. Initial volume received from the pharmacy, and drug concentration, are recorded. Volumes of each dose given at home (in increments of 0.1 mL) are recorded by caregivers on the Study Diary.

At the end of the two week postoperative period, during Telephone Call #2, caregivers will measure the remaining volume of unused oxycodone and acetaminophen, to the nearest 1 mL, using an appropriate syringe (e.g. 20 cc) given to them on the surgery day.

### 4.9.4 Return to Normal Diet Assessment

Each day on the study diary, subjects record whether their diet was predominantly liquid diet, soft diet, or normal diet that day.

### 4.9.5 Data Collection from Hospital Readmissions

Readmission rates for excess postoperative pain and dehydration are considered efficacy measures because they are caused by inadequate pain control. Medical records are reviewed from each hospital visit (Emergency Department, Emergency Dept. Extended Care Unit, or inpatient records): date, reason for readmission, diagnosis, laboratory studies, medications administered (analgesics, antiemetics, steroids, antibiotics), and other treatment administered (intravenous fluids, oral fluids, surgical reoperation, observation for bleeding).

## 4.10 Safety Evaluation

Subject safety will be monitored by adverse events, which include the serious adverse event of postoperative hemorrhage. The PI reviews SAEs immediately, and other AEs every 2 weeks with the study team. As described in section 5.2.4 above, data is collected for all hospital readmissions in the 30 days following surgery, and this includes the AE data listed in that section. Further details are in Section 8 below.

# 5 STATISTICAL CONSIDERATIONS

## 5.1 Primary Endpoint

The primary endpoints are (1) number of days on narcotic medication, and (2) total amount of rescue narcotic pain medication consumed.

## 5.2 Secondary Endpoints

Secondary endpoints will include the following:

- Efficacy based on time to return to normal diet, quantity of rescue acetaminophen used, and rate of readmission for dehydration or excessive pain.
- Safety based on rates of postoperative hemorrhage.
- Safety and tolerability of celecoxib based on Adverse Events.

## 5.3 Statistical Methods

### 5.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

### 5.3.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects who are randomized.

The primary efficacy endpoint will be (1) the difference in number of days on narcotic medication, and (2) the difference in total amount of rescue narcotic pain medication consumed in the 2-week postop period. For the latter, total amount of oxycodone consumed will be expressed as morphine equivalents per kg body weight.

Secondary efficacy endpoints will include the difference in time to return to normal diet, difference in amount of rescue acetaminophen used, and difference in rate of readmission for dehydration or excessive pain.

The above efficacy variables will be compared between the two treatment groups by a two-sample t-test.

Note: Statistical analysis is the same for all subjects, regardless of whether or not they became pain-free and discontinued study drug before the maximum10 days of dosing.

Subjects who miss more than 3 of the scheduled doses of study drug during the first 5 days, will not be included in the efficacy analysis. These subjects continue their study medication per protocol, but their efficacy data will be analyzed separately at the end of the study. All will continue to be included in the safety analysis.

### 5.3.3 Safety Analysis

All subjects entered into the study at the preoperative visit will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail. The frequency of postoperative hemorrhage will be summarized.

Postoperative hemorrhage and AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

## 5.4 Sample Size and Power

Sample size estimation was based on available data from a prior pilot study of celecoxib use at University of Iowa in adults after tonsillectomy, and baseline data from a tonsillectomy pain study done at CHOP (referred to below as the Microdebrider study) [Sobol et al 2006]. Sample size estimates were made separately for both primary efficacy endpoints, based on the available data. This was done with two-sample power analysis based on average values, using an alpha of 0.05 and beta 80%. If variance for the experimental group was not available, an assumption of equal variance as the control group was made.

We determined the sample size needed to detect the following meaningful differences: a reduction of 1 day in number of days on narcotic medication, as recommended in Sobol et al [2006], and a reduction of 20% in total narcotic consumed.

Days on narcotic pain medication: The CHOP Microdebrider study reported that children in their control group required narcotic medication a mean 8.2 days (SD 2.7 days). These children underwent standard electrocautery tonsillectomy, and so were essentially identical to our placebo control group. Based on these results and assuming equal variance in both groups, a sample size of 90 per group is required to detect a 1-day improvement in this outcome variable.

Total narcotic pain medication consumed: The University of Iowa pilot study [Van Daele et al 2014] reported rescue narcotic consumption in a small group of adults randomized to either celecoxib or placebo. Narcotic equivalents were consumed as follows: 632 (381) in placebo group; 262 (148) in celecoxib group. Based on these results, a sample size of 65 per group is required to detect a 20% improvement in this outcome variable.

We expect a dropout rate of up to 40%, mainly from subjects who never return their Study Diary, or who do so without accurately recording total narcotic consumed. This estimate is based on our experience with diary returns in prior tonsillectomy studies, which are lower than other trials because of the fact there is no routine post-operative clinic visit after routine tonsillectomy surgery. Based on this rate, a final sample size estimate of 150 per group is needed to yield the 90 per group needed to assess our primary endpoints.

## 5.5 Interim Safety Analysis

No interim analysis for efficacy will be performed in this study. However, an interim analysis for safety may be performed under certain conditions described below.

As noted previously, postoperative hemorrhage is not rare after tonsillectomy (typical rates 2-5%), and so is expected to occur in 6 to 14 children over the entire study. We anticipate similar hemorrhage rates between the two groups, so up to 7 children per group. As noted earlier, these subjects discontinue study drug and undergo clinical care, but remain blinded and continue on the study to undergo monitoring procedures.

Even though blinded, the PI can monitor the hemorrhage rates in each group separately throughout the study. An interim safety analysis (with unblinding) will then be performed in either of the following cases:

- If, after the first 50 subjects are treated in either group, greater than 5 children experienced significant hemorrhage in that group, OR
- If at any point in the study, the PI otherwise judges that there is a concerning difference in bleeding rate between the 2 groups.

The study would then be stopped if the unblinding then revealed both that the higher rate occurred in the celecoxib group, and that the hemorrhage events were probably or definitely related to the study drug.

# 6 STUDY MEDICATION

## 6.1 Description

The study drug is celecoxib (Celebrex, Pfizer, or generic equivalent). Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities. 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.

Suspension formulations: While a suspension of celecoxib is still not commercially available, several investigational suspensions have been studied. The FDA reviewed Pfizer RR-754-00049 reporting pharmacokinetic study of celecoxib suspension (Study 195), which included suspensions of 50 mg/5mL and 100 mg/5 mL in 242 children at 60 sites. Of these, 202 went on to open-label use of the suspensions at 3 mg/kg BID. [FDA, BCPA Summary for NDA 20-998, Supplement 021]. In a published study, PK and efficacy were studied in children with JRA using an investigational suspension, in 152 JRA patients aged 2 to 17 years [Krishnaswami et al 2012]. The Children's Hospital of Eastern Ontario reported on their 10 mg/mL suspension in Ora-Blend [Donnelly et al, 2009]. This suspension is stable for at least 90 days, either at room temperature or refrigerated. This suspension was used safely in their recent large clinical trial in pediatric tonsillectomy [Murto et al 2015].

For this study, bulk drug will be obtained by the CHOP or Penn Investigational Pharmacy and mixed into suspension at concentration 100 mg/5 mL (20 mg/mL) in Ora-Blend or equivalent, following Donnelly et al [2009].

Placebo, with appearance, taste and consistency as similar as possible to the active drug, will be mixed in identical fashion. Placebo consists of calcium carbonate powder suspended in the same syrup as the active drug. The dose of elemental calcium is 3 mg/kg/day. Calcium carbonate in this concentration provides a cloudy appearance identical to celecoxib suspension, with no characteristic taste.

### 6.1.1 Packaging

Celecoxib and placebo capsules or bulk powder are obtained from the manufacturer by the CHOP Investigational Pharmacy. They are then suspended as above and stored in amber bottles under refrigeration until they are dispensed to the subject, after which they will be kept at room temperature. They are labeled in a fashion that maintains double blinding. Total volume dispensed to each subject is enough to supply a total 20 doses.

### 6.1.2 Labeling

Labeled by the Investigational Pharmacy as described above.

### 6.1.3 Dosing

Dosing of celecoxib is 6 mg/kg BID, maximum 300 mg BID. All ages are given the suspension, following standard practice after tonsillectomy. The first dose is given

preoperatively, within 1 hour prior to entering the operating room. The second dose is given at bedtime on the night of surgery. Subsequent doses are given 12 hours apart.

### 6.1.4 Treatment Compliance and Adherence

Caregivers are instructed in study drug administration by study staff during their stay in the recovery room. Compliance with drug administration is assessed at each Postoperative telephone call, and also upon review of the Study Diary returned at the end of the study.

### 6.1.5 Drug Accountability

At the Day 14 telephone call, the study team member will ask the patient to measure the amount of study drug remaining. Since all subjects initially received 20 doses, calculation of accountability is straightforward. This information is entered into the CRF and communicated to the Pharmacy. The family will then dispose of the unused medication at home.

Adequate records of study drug receipt and disposition will be maintained by the CHOP Pharmacy. Records of receipts, investigational drug orders, dispensing records, and disposition forms will be examined during the course of the study. The purpose of these records is to ensure regulatory authorities that the investigational drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the Investigator or designee and may not be used for any purpose other than that described in this protocol.

# 7 SAFETY MANAGEMENT

## 7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study. The procedures for obtaining this information (via phone interview, recording of data from unscheduled admissions, and study diaries) were described in Section 5.1, with the schedule in Table 1.

## 7.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

## 7.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received the study drug (celecoxib or placebo). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

## 7.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening event (at risk of death at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

### 7.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study drug should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

## 7.5 Anticipated SAEs

The following are the known SAEs related to surgery that are anticipated based on current clinical experience, and the approximate rates that are expected. These SAEs will be recorded and their rates monitored carefully, but are reported differently to the IRB from the unanticipated SAEs, as discussed in Section 8.6 below.

1. Postoperative hemorrhage (expected rate up to 10%)

   Hemorrhage is not rare after tonsillectomy, and so is anticipated in both treatment groups. Rates are typically 2-5%, but rates up to10% have been observed in some months at CHOP. Hemorrhage is always considered a life-threatening SAE. We further anticipate that rates of the two groups will be similar. Hemorrhage events, including hospitalization and surgical management, will be recorded, and their rates and outcomes monitored by the PI throughout the study.

2. Postoperative readmission (expected rate up to 10%).

   From internal quality monitoring data over the last 2 years, rates of readmission of up to 10% have been observed. Historically these result from hemorrhage (described separately above), pain-related complications (uncontrolled pain, dehydration), and side effects from narcotics or anesthesia (e.g., nausea, vomiting).

3. Prolonged initial admission (expected rate up to 30% of those kept overnight).

   Children who are admitted overnight after surgery often stay hospitalized a second night or longer. The most common reason is inadequate oral intake, which is most common in the younger children. Other reasons include inadequate pain control, the need for more time to wean off supplemental oxygen, or the need for an additional night of respiratory monitoring due to episodes of oxygen desaturation recorded the first night.

## 7.6 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below.

| Type of Unanticipated Problem | Initial Notification (Phone, Email, Fax) | Written Report |
|---|---|---|
| Death or Life Threatening SAEs (not listed in Section 8.5)* | 24 hours | Within 2 calendar days |
| All other SAEs (not listed in Section 8.5)* | 7 days | Within 7 business days |
| Unanticipated Problems Related to Research | 7 days | Within 7 business days |
| All other AEs | N/A | Brief Summary of important AEs may be reported at time of continuing review |

*For the ***Anticipated SAEs*** listed in Section 8.5 above, the Investigator will report these events differently than other SAEs. If rates of ***Anticipated SAEs*** fall within the expected ranges listed in Section 8.5, they will be reported similarly to AEs, as a summary at the time of Continuing Review. However, if their rates exceed the expected ranges, they will be reported promptly to the IRB as per the above table (i.e., 24 hours for life threatening SAEs, 7 days for all other SAEs). Death will always be reported within 24 hours regardless of the circumstances.

### 7.6.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

## 7.7 Investigator Reporting of Serious Adverse Events to Funder

Reporting of SAEs will be consistent with funder requirements (*Safety Reporting Reference Manual for IIR Studies with Pfizer Products*). Subjects are identified only by Study ID number.

## 7.8 Medical Emergencies

On the day of surgery, initial study procedures occur within the perioperative complex at CHOP or a CHOP ambulatory surgery center. Any medical or surgical emergencies at that

time are handled in the usual fashion by the anesthesia and surgical specialists at the site. Postoperatively, some patients are discharged (Day Surgery) while others are admitted overnight for observation, as per clinical care. For the latter, any emergencies during the admission are handled by the Otolaryngology inpatient service. During the home recovery period for all subjects, medical emergencies common during the postoperative period (for example, dehydration and hemorrhage) are managed in the same way as outside the research, per well-established protocols. Any unusual emergencies besides those occurrences are not expected, but if they occur, each will be assessed by our postoperative triage phone nurses, or the physician on call after hours, with subjects directed to the Emergency Department as needed.

# 8 STUDY ADMINISTRATION

## 8.1 Treatment Assignment Methods

### 8.1.1 Randomization

Between the Pre-op Visit and Surgery Day, subjects are randomized in equal numbers to each treatment group. Randomization sequence will be generated and maintained by the CHOP Investigational Pharmacy. The resulting group assignments and Study ID numbers are used to prepare study medication and containers for use on Surgery Day. Siblings undergoing surgery on the same day will be randomized to the same treatment group.

### 8.1.2 Blinding

Treatment group assignment will be concealed from subjects, investigators, and caregivers, including perioperative personnel and phone triage nurses. This blinding will be maintained throughout the study.

Blinding of subjects will be further assured by providing both celecoxib and placebo as identical-appearing suspensions and packaging. Because drug is administered as a suspension, blinding will be further assured by the ensuring placebo tastes as similarly as possible to celecoxib.

### 8.1.3 Unblinding

Breaking the blind will only occur if the information is required in an emergency situation. This is very unlikely, as the clinical management of complications such as bleeding does not depend upon on a subject's current medications. The most notable example of such a situation is hemorrhage. All patients who experience hemorrhage immediately stop their study drug, whether active or placebo, and then subsequent clinical management is the same regardless of which group they were assigned.

## 8.2 Data Collection and Management

Source documents consist of hospital and otolaryngology records and will be viewed only long enough to collect data specified. Data is logged into REDCap kept on encrypted hospital-issued computers. Data will be managed and stored using the research-focused electronic data capture system REDCap, under an agreement with the software's development consortium, led by Vanderbilt University. REDCap supports two secure, web-based applications designed exclusively to support data capture for research studies.

REDCap as implemented at CHOP includes daily destructive database backup files that are stored on the database server and are deleted only after successful backup of the entire database to file. Data and backups are stored in the CHOP Research Information Systems Storage Area Network (SAN). Access to the SAN directories where data are stored will be limited to Research Information Systems personnel, with authentication performed using CHOP's enterprise Active Directory service.

Data are recorded either directly into REDCap, or initially on paper forms then transferred to REDCap in a timely fashion, then the paper forms destroyed. The datasheets and REDCap database will contain only coded information. Only limited datasets will be exported from

REDCap. All PHI will be contained in REDCap. Access to the data in REDCap will be limited only to study team members.

All Study Team members have completed HIPAA and all required institutional training relevant to clinical research.

1. Confidentiality of Data. The investigators will not take data off-site. Data will be coded in REDCap by study number.

2. Security. Data are secured by REDCap under the protections described above.

3. Deidentification or destruction. Identifiers will be destroyed 5 years after results are accepted for publication. This is necessary in case of drug-related questions from the FDA or other regulatory agencies. During the 5-year period, identifiers are kept exclusively in REDCap. Thus, the coding is maintained.

4. Only study team members will have access to all the identifiable information.

## 8.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Investigators and other personnel will not use such data and records for any purpose other than conducting the study, unless the IRB approves (or exempts) other uses. Safeguards are described under Data Collection and Management. If any investigator leaves the institution he or she will surrender any identifiable data. It is expected that publications or presentations will include only aggregate data.

Confidentiality will be maintained by REDCap, which assigns each subject with a Subject ID and keeps identifying information separate from the data. Once data is collected, the PHI will be accessed only in the event, prior to publication, that the charts need to be accessed a second time. This would occur if only if questions arise from reviewers or regulatory agencies that were not recorded during the original data collection. Thus, maximum privacy of patient identifying information is ensured, while at the same time maintaining a secure link necessitated by the nature of this study.

During the data collection process, the temporary paper data collection forms, charts and other records will not leave the CHOP premises, and will be kept in a locked office. Access will be limited only to the study team members. Digital data will be accessed only using CHOP hospital computers and secure servers.

## 8.4 Regulatory and Ethical Considerations

### 8.4.1 Data and Safety Monitoring Plan

The P.I. will be responsible for monitoring the integrity of the data and the safety of all subjects. The PI reviews SAEs immediately, and other AEs during regular meetings with the study team approximately every 2 weeks. As described in section 5.2.4 above, data is collected for all hospital readmissions in the 30 days following surgery, and this includes the

AE data listed in that section. AEs are reported to the IRB as noted in the above sections. There is no Data Safety Monitoring Board for this study.

### 8.4.2 Risk Assessment

Risk level in subjects receiving celecoxib is greater than minimal, and is detailed below. Risk level in the placebo group is minimal and is discussed further at the end of this section.

**1. Risks of Celecoxib Administration.**

Celecoxib has a favorable safety profile in children and adults, with most of its adverse effects being associated with chronic, long term use, or with use in certain conditions not applicable to children or to the current study (e.g., cardiovascular thrombotic disease). Importantly, essentially all of the risks described below are not unique to celecoxib, but rather apply to all NSAIDs. Of course, other NSAIDs are already used extensively in children of all ages, especially for short term therapy, including postoperative pain control.

Below, we first discuss risks most applicable to short-term administration in this study, followed by discussion of adverse effects seen during long-term treatment. Each is followed by discussion of risk minimization in the current study. The risk discussions are based on information from the manufacturer (Pfizer *Celebrex Full Prescribing Information* document).

**Risks applicable to short-term therapy**

Aspirin-Sensitive Asthma -- All NSAIDs may precipitate bronchospasm in patients with Aspirin triad asthma. It is well known that aspirin may cause severe bronchospasm in patients with aspirin-sensitive asthma, which can be fatal. Since cross reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, celecoxib could cause this event in patients with this form of aspirin sensitivity. More generally, the manufacturer recommends using celecoxib with caution in patients with preexisting asthma. This risk is minimized in the present study by excluding subjects with aspirin-sensitive asthma, any prior severe reactions to aspirin or NSAIDs, or any form of moderate to severe asthma, even in the absence of known aspirin sensitivity.

Anaphylactic Reactions -- As with all NSAIDs in general, rare anaphylactoid reactions have occurred in patients, even without known prior exposures. In post-marketing experience reported by the manufacturer, rare cases of anaphylactic reactions and angioedema have been reported in patients receiving celecoxib. This risk is minimized in the present study by excluding subjects with any prior reactions to aspirin or NSAIDs.

Skin Reactions -- Celecoxib is a sulfonamide and can cause rare but serious skin reactions such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which can be fatal. These serious events can occur without warning and in patients without prior known sulfa allergy. This risk is minimized in the present study by excluding subjects with sulfonamide allergy, and subjects are informed about the signs and symptoms of serious skin manifestations and counseled to stop the study drug at the first appearance of skin rash or any other sign of hypersensitivity.

Postoperative Hemorrhage -- As described in earlier sections, use of celecoxib does not appear to increase bleeding risk after surgical procedures. On the contrary, Cox-2 inhibitors actually reduce the amount of blood loss during orthopedic procedures [Li et al 2009]. Preliminary data after tonsillectomy (discussed above) suggests that bleeding risk is not increased for this surgery either. Nevertheless, since no large studies have yet been performed, the effects of celecoxib on bleeding risk after tonsillectomy must be considered unknown at this time. Of course, our hypothesis is that celecoxib will actually reduce bleeding risk, due to its absence of platelet inhibition. This risk is minimized in the present study by (1) the nature of celecoxib as a selective COX-2 inhibitor; (2) excluding subjects with coagulation disorders, and (3) by close monitoring of the rates of this SAE as described in this protocol.

**Other side effects reported in clinical trials:**

***Adults*** **–** the following side effects occurred at a rate greater than placebo, and in >2% of adults, in the pre-marketing controlled arthritis trials. Notably, all of these were the same or less than for the other NSAIDs in the trial (naproxen, diclofenac, ibuprofen):

Gastrointestinal
- Abdominal Pain
- Diarrhea
- Dyspepsia
- Flatulence

Body as a whole
- Peripheral Edema

Respiratory
- Pharyngitis
- Rhinitis /Sinusitis

***Children*** **--** Below (Table 3) are the AEs reported during chronic long term use in children for JRA, as reported by the manufacturer. The side effect profile appears very similar to naproxen, another NSAID.

**Table 3. Adverse events occurring in >5% of JRA patients in any treatment group, by system organ class (% of patients with events)**

| System Organ Class<br>Preferred Term | Celecoxib 3 mg/kg BID N=77 | Celecoxib 6 mg/kg BID N=82 | Naproxen 7.5 mg/kg BID N=83 |
|---|---|---|---|
| **Any Event** | **64** | **70** | **72** |
| **Eye Disorders** | **5** | **5** | **5** |
| **Gastrointestinal** | **26** | **24** | **36** |
| Abdominal pain NOS | 4 | 7 | 7 |
| Abdominal pain upper | 8 | 6 | 10 |
| Vomiting NOS | 3 | 6 | 11 |
| Diarrhea NOS | 5 | 4 | 8 |
| Nausea | 7 | 4 | 11 |
| **General** | **13** | **11** | **18** |
| Pyrexia | 8 | 9 | 11 |
| **Infections** | **25** | **20** | **27** |
| Nasopharyngitis | 5 | 6 | 5 |
| **Injury and Poisoning** | **4** | **6** | **5** |
| **Investigations*** | **3** | **11** | **7** |

| | | | |
|---|---|---|---|
| **Musculoskeletal** | **8** | **10** | **17** |
| Arthralgia | 3 | 7 | 4 |
| **Nervous System** | **17** | **11** | **21** |
| Headache NOS | 13 | 10 | 16 |
| Dizziness (excl vertigo) | 1 | 1 | 7 |
| **Respiratory** | **8** | **15** | **15** |
| Cough | 7 | 7 | 8 |
| **Skin & Subcutaneous** | **10** | **7** | **18** |

*Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, Blood creatine phosphokinase increased, Blood culture positive, Blood glucose increased, Blood pressure increased, Blood uric acid increased, Hematocrit decreased, Hematuria present, Hemoglobin decreased, Liver function tests NOS abnormal, Proteinuria present, Transaminase NOS increased, Urine analysis abnormal NOS.

**Risks unlikely in short term use in pediatric subjects:**

Cardiovascular effects --NSAIDs now carry a Boxed Warning regarding this risk. All NSAIDs are associated with increased risk of serious adverse cardiovascular thrombotic events, including myocardial infarction and stroke. These risks are increased with long term use and pre-existing cardiovascular disease or risk factors. Celecoxib is believed to be similar to all the other NSAIDs regarding this risk. Likewise, all NSAIDs, including celecoxib, also can lead to the onset of new hypertension or worsening of preexisting hypertension, and may cause fluid retention or edema in the setting of congestive heart failure. None of these events or effects have been reported in children.

These risks are essentially nonexistent in our subjects, who are children, and who are receiving very short term therapy. Risk is further minimized by excluding any patient with preexisting cardiac disease or hypertension.

Serious GI events – All NSAIDs, including celecoxib, can cause serious gastrointestinal events including bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal. NSAIDs now carry a Boxed Warning regarding this risk. These events were reported during chronic use in adults, where the overall rate of complicated and symptomatic ulcer rates was reported as 0.78% (CLASS trial). Higher rates were found in adults with risk factors, including prior history of peptic ulcer disease and/or gastrointestinal bleeding (10-fold increased risk), concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status.

These risks are exceedingly small in our subjects, who are children and receiving very short term therapy. Risk is further minimized by excluding any patient with history of GI bleeding, or chronic GI condition that would increase risk of bleeding, ulceration, or perforation, and presence of other risk factors for GI bleeding (aspirin, other anticoagulants, chronic steroids).

Effects on Renal Function – all NSAIDs may compromise renal function, and should be avoided in patients with impaired renal function. Clinical trials show celecoxib is no different from the other NSAIDs. This risk is minimized in the present study by excluding any subjects with a history of renal disease.

Volume depletion may increase the chance of renal injury from NSAIDs [Misurac 2013]. However, some authors have not found such an association with short term NSAID use [Lesko, 1997]. Subjects undergoing tonsillectomy may experience dehydration due to inadequate pain control, with rates of readmission for dehydration observed from 1-5% at CHOP. This risk is minimized in the present study as follows:

1. Excluding any subjects with pre-existing renal disease.
2. Subjects' self-monitoring of intake and urine output to ensure early detection of dehydration, as described in section 3.1.2.
3. Nurse call on Day 3 with specific query about dehydration parameters.
4. Referral of possibly dehydrated subjects to the ED, where electrolytes and renal function are assessed, and subjects rehydrated as per standard pathways.
5. Discontinuation of study drug if dehydration is serious enough to require intravenous fluids, or if abnormal renal function is observed (elevated creatinine).
6. Better pain control in the NSAID group -- we expect subjects in the celecoxib group will have better pain control, and thus less risk of dehydration, than placebo subjects or children outside the research.

Effects on Hepatic function -- Borderline elevations of one or more liver-associated enzymes may occur in up to 15% of patients taking NSAIDs, and "notable" elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. For celecoxib specifically, the incidence was lower, in fact similar to placebo (borderline elevation of 6% for celecoxib and 5% for placebo, and "notable" elevations in only 0.2% taking celecoxib and 0.3% taking placebo). These risks are exceedingly small in our subjects, who are children on very short term therapy. Risk is further minimized by excluding any patient with a history of hepatic disease.

Coagulation effects in Systemic Onset JIA/JRA: The preclinical JRA studies found that children with systemic onset JRA (without active systemic features) were at risk for the development of abnormal coagulation laboratory tests. This risk is minimized in the present study by excluding any subjects with this disease.

Anemia -- Anemia was observed in chronic celecoxib trials at a slightly higher rate than placebo (0.6% vs 0.4%). This risk is minimized in the present study by excluding subjects with preoperative anemia (Hgb <9 g/dL).

Minimizing Risks of Celecoxib in this Study

Risks of study medication are minimized as noted above under each risk category. They are also minimized by the study design and execution:

- Dosing has been used safely in both children and adults. Further, the same dosing was used safely in children for up to 24 weeks [Foeldvari 2009], whereas in the present study dosing is only short term (10 days).
- The exclusion criteria minimize risk by excluding subjects at higher risk of adverse effects of celecoxib, as noted above.
- Adverse events are closely monitored by the PI and study team as described.

**2. Risk Assessment: Placebo administration**

The risk level in the placebo group is minimal, since these subjects essentially undergo the same management as would occur outside the research. Pain levels will be the same as current standard of care, as is bleeding risk. Pain is mitigated by the availability of rescue analgesics, which is the same as outside the research. All subjects receive the same dose and quantity of oxycodone/acetaminophen as those currently given to children in clinical care. As in clinical care, placebo subjects receive around-the-clock dosing of acetaminophen, but instead of doing so for an unspecified duration, it will be specified as the first 5 days. This should not increase risk to subjects in the placebo group compared to standard care. In fact, it may even reduce risk, as it may result in less total narcotic consumption over the first 5 days.

The placebo excipient (calcium carbonate) is a ubiquitous dietary calcium supplement and mild antacid (e.g., Tums). The dose used in this study (elemental calcium dose of 3 mg/kg/day) is far lower than therapeutic dosing required for any indication (range 50-150 mg/kg/day). Allergy to calcium carbonate is rare, and children with such an allergy are excluded at the time of screening.

**3. Risks of other study procedures**

Risks associated with interviews and Study Diary are minimal. There is risk of temporary embarrassment on answering medical questions during interviews.

### 8.4.3 Potential Benefits of Trial Participation

Subjects in the celecoxib group will likely directly benefit from improved pain control, and less requirement for narcotic analgesics. This is meaningful, given the well-known side effects of narcotics. Narcotics are notable for their tendency to cause GI disturbance, constipation, of narcotics, including GI symptoms, somnolence and respiratory depression. The latter is especially concerning in patients undergoing tonsillectomy for sleep disordered breathing, which is the majority of the children in this age group. In fact, this has been one of the main factors motivating the search for alternatives to opioids after this surgery.

Subjects in the placebo group will not directly benefit from this study.

This study will have indirect benefits to all children undergoing tonsillectomy, or any other surgery, since it may help establish a new alternative to narcotics for postoperative pain. It will also help provide future patients an alternative to traditional NSAIDs that provides symptom relief without increasing bleeding risk.

### 8.4.4 Risk-Benefit Assessment

In light of the above discussions, the risk-benefit ratio is favorable and justifies proceeding with this research.

## 8.5 Recruitment Strategy

Potential subjects will have already completed their clinical evaluation by otolaryngology at any of our outpatient clinics, and the decision for surgery (tonsillectomy with or without adenoidectomy) will have already been made. During the same visit, the pre-operative nurse practitioner (NP) history and physical will have already been performed as part of standard clinical care. This NP will notify the study staff of the potential subject. At this point, a member of the study staff will approach potentially eligible subjects to explain the study and determine if the family is interested in enrolling. Interested families then proceed with the remainder of the procedures listed under Screening Visit, above. Informed consent is then obtained as per the next section. This pre-operative clinic visit is anywhere from 2 days to several months before surgery, but is most typically 2-6 weeks prior to the procedure date.

It is possible some potential subjects will be interested in the study, but will be unable to complete screening procedures on the same day as the preoperative clinic visit. An example might be subjects recruited from clinic visits at the CHOP Specialty Care Centers, where a Study Team Member is not immediately available. These subjects will be given a blank consent document, with instructions to read it at home. They will receive a telephone call from a member of the Study Team within the next few days. The Team member will explain the research study in detail, answer any questions, and perform screening procedures as indicated above. A time will then be arranged to perform the Informed Consent process below, electronically or in person, before the scheduled surgery.

## 8.6 Informed Consent/Assent and HIPAA Authorization

At the end of the pre-operative clinic visit, a member of the study staff screens interested patients and reviews inclusion and exclusion criteria as described in the Screening Visit section. The study and its risks are explained to the subject and family and informed consent (and assent, if applicable) is obtained. An otolaryngology physician will be immediately available to answer any questions about the study procedures or risks. The family is then given a copy of the Informed Consent document at the end of the visit. This document is a combined consent/assent and HIPAA authorization. These discussions occur in a private room in the outpatient clinic.

For the subjects described in Section 8.5, who were unable to perform the Informed Consent process at the clinic visit, the following will occur. A Study Team member will telephone the potential subject well ahead of the surgery day, explain the study to them, and perform screening assessments as described above. The actual Informed Consent/Assent process will occur as follows. For those subjects who are scheduled for any visit to Main Campus prior to the surgery date, consent/assent will simply be obtained in person at that visit. An otolaryngology physician will be immediately available by telephone to answer any questions about the study procedures or risks. The family is then given a copy of the Informed Consent document at the end of that visit.

For the remaining subjects not coming to Main Campus prior to surgery, an electronic/ remote written consent process will be implemented, following FDA guidelines. For any subject who does not yet have the consent form, or lost it, it will first be sent to them by facsimile, e-mail, or mail. The consent interview is then conducted by telephone when the

parent can read the consent form during the discussion (and when the child is available for assent, if applicable). After the consent discussion, the parent (and child, if applicable) will sign and date the consent form and return the entire consent form to us by facsimile, by scanning and sending via a secure e-mail account, or by mail. This team member obtaining consent will document in REDCap that the person signing the document is the subject/parent who will be participating in the research. The parent will have the opportunity to ask questions and receive answers prior to signing the form. An otolaryngology physician will either be immediately available during the call to answer any questions about the study procedures or risks, or the parent will be given a description of how and when they will receive answers to their questions (usually by a telephone call later from the physician). The family keeps their copy of the signed Informed Consent document. Upon receipt, the team member who obtained the remote consent will then file the complete document, after first signing and dating the signature pages. If the child is 7 or older and cannot be present during the phone call, assent will be documented on the ICF on the day of surgery, before any study procedures occur.

Regardless of method of obtaining consent, subjects will be instructed to not sign the document until all questions they have for a physician are answered. Subjects are counseled that they may freely choose not to participate in the study, but if so, they will not receive celecoxib. They will be informed that this will not otherwise affect their other medical care or treatment. In particular, it will be emphasized that their pain control would follow standard of care outside the study, and that they will still obtain the recommended surgery in the usual fashion. Families are given as much time as they need to make their decision and ask questions of the staff and physician, who will ensure that subjects comprehend the nature of the study, the study procedures and the risks and benefits of participation before providing consent.

## 8.7 Payment to Subjects/Families

### 8.7.1 Reimbursement for travel, parking and meals

Not applicable. There are no study visits separate from clinical care.

### 8.7.2 Payments to parent for time and inconvenience (i.e. compensation)

Parents who complete all study procedures and return their Study Diary will receive a $25.00 gift card. This incentive is critical to the success of the study, as in prior tonsillectomy studies we have found poor compliance rates with completing/ returning diaries when no incentive is offered. This is especially important in this study design, since subjects do not routinely return for any visits postoperatively, and must complete these materials at home, and mail them back to us. This is an inconvenience to parents, who must perform extra work at home (completing Diaries, measuring pain, logging doses of pain medication, and mailing the Diary back) during an often difficult and painful postoperative recovery period.

### 8.7.3 Payments to subject for time, effort and inconvenience (i.e. compensation)

No payment to subjects themselves. Because the side effects of study drug are expected to be minimal, the hardship, effort, and inconvenience for the pediatric subjects are similar as outside the research.

### 8.7.4 Gifts

Not applicable.

## 9 PUBLICATION

Results of this research will be presented at national meetings and will be published in relevant journals. Appropriate disclosure will be made that the research was conducted under off-label use of the study medication.

## 10 REFERENCES

Baugh RF, Archer SM, Mitchell RB, Rosenfeld RM, Amin R, Burns JJ, Darrow DH, Giordano T, Litman RS, Li KK, Mannix ME, Schwartz RH, Setzen G, Wald ER, Wall E, Sandberg G, Patel MM. Clinical practice guideline: tonsillectomy in children. Otolaryngol Head Neck Surg. 2011;144:S1-30.

Cardwell ME, Siviter G, Smith AF. Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. Cochrane Database Syst Rev. 2005;(2):CD003591.

Derry S, Moore R. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database Syst Rev 2013;10:CD004233.

Donnelly RF, Pascuet E, Ma C, Vaillancourt R. Stability of celecoxib oral suspension. Can J Hosp Pharm. 2009;62:464-8.

Foeldvari I, Szer I, Zemel L, et al. A Prospective Study Comparing Celecoxib with Naproxen in Children with Juvenile Rheumatoid Arthritis. J Rheumatol 2009;36:174-182.

Hippisly-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005; 331:1310-1316.

Joshi W, Connelly NR, Reuben SS, Wolckenhaar M, Thakkar N. An evaluation of the safety and efficacy of administering rofecoxib for postoperative pain management. Anesth Analg. 2003;97:35-8.

Krishna S, Hughes LF, Lin SY. Postoperative hemorrhage with nonsteroidal anti-inflammatory drug use after tonsillectomy: a meta-analysis. Arch Otolaryngol Head Neck Surg. 2003;129:1086-1089.

Krishnaswami S1, Hutmacher MM, Robbins JL, Bello A, West C, Bloom BJ. Dosing celecoxib in pediatric patients with juvenile rheumatoid arthritis. J Clin Pharmacol. 2012;52:1134-49.

Kuehn BM. FDA: No Codeine After Tonsillectomy for Children. JAMA. 2013;309(11):1100.

Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. Pediatrics. 1997;100:954-7.

Lewis SR, Nicholson A, Cardwell ME, Siviter G, Smith AF. Nonsteroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. Cochrane Database of Systematic Reviews 2013;(7): CD003591.

Li W, Lian YY, Yue WJ, et al. Experimental study of COX-2 selective and traditional non-steroidal anti-inflammatory drugs in total hip replacement. Journal of International Medical Research 2009; 37:472-78.

Misurac JM, Knoderer CA, Leiser JD, Nailescu C, Wilson AC, Andreoli SP. Nonsteroidal anti-inflammatory drugs are an important cause of acute kidney injury in children. J Pediatr. 2013;162:1153-9.

Møiniche S, Rømsing J, Dahl JB, et al. Nonsteroidal anti-inflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. Anesth Analg. 2003;96:68-77.

Murto K, Lamontagne C, McFaul C, MacCormick J, Ramakko KA, Aglipay M, Rosen D, Vaillancourt R. Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study. Can J Anaesth. 2015;62:785-97.

Nikanne E, Kokki H, Salo J, Linna TJ. Celecoxib and ketoprofen for pain management during tonsillectomy: a placebo-controlled clinical trial. Otolaryngol Head Neck Surg. 2005;132:287-94.

Sobel R, Lovell D, Brunner H, et al. Safety of celecoxib and nonselective nonsteroidal anti-inflammatory drugs in juvenile idiopathic arthritis: results of the phase 4 registry. Pediatr Rheumatol Online J 2014;12:29.

Sobol SE, Wetmore RF, Marsh RR, Stow J, Jacobs IN. Postoperative recovery after microdebrider intracapsular or monopolar electrocautery tonsillectomy: a prospective, randomized, single-blinded study. Arch Otolaryngol Head Neck Surg. 2006;132:270-4.

Stempak D, Gammon J, Klein J, Koren G, Baruchel S. Single-dose and steady-state pharmacokinetics of celecoxib in children. Clin Pharmacol Ther. 2002;72:490-7.

Titchen T, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. British J Clin Pharm 2005; 59:718-723.

Van Daele DJ, Hershberger JM, Bodeker KL, Trask DK. Celecoxib vs. Placebo in Tonsillectomy: A Randomized Double Blind Placebo Controlled Trial Comparing Analgesia. Triological Society, Combined Sections Meeting, Miami Beach, Florida January 10-12, 2014.

Wei JL, Beatty CW, Gustafson RO. Evaluation of posttonsillectomy hemorrhage and risk factors. Otolaryngol Head Neck Surg. 2000;123:229-35.

Wong D, Baker C. Pain in children: comparison of assessment scales, Pediatric Nursing 1988; 14:9-17.

# APPENDIX

1. Wong-Baker FACES scale for estimating pain level in children 3 and older [Wong and Baker 1988].


2. Ten-point Pain Scale for estimating pain level in older children (ages 10 and above).