

Randomized Clinical Trial Examining Use of Adjunct Exparel® for Post-tonsillectomy Pain Management in Adults

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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from the Principal Investigator.

Statement of Compliance

This investigation will be conducted in compliance with the protocol, as well as applicable regulatory requirements including the requirements for review by an Institutional Review Board (21 Code of Federal Regulations [CFR] Part 56), for protection of human subjects and informed consent (21 CFR Part 50); and Title 45: Part 160, Part 162, and Part 164 of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. This study was reviewed by the Food and Drug Administration (FDA). On 04/12/17, the FDA rendered the decision that the study meets all of the requirements for exemption from the Investigational New Drug (IND) regulations, and therefore an IND application is not required to conduct the investigation (FDA letter attached).

Study team members completed education about protection of human subjects and the certificates of completion are attached. In addition, study team members indicate that they have no conflict of interest to disclose.

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List of Abbreviations

AE	Adverse Event/Adverse Experience
Bupivacaine	bupivacaine hydrochloride (HCl) 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL)
CFR	Code of Federal Regulations
CRF	Case Report Form
Exparel®	bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL)
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICD	Informed Consent Document
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MOSA	Michigan Otolaryngology Surgery Associates
N	Number of participants
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SJMAA	St. Joseph Mercy Ann Arbor
SJMHS	St. Joseph Mercy Health System
SOC	Standard of Care

Protocol Summary

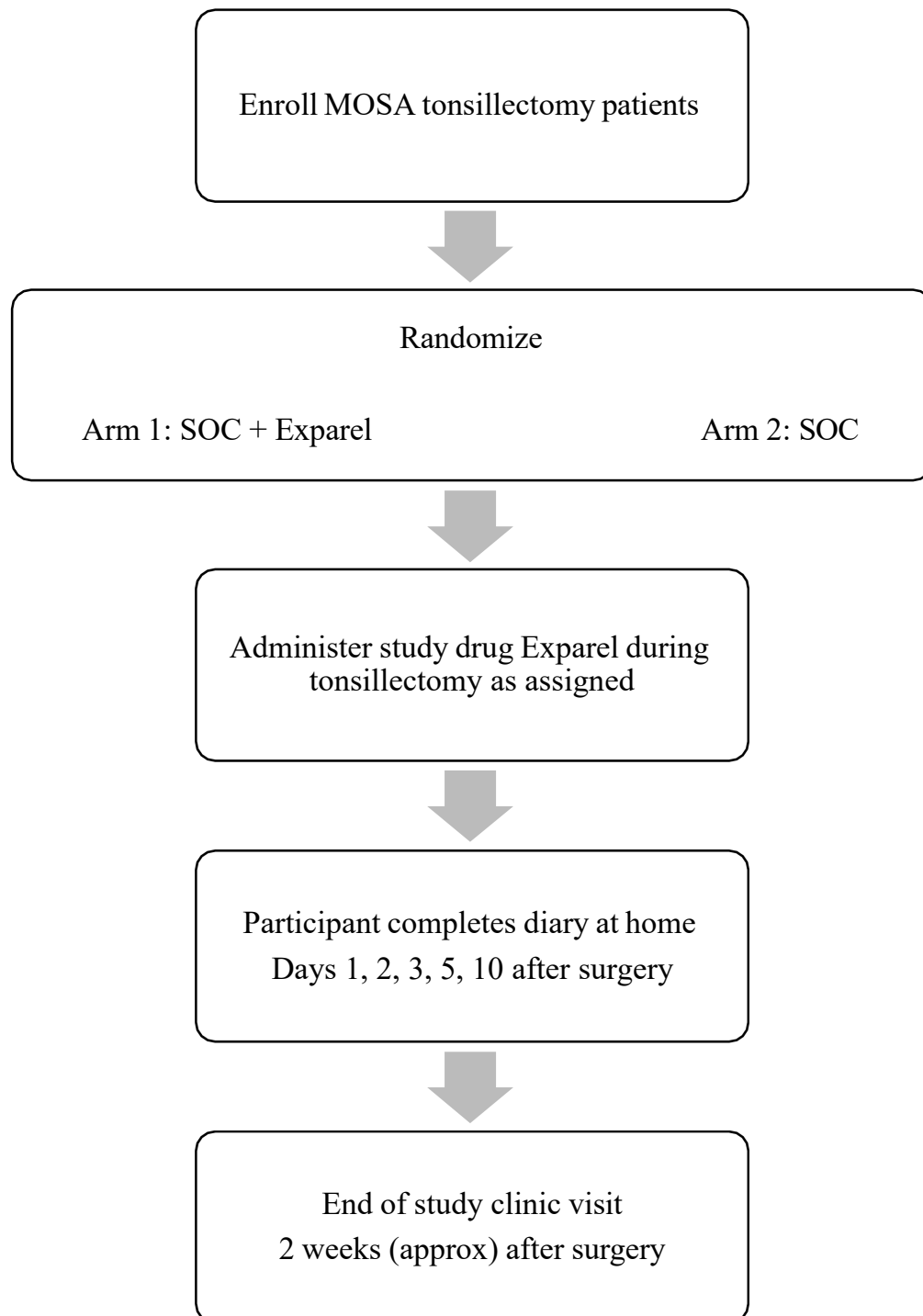
Full Title	Randomized Clinical Trial Examining Use of Adjunct Exparel® for Post-tonsillectomy Pain Management in Adults
Short Title	Exparel® Clinical Trial for Post-tonsillectomy Pain Control (EXPCT)
Clinical Trial Phase	Post marketing Phase IV
IND Sponsor (if applicable)	No applicable. IND exempt per 04/12/17 FDA decision
Sponsor Investigator	Paul T. Hoff, MD
Sample Size	To achieve 80% power, assuming a difference of 1 point in pain rating with a common standard deviation of 1 point, the minimum sample size is 34 patients—17 each in the treatment and control groups
Study Population	Adults 18 years and older, undergoing bilateral palatine tonsillectomy and no other procedure for recurrent tonsillitis or obstructive pathologies
Accrual Period	About 12 months, given enrollment of 3 – 4 patients per month
Study Design	<p>Open label, single blind (participant), parallel assignment, randomized clinical trial</p> <p>N = 34 patients</p> <p>17 in the adjunct Exparel® treatment arm (Arm 1)—After removal of the tonsils and before extubation, infiltration of the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) followed by adjunct Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL)</p> <p>17 in the standard of care medication arm (Arm 2)—After removal of the tonsils and before extubation, infiltration of bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone</p>
Study Duration	<p>After providing informed consent, the study duration for each enrolled participant begins with the day of surgery and ends after the approximately two-week postoperative follow-up visit and Postoperative Diary reporting.</p> <p>The total planned study duration is about 18 months, from participant accrual through data analysis, interpretation, and reporting.</p>

Study Agent/Intervention Description	<p>The study agent is Exparel® 1.3% bupivacaine liposome injectable suspension (13.3 mg/mL), a long acting local anesthetic.</p> <p>Intervention description: Arm 1 – Adjunct Exparel Treatment After removal of the tonsils and before extubation, the principal investigator will infiltrate 0.5 mL of the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left side of the oropharynx for a volume of 2 mL or 5 mg of bupivacaine HCl with 10 mcg epinephrine on each side. Following the standard medication, the principal investigator will infiltrate 0.5 mL of Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left side of the oropharynx for a volume of 2 mL or 26.6 mg of Exparel on each side.</p> <p>Standard of care medication: Arm 2 – Standard medication After removal of the tonsils and before extubation, the principal investigator will infiltrate 0.5 mL of the standard of care medication bupivacaine HCl 0.25% (2.5 mg/ mL) with epinephrine (5 mcg/mL) into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left side of the oropharynx for a volume of 2 mL or 5 mg of bupivacaine HCl with 10 mcg epinephrine on each side.</p>
Primary Objective	<p>To examine post tonsillectomy pain ratings in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL), compared with adults who receive the standard of care post-excision medication bupivacaine HCl 0.25% with epinephrine alone</p> <p>Primary outcome measures:</p> <ul style="list-style-type: none"> • Three day mean of the average pain ratings from Day-1 through Day-3 • Three day mean of the maximum pain ratings from Day-1 through Day-3
Secondary Objectives	<p>To examine post tonsillectomy pain medication requirements in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL), compared with adults who receive the post-excision standard of care medication bupivacaine HCl 0.25% with epinephrine alone</p> <p>Secondary outcome measures:</p>

	<ul style="list-style-type: none"> • Three day cumulative amount of prescribed narcotic medication in mg used from Day-1 through Day-3 • Three day cumulative amount of over the counter pain medication in mg used from Day-1 through Day-3
Exploratory Objectives	<p>To explore post-tonsillectomy recovery outcomes in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care medication bupivacaine HCl 0.25% with epinephrine alone</p> <p>Exploratory outcome measures:</p> <ul style="list-style-type: none"> • The average and maximum pain rating variability on Day-5 and Day-10 • The amount of prescribed narcotic and over the counter pain medication used on Day-5 and Day-10 • The amount of fluid intake in ounces on Day-1, -2, -3, -5, and -10 • Time to change in food intake from clear liquids to other thicker foods such as smoothies, cream soups, pudding, etc., and solid food such as soft eggs on Day-1, -2, -3, -5, and -10 • Time to first physical activity outside of the house, such as running an errand on Day-1, -2, -3, -5, and 10 • Adverse events during the operation, in PACU, and during the follow-up period • Patient rated satisfaction with the treatment
Risks/Benefits	<p>There are side effects associated with Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL).</p> <p>Common side effects include nausea, constipation, vomiting, and numbness around the surgical site.</p> <p>Serious side effects can include signs of allergic reaction, cardiovascular problems, and neurologic problems.</p> <p>If a serious side effect occurs immediately following surgery while in the Outpatient Surgery Center after administration of the study drug and before discharge, the nursing staff, anesthesiologist, surgeon and/or PI, will provide appropriate emergency care.</p>

	<p>For events after discharge, participants are instructed at consent, with a written reminder in the Postoperative Diaries, and with a wallet card to contact the clinic of the PI for any questions or concerns regarding adverse events which do not require immediate medical attention. In an emergency they are instructed to bring the wallet card with them and go to the nearest Emergency Center, notify the care team of the study, and contact the PI as soon as possible afterwards..</p> <p>Benefits The use of Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) has been reported to decrease narcotic requirements and improve pain rating scores in patients who underwent a variety of surgical procedures (mammoplasty, knee arthroplasty, hemorrhoidectomy, and inguinal hernia repair). Decrease in narcotic pain medication requirements may be an important therapeutic advantage in light of the current opioid epidemic. In other studies which examined the safety, efficacy, and pharmacokinetic profile of Exparel, investigators noted that Exparel showed rapid uptake during the first few hours after surgery and prolonged release through 96 hours after administration. Therefore, extended pain control with use of Exparel may decrease the potential for limited fluid intake which could contribute to postoperative dehydration and other complications. Investigators also noted that there were fewer adverse events reported with smaller doses of Exparel than with larger doses. In this study the dose of Exparel will be limited to a total of 53.2 mg. and may be well tolerated by study participants.</p>
Endpoints	<p>Primary study endpoint: Patient reporting of Postoperative Diary information regarding post tonsillectomy pain ratings for Day-1 through Day-3</p> <p>Secondary endpoint: Patient reporting of Postoperative Diary information regarding pain medication use for Day-1 through Day-3</p> <p>Exploratory endpoints: Patient reporting of Postoperative Diary information regarding factors related to the recovery process (pain ratings and medication use for Day-5 and Day-10; food and fluid intake, activity, and any unexpected event for Day-1, -2, -3, -5, and -10)</p> <p>Final study endpoint: Patient postoperative follow-up visit at Michigan Otolaryngology Surgery Associates office.</p>

	<p>The following events will lead to terminating a participant's participation in the clinical trial.</p> <ul style="list-style-type: none">• Voluntary participant withdrawal• Any reason that could jeopardize the safety of the participant in the judgement of the investigator.
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1. KEY ROLES

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Exparel® (Pacira Pharmaceutical, Inc., San Diego, CA) is a non-narcotic long acting local anesthetic agent, bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL), also used to produce postsurgical analgesia after infiltration into the surgical site. The Exparel DepoFoam® drug delivery system allows slow release of the bupivacaine liposome suspension which extends the analgesic effect up to 96 hours.¹ For this proposed study, our goal is to evaluate the use of Exparel as an adjunct to the standard of care medication bupivacaine hydrochloride (HCl) 0.25% (2.5 mg/mL) with epinephrine 5 mcg/mL (Hospira, Inc., Lake Forest, IL)² to manage pain experienced by adult patients after bilateral palatine tonsillectomy.

Tonsillectomy is one of the most commonly performed surgical procedures in the United States. In 2006, there were approximately 680,000 ambulatory surgery visits for chronic diseases of the tonsils and adenoids in children and adults.³ Indications for tonsillectomy in the adult population include recurrent pharyngitis, chronic tonsillitis, and obstructive pathology. Tonsillectomy is often associated with severe postoperative pain, which can result in prolonged poor oral intake, dehydration, and the need for high dose narcotics.⁴ In severely dehydrated patients, epithelial shedding and necrosis of soft tissues at the surgical site can lead to postoperative complications such as bleeding, delayed healing, and severe pain.

Increasingly, the quality of surgical care is evaluated by examining readmission and complication rates. In a cross-sectional analysis of ambulatory surgery and hospital databases from New York, Florida, Iowa, and California for 2010, investigators identified a revisit rate of 11.3% in 7,748 adult patients who underwent bilateral tonsillectomy.⁵ Additionally, the investigators noted the primary diagnoses at first revisit were bleeding (41.3%), acute pain (22.1%), and fever/dehydration (13.2%).⁵ Improving pain control after tonsillectomy has the potential to decrease patient morbidity and the financial burden to the health care system.

Investigators have examined a number of methods to reduce postoperative pain, including variation of surgical technique; preoperative, intraoperative, and postoperative medications; and pre-incisional or post-excisional injections of local anesthetics.⁶⁻⁸ Several studies have demonstrated short-term improvement in pain control with local infiltration of bupivacaine into the surgical site. Pre-incisional and/or post-excisional injection of bupivacaine is now commonly used for pain management in patients undergoing tonsillectomy. However, one of the limitations of local anesthetics such as bupivacaine is the relatively short duration of action, about 3 – 6 hours.

Pharmaceutical companies have recently developed new technologies for drug delivery, such as long acting carriers of local anesthetic using multi-vesicular liposomes to increase drug duration of action.^{9, 10} Exparel® (1.3% bupivacaine liposome injectable suspension (13.3 mg/mL) is one such formulation, with an average duration of action of 72 hours.¹ In a clinical review of the literature, Tong, Kaye, and Urman noted that use of liposomal bupivacaine decreased narcotic requirements and improved pain ratings in patients who underwent mastoplasmy, knee arthroplasty, hemorrhoidectomy, and inguinal hernia repair.¹¹

To the best of our knowledge, there are two studies in published literature that evaluated the use of Exparel® (bupivacaine liposome injectable suspension 1.3%) for pain management in adults after tonsillectomy. One small scale study was done to characterize the pharmacokinetic profile of single dose Exparel infused intraoperatively for prolonged analgesia in 12 adults undergoing tonsillectomy.¹² In another study, the investigator examined postoperative use of liposomal bupivacaine (Exparel) for pain management compared to no postoperative treatment in 39 adult patients.¹³ A small but statistically significant difference in pain ratings was seen between the Exparel active comparator and the no treatment group on the day of surgery.

For this proposed study, our goal is to evaluate the use of Exparel® (bupivacaine liposome injectable suspension 1.3%) to manage pain experienced by adult patients after tonsillectomy. We hypothesize that Exparel, when used as a post-excision adjunct to standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) after tonsillectomy, will decrease the patient's experience of pain intensity, especially for the first three days after surgery and correspondingly reduce the requirement for pain medications.

2.1.1 Description of the Study Agent/Intervention^{1, 2}

Exparel® is a slow release, long acting, non-narcotic local anesthetic agent containing the active ingredient bupivacaine in a liposomal suspension. The average duration of action for Exparel is about 72 hours. Exparel has been used to produce post-surgical analgesia and is the agent to be studied. Microscopic particles of bupivacaine—multivesicular liposomes—in Exparel are enclosed in a DepoFoam® drug delivery system that slowly releases the medication over time to extend the pharmacologic effect of Exparel. Bupivacaine is present in Exparel® in a concentration of 1.3% (13.3 mg/mL). The onset of action with Exparel® is gradual, and the duration of action may extend up to 96 hours.¹

Bupivacaine HCl with epinephrine injectable solution is a local anesthetic agent that blocks the generation and conduction of nerve impulses. Infiltration of bupivacaine HCl is used to produce local or regional anesthesia or analgesia for surgery; dental and oral surgery procedures; diagnostic and therapeutic procedures; and for obstetrical procedures. The onset of action with bupivacaine HCl is rapid—often minutes—and the duration may extend up to six or seven hours. In this study, bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) is the local standard of care medication used by the principal investigator for immediate post tonsillectomy pain management. The dilute concentration

of epinephrine usually reduces the rate of bupivacaine absorption and may prolong the duration of action.²

2.1.2 Summary of Previous Pre-clinical Studies^{1, 2}

The pharmaceutical manufacturer of Exparel® reported the following information regarding pre-clinical animal studies of bupivacaine HCl, the active drug in Exparel. In animal studies during organogenesis, bupivacaine HCl was administered subcutaneously to rats and rabbits at doses from 0.1 to 1.6 times the maximum recommended human dose. There were no embryo-fetal deaths in rats, but high doses produced maternal lethality. In rabbits, high doses resulted in increased embryo-fetal deaths but no maternal toxicity. Decreased pup survival was observed in rats during pregnancy through lactation when doses of 1.5 times the maximum recommended human dose was administered to pregnant animals.¹

2.1.3 Summary of Relevant Clinical Studies^{1, 2}

Exparel® safety was evaluated in 10 randomized, double-blind clinical studies that involved surgical site infiltration of the drug in 823 patients undergoing various surgical procedures. Exparel doses administered in these studies ranged from 66 to 532 mg. The most common adverse reactions, those occurring at an incidence greater than or equal to 10%, following Exparel administration were nausea, constipation, and vomiting. Pyrexia, dizziness, edema peripheral, anemia, hypotension, pruritus, tachycardia, headache, insomnia, postoperative anemia, muscle spasms, hemorrhagic anemia, back pain, somnolence, and procedural pain were common adverse reactions that were reported to occur at an incidence greater than or equal to 2% to less than 10% after Exparel administration. Additional reported rare adverse reactions with an incidence of less than 2% following Exparel administration included chills, erythema, bradycardia, anxiety, urinary retention, pain, edema, tremor, postural dizziness, paresthesia, syncope, incision site edema, procedural hypertension and hypotension; procedural nausea, muscular weakness, neck pain, generalized pruritus and pruritic rash; hyperhidrosis, cold sweat, urticaria, bradycardia, palpitations, sinus bradycardia, supraventricular and ventricular extra systoles; ventricular tachycardia, hypertension, pallor, anxiety, confusional state, depression, agitation, restlessness, hypoxia, laryngospasm, apnea, respiratory depression, respiratory failure, increased body temperature and increased blood pressure; decreased blood pressure and oxygen saturation; urinary incontinence, vision blurred, tinnitus, as well as drug hypersensitivity.

In summary, nervous system adverse reactions with an incidence greater than or equal 1% following Exparel® administration were dizziness (6.2%), headache (3.8%), somnolence (2.1%), hypoesthesia (1.5%), and lethargy (1.3%). Tachycardia (3.9%) and bradycardia (1.6%) were cardiac system adverse reactions identified with an incidence greater than or equal to 1% following Exparel administration.

2.1.4 Summary of Epidemiological Data¹

There were 171 participants age 65 and older out of 823 patients in the 10 clinical studies using infiltration of Exparel® into surgical sites; 47 patients were greater than or equal to 75 years of age. Although there were no overall differences in safety or effectiveness observed between patients over age 65 and younger patients in the 10 clinical studies, the manufacturer advises caution that some older individuals may demonstrate greater sensitivity to Exparel. Because bupivacaine is excreted by the kidney, risk of adverse reactions to Exparel may be increased in patients with impaired renal function. Elderly patients are more likely to have diminished renal function, therefore, the practitioner judiciously needs to consider Exparel dosing in older adults. In addition, amide-type local anesthetics such as bupivacaine are metabolized in the liver and should be used with caution in patients with liver disease.

Exparel® is not recommended for pediatric use as safety and effectiveness have not been established in pediatric populations. There is no available information about the effects of bupivacaine in the breast fed infant or effects on breast milk production. Therefore a similar advisory is suggested for women who are pregnant, planning on becoming pregnant, and/or lactating.

2.2 Rationale

In this prospective randomized clinical trial, we plan to evaluate patient outcomes in adults after palatine tonsillectomy when treated with post-excision infiltration of Exparel® 1.3% bupivacaine liposome injectable suspension (13.3 mg/mL) as an adjunct to the post-excision standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) infiltration into the upper and lower poles of the anterior and posterior tonsillar pillars, compared with patients receiving standard of care post-excisional bupivacaine with epinephrine alone. Because the average duration of action for Exparel is about 72 hours, we expect that patients treated with Exparel will report a greater difference in pain ratings during the 3-day postoperative period and thereafter, from those treated with post-excisional bupivacaine HCl with epinephrine alone.

Typically, patients report high to moderate pain ratings after tonsillectomy and through the first week after surgery. By the second week around days 12 to 14, patients' indicate that their pain begins to stabilize and resolve. These clinical observations were similarly noted in a Danish study by Kamarauskas, Dahl, Hlidarsdottir, Mainz, and Ovesen. The authors noted that 89% of 614 enrolled patients returned questionnaires about patient reported outcomes on quality of outpatient tonsillectomy in ear, nose, and throat practices.¹⁴

The proposed clinical trial will provide important information about patients' perception of pain control and the amount of narcotic and over the counter medication taken to control pain. Theoretically, improved pain control may lead to improved oral intake and earlier patient mobilization, thereby decreasing the risk of dehydration and short-term morbidity associated with tonsillectomy.

Study hypotheses:

1. There will be a decrease in pain ratings in adult patients receiving post-excision Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after palatine tonsillectomy compared to adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone, with the most significant decrease in pain ratings reported during the 3-day period after surgery.
2. There will be a decrease in narcotic requirement in adult patients receiving post-excision Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after palatine tonsillectomy compared to adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone, with the most significant decrease in narcotic requirements reported during the 3-day period after surgery.
3. There will be a decrease in time to resumption of eating, drinking, and activity in adult patients receiving post-excision Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after palatine tonsillectomy compared to adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone, with the most significant decreases reported during the 3-day period after surgery.

2.3 Potential Risks and Benefits

The purpose of this study is to determine whether use of Exparel®, a long acting non-narcotic local anesthetic agent, influences patients' pain management outcomes after surgery.

2.3.1 Potential Risks^{1, 2}

The most common adverse reactions associated with administration of Exparel® (those occurring at an incidence greater than or equal to 10%) include nausea, vomiting, and constipation.

Signs of common adverse reactions that were reported to occur at an incidence greater than or equal to 2% to less than 10% after Exparel® administration include those listed below.

- Pyrexia
- Dizziness
- Peripheral edema
- Anemia
- Hypotension
- Pruritus
- Tachycardia

- Headache
- Insomnia
- Postoperative anemia
- Muscle spasms
- Hemorrhagic anemia
- Back pain
- Somnolence
- Procedure pain

Additional rare adverse reactions that occurred at an incidence of less than 2% in previous studies after administration of Exparel® include:

- Chills
- Erythema
- Bradycardia
- Anxiety
- Urinary retention
- Pain
- Edema
- Tremor
- Postural dizziness
- Paresthesia
- Syncope
- Incisional site edema
- Procedural hypertension
- Procedural hypotension
- Procedural nausea
- Muscular weakness
- Neck pain
- Generalized pruritus
- Pruritic rash
- Hyperhidrosis
- Cold sweat
- Urticaria
- Bradycardia
- Palpitations
- Sinus bradycardia
- Supraventricular extra systoles
- Ventricular extra systoles
- Ventricular tachycardia
- Hypertension
- Pallor
- Anxiety
- Confusional state
- Depression

- Agitation
- Restlessness
- Hypoxia
- Laryngospasm
- Apnea
- Respiratory depression
- Respiratory failure
- Increased body temperature
- Increased blood pressure
- Decreased blood pressure
- Decreased oxygen saturation
- Urinary incontinence
- Blurred vision
- Tinnitus
- Drug hypersensitivity

If a serious side effect occurs in the Outpatient Surgery Center after administration of the study drug and before discharge, the nursing staff, anesthesiologist, surgeon, and/or PI, will provide appropriate emergency care.

Participants are instructed at consent, with a written reminder in the Postoperative Diaries, and with a wallet card to contact the clinic of the PI for any questions or concerns regarding adverse events which do not require immediate medical attention. In an emergency they are to bring the wallet card with them and go to the nearest Emergency Center, notify the care team of the study, and contact the PI as soon as possible afterwards.

2.3.2 Potential Benefits

As noted previously, Tong et al. in the review of randomized clinical trials stated that use of liposomal bupivacaine decreased narcotic requirements and improved pain rating scores in patients who underwent mastectomy, knee arthroplasty, hemorrhoidectomy, and inguinal hernia repair¹¹ Further, Tong et al. stated that a single administration of liposomal bupivacaine was well tolerated for pain management after surgical site infiltration. Likewise, we expect that patients treated with adjunct Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) and bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) after tonsillectomy will report a greater difference in pain ratings during the 3-day postoperative period and thereafter, from those treated with post-excision bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

Hu, Onel, Singla, Kramer, and Hadzic reviewed use of bupivacaine liposome suspension as a single administration into a surgical site in four studies—inguinal hernia repair, total knee arthroplasty, hemorrhoidectomy, and bunionectomy¹⁵ The investigators in each study evaluated the safety, efficacy, and pharmacokinetic profile of liposomal

bupivacaine as part of multimodal pain management. Hu et al. noted that liposomal bupivacaine showed rapid uptake during the first few hours after surgery and prolonged release through 96 hours after administration. In doses of less than or equal to 266 mg, there were fewer adverse events reported with smaller doses than with larger doses. The authors concluded that liposomal bupivacaine was well tolerated by participants in the four studies reviewed.¹⁵

Potential benefits to participants in this clinical trial would be the prospect for improved pain control with a decreased need for postoperative narcotic medication to manage pain. Theoretically, improved pain control could lead to improved oral intake and earlier patient mobilization, thereby decreasing the risk of dehydration and short-term morbidity associated with tonsillectomy.

3. STUDY OBJECTIVES

The purpose of this investigation is to examine post tonsillectomy outcomes in adult patients who receive post-excision Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive standard of care post-excision bupivacaine 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

The general purpose of the study is to examine the effectiveness of Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) in adult patients for pain management after palatine tonsillectomy, compared with those who receive standard of care bupivacaine 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

The study drug is Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) an amide local anesthetic with an average duration of action of 72 hours. It is slowly infiltrated into the soft tissue at the surgical site to produce post-surgical analgesia. The recommended dose of Exparel is based on the size of the surgical site; the volume required for covering the surgical area; and individual patient factors that may impact the safety of an amide local anesthetic such as kidney and liver function.

Bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) is a local anesthetic agent that blocks the generation and conduction of nerve impulses. Infiltration of bupivacaine is used to produce local or regional anesthesia for surgery, such as dental and oral surgery procedures; diagnostic and therapeutic procedures; and obstetrical procedures. Additionally, bupivacaine is used to produce post-procedure analgesia. The half-life of bupivacaine HCL with epinephrine infiltration in adults is about 3 hours.

Arm 1, Adjunct Exparel® treatment:

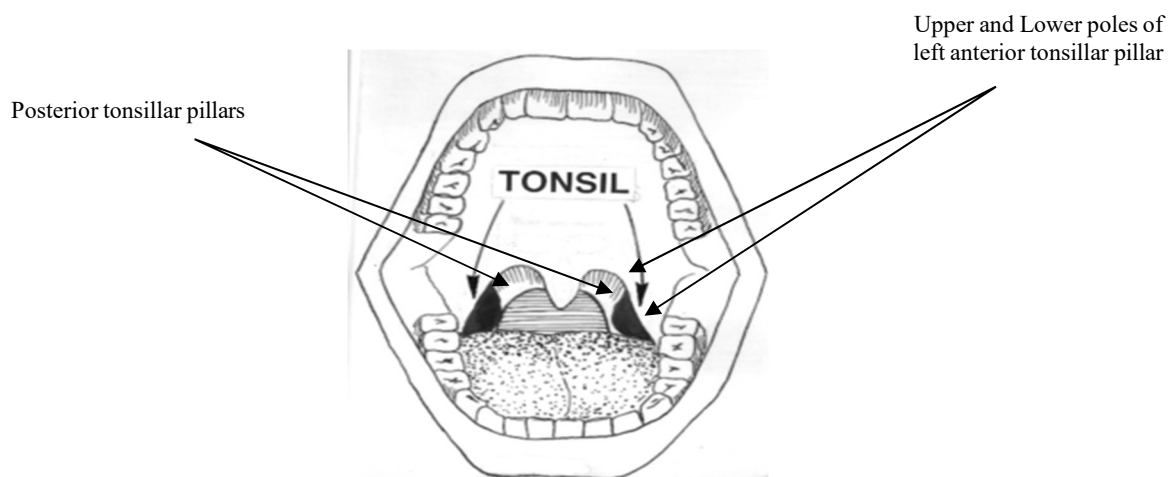
After removal of the tonsils and before extubation, participants randomly assigned to Arm 1, adjunct Exparel treatment, will receive the standard of care medication

bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) followed by Exparel bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL). The principal investigator will infiltrate 0.5mL of bupivacaine HCl 0.25% with epinephrine into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx. The standard medication will be followed by infiltration of 0.5 mL of Exparel into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx (Figure 1). A total volume of 2 mL bupivacaine HCl 0.25% (total dose of 5 mg) with epinephrine (total dose of 10 mcg) will be injected on the right and left sides of the oropharynx, followed by a total volume of 2 mL Exparel bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) for a total dose of 26.6 mg on each side.

Arm 2, standard of care medication:

After removal of the tonsils and before extubation, participants randomly assigned to Arm 2, standard of care medication will receive bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL). The principal investigator will infiltrate 0.5mL of bupivacaine HCl 0.25% with epinephrine into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx. A total volume of 2 mL bupivacaine HCl 0.25% (total dose of 5 mg) with epinephrine (total dose of 10 mcg) will be injected into the upper and lower poles of the anterior and posterior tonsillar pillars on each side of the oropharynx.

Figure 1. Oropharynx and Tonsils



Oropharynx and Tonsils. All study participants will receive the standard of care medication-bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL): 0.5mL infiltrated into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx for a total volume of 2 mL bupivacaine HCl (total dose of 5 mg) with epinephrine (total dose of 10 mcg) on each side. Afterward, participants assigned to the adjunct Exparel® treatment group will receive the study drug

Exparel bupivacaine liposome suspension 1.3% (13.3 mg/mL): 0.5 mL infiltrated into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx for a total volume of 2 mL of Exparel (total dose of 26.6 mg) on each side of the oropharynx. (Figure adapted from Clip Art. Used with permission from Microsoft.)

3.1 Primary Objective

The primary objective is to examine post tonsillectomy pain ratings in adult patients who receive post-excision Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone.

Primary outcome measures include post tonsillectomy pain ratings from Day-1 through Day-3.

- Three-day mean of the average pain rating from Day-1 to Day-3.
- Three-day average of the maximum pain rating from Day-1 to Day-3.

3.2 Secondary Objectives

The secondary objective is to examine post tonsillectomy pain medication requirements in adult patients who receive post-excision Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone.

Secondary outcome measures include post tonsillectomy pain medication use from Day-1 through Day-3.

- Three-day cumulative amount of prescribed narcotic medication in mg used from Day-1 through Day-3.
- Three-day cumulative amount of over the-counter pain-medication in mg used from Day-1 through Day-3.

3.3 Exploratory Objectives:

To examine the post-tonsillectomy recovery outcomes (Day-5 and Day-10 pain ratings and pain medication taken; Day-1, -2, -3, -5, and -10 fluid and solid food intake; resumption of activity; and adverse events) in adult patients who receive post-excision Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone.

Exploratory outcome measures:

- The average and maximum pain rating variability on Day-5 and Day-10
- The amount of narcotic and over the counter pain medications used on Day-5 and -10
- The amount of fluid intake on Day-1, -2, -3, -5, and -10
- Time to change in food intake (for example from clear liquids to other thicker foods such as smoothies, cream soups, pudding, etc., and solid food such as cooked eggs, mashed potatoes, cottage cheese, etc.) on Day-1, -2, -3, -5, and -10
- Time to first physical activity outside of the house (for example running an errand) on Day-1, -2, -3, -5, and -10-
- Adverse events during the operation, in PACU, and during the follow-up period
- Patient rated satisfaction with the treatment at follow-up visit

4. STUDY DESIGN

4.1 Description of the Study Design

This is a single site, post marketing, open label, randomized clinical trial with two arms. There will be 19 participants in each arm with parallel assignment to the arms. In Arm 1, the treatment arm, the participant will receive the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) followed by the study drug, Exparel bupivacaine liposome suspension 1.3% (13.3 mg/mL). In Arm 2, the standard care arm, the participant will receive the standard of care drug bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone. The participant will be blind to group assignment.

We plan to examine the effectiveness and superiority of administration of Exparel® 1.3% bupivacaine liposome suspension (13.3 mg/mL) in adult patients after palatine tonsillectomy as adjunct to standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) infiltration for pain management, compared with adult patients receiving the post-excision standard of care medication bupivacaine HCl 0.25% with epinephrine alone. The principal investigator will provide the study intervention in the Outpatient Surgery Center at St. Joseph Mercy Ann Arbor after excision of the palatine tonsils and before extubation. Patients will be admitted and discharged from the Outpatient Surgery Center on the same day. Patients will participate in pre-operative assessment and postoperative follow at the Michigan Otolaryngology Surgery Associates (MOSA) office.

We project that it may take approximately 12 months to complete study accrual with a possible enrollment of 3 to 4 patients per month. After providing informed consent, the expected duration of active participation for each participant will be from the day of surgery through the post-surgical follow-up visit approximately two weeks after tonsillectomy. Although some patients may enroll several weeks prior to surgery due to their individual schedules, patients will be considered active from the day of surgery through follow up at MOSA. Participants will maintain a Postoperative Diary in which

they will record pain ratings, pain medications used, fluid and food intake, activity, and any unexpected events.

4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint will be patient reported Postoperative Diary recording of pain ratings for Day-1 through Day-3.

Primary outcome measures include post tonsillectomy pain ratings from Day-1 through Day-3.

- Three-day mean of the average pain rating from Day-1 through to Day-3.
- Three-day average of the maximum pain rating from Day-1 through Day-3.

4.2.2 Secondary Endpoints

The secondary endpoint will be patient reported Postoperative Diary recording of pain medications used Day-1 through Day-3.

Secondary outcome measures include post tonsillectomy pain medications used from Day-1 through Day-3.

- Three-day cumulative amount of prescribed narcotic medication used.
- Three-day cumulative amount of over the-counter pain-medication used.

4.3 Exploratory Endpoints

The exploratory endpoints will be patient reported Postoperative Diary recordings of outcomes related to the recovery process during the period of Day-1, -2, -3, -5, and -10.

Exploratory outcome measures:

- The average and maximum pain rating variability at Day-5 and -10
- The amount of pain medications used at Day-5 and 10
- The amount of fluid intake at Day-1, -2, -3, -5, and -10
- Time to change in food intake (for example, from clear liquids to other thicker foods such as smoothies, cream soups, pudding, etc., and solid food such as soft eggs, mashed potatoes, cottage cheese, etc.) on Day-1, -2, -3, -5, and -10
- Time to first physical activity outside of the house, (for example, running an errand) on Day-1, -2, -3, -5, and -10
- Adverse events during the operation, in PACU, and during the follow-up period.
- Patient rated satisfaction with the treatment.

The day of surgery is identified as Day-0. The average pain rating in PACU on Day-0 will be considered baseline. For Day-1, the patient will record pain ratings; medications used; fluid and food intake; activity; and unexpected or adverse events beginning at midnight after discharge from the Outpatient Surgery Center through 11:59 P.M. Each

successive designate point, (Day-2, -3, -5, and -10) will begin at midnight and extend through 11:59 P.M. Participants will maintain Postoperative Diary entries for the designated points, and will be encouraged to record information every 2-4 hours while awake.

Participants will be scheduled for a final postoperative follow-up visit with the principal investigator approximately two weeks after surgery. Participants will return completed paper copies of the Postoperative Diary at this final visit and will complete a brief patient satisfaction questionnaire.

5. STUDY POPULATION

5.1 Description of the Study Population

The study population will be drawn from patients with recurrent tonsillitis or obstructive pathologies seeking care at the MOSA office in Ann Arbor. Patients will be invited to participate in the clinical trial by the principal investigator and/or primary coordinator, and may agree to or decline the invitation. Individuals under age 18 years and women known to be pregnant, planning to become pregnant, or who are lactating are excluded because Exparel® has not been evaluated for use in these populations.

5.1.1 Participant Inclusion Criteria

Patients must meet all of the following inclusion criteria to participate in the study.

1. Scheduled to undergo bilateral palatine tonsillectomy as the only procedure
2. Adults age 18 years and older.

5.1.2 Participant Exclusion Criteria

Patients must not meet any one of the following exclusion criteria to participate in the study.

1. Severe systemic disease that is clinically significant in the judgement of the investigator.
2. Coagulation disorder that is clinically significant in the judgement of the investigator.
3. Current or previous history of analgesic dependence
4. Allergy to any of the drugs used in the study (bupivacaine)
5. Women known to be pregnant, planning to become pregnant, or lactating
6. Hearing impairment that is clinically significant in the judgement of the investigator.
7. Cardiovascular disease that is clinically significant in the judgement of the investigator.
8. Impaired liver function that is clinically significant in the judgement of the investigator.
9. Impaired renal function that is clinically significant in the judgement of the investigator.

10. Unable to provide consent.
11. Additional surgical procedures planned concurrently with palatine tonsillectomy.
12. Planned use of topical or injected anesthetics other than those administered by the study within the two week follow up.

5.1.2.1 Enrollment Guidelines

This is a relatively short term study, extending for approximately two weeks after surgery. However, patients will be encouraged to refrain from enrolling in another study while participating in this clinical trial. This study involves sustained participant attention from the day of surgery through Day-3 and on Day-5 and Day 10 after surgery for recording and reporting of post tonsillectomy experiences. Because patients will be recovering from surgery and experiencing pain, they may have limited ability to focus on concomitant or competing requirements from an additional or new study.

5.2 Strategies for Recruitment and Retention

The MOSA office will be the first contact for recruiting patients for the clinical trial. The principal investigator will educate MOSA office staff and other MOSA surgeons about the clinical trial. The intention of the education is to have MOSA office staff feel adequately informed to lend clerical and scheduling support and avoid creating unintentional barriers to study progress. Office staff may facilitate communication between the study coordinators, patients, and PI.

Retention of active participants for two-weeks after the study intervention may not be a substantial issue as in a longer term longitudinal study. However, a concern is participant adherence with specific daily requirements for recording and reporting post tonsillectomy pain control; fluid and food intake; activity; and adverse events. We hope to avoid drop-out and enhance adherence through projected friendly and focused contact reminders from the primary coordinator at the identified time points regarding the patient's Postoperative Diary content.

If there is study drop-out of greater than 10% before Day-3, the investigators may need to examine study progress and submit a request to the Saint Joseph Mercy Health System (SJMHS) Institutional Review Board (IRB) to revise the enrollment projection and the study protocol if needed.

6. STUDY AGENT/INTERVENTIONS

6.1 Study Agent Acquisition

Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) is the study agent being tested in this clinical trial and will not be a patient charge item. All other procedures and medications related to tonsillectomy are considered routine or standard of care for adult patients undergoing tonsillectomy and will be charged to the patient and/or

the patient's insurance provider. The principal investigator will collaborate with the SJMAA Inpatient Pharmacy Investigational Drug Services Pharmacist and Surgical Services Medication Safety Pharmacist for study drug acquisition, storage, tracking, and dispensing in accordance with SJMH Pharmacy Policies.

The standard of care product is bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) which will be obtained via standard of care procurement procedures through SJMH Inpatient Pharmacy. SJMH Inpatient Pharmacy standard of care storage, tracking, and dispensing practices will be used with the standard of care product.

6.1.1 Study Agent/Intervention # 1

Exparel® is a local anesthetic agent with duration of action up to 96 hours. Exparel will be used in study treatment Arm 1 as adjunct medication following administration of the standard of care postoperative bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL).

The study drug will be purchased commercially by SJMAA Inpatient Pharmacy Investigational Drug Services for use in this clinical trial, and will not be a patient charge item. Funding for Exparel® will be provided through an internal St. Joseph Mercy Ann Arbor (SJMAA) Research Committee grant. The Research Accountant in the Academic Research Department will receive an invoice from the SJMAA Inpatient Pharmacy for the cost of the medication which will be paid through internal transfer of funds.

6.1.1.1 Formulation, Packaging, and Labeling

Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) is a sterile preservative free aqueous suspension of bupivacaine multivesicular liposomes in a DepoFoam® drug delivery system. Exparel is indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia. Exparel is packaged in 10 mL single use vials, and contains bupivacaine at a concentration of 1.3% or 13.3 mg/mL.

6.1.1.2 Preparation, Administration, Storage, and Dosage of Study Agent(s)/ Intervention(s)

Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) will be used as adjunct analgesia following administration of the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL). The Exparel vial should be inverted to assure that particles are in suspension prior to withdrawing the drug, and may require multiple inversions if the contents of the vial have settled. The registered nurse accessing and preparing the study medication in collaboration with the principal investigator will use aseptic technique. The principal investigator will administer the drug to the treatment group after removal of the tonsils and prior to extubation. Excess Exparel will be disposed of as pharmaceutical waste in accordance with Pharmacy Medication Use Policy #506, via sink. Empty Exparel drug vials will be disposed of as solid waste in the trash.

The principal investigator will infiltrate Exparel® into the soft tissue of the surgical site with a 25-gauge or larger bore needle using frequent aspiration to check for blood and minimize the risk of inadvertent intravascular injection. Exparel is not to be used if the product is discolored. The principal investigator will administer Exparel to the treatment group as adjunct treatment after routine or standard of care post-excision administration of bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL).

Exparel® vials should be refrigerated between 36°F to 46°F and may be stored in sealed, unopened vials by the Pharmacy in this manner for up to 30 days. Vials should not be re-refrigerated. Exparel is not to be used if it is suspected that the vial has been frozen or exposed to high temperatures (greater than 40°C or 104°F) for an extended period or if the vial stopper is bulging. After the dose of Exparel has been withdrawn from the vial, it may be stored at controlled room temperature of 68°F to 77°F for up to four hours until administration.

All study participants will receive the standard of care medication-bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL): 0.5mL infiltrated into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx for a total volume of 2 mL bupivacaine HCl (total dose of 5 mg) with epinephrine (total dose of 10 mcg) on each side. Afterward, participants assigned to the adjunct Exparel® treatment group will receive the study drug Exparel bupivacaine liposome suspension 1.3% (13.3 mg/mL): 0.5 mL infiltrated into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx for a total volume of 2 mL of Exparel (total dose of 26.6 mg) on each side of the oropharynx.

Bupivacaine HCl administered together with Exparel® may impact the pharmacokinetic and/or physicochemical properties of Exparel, and this effect is concentration dependent. The prescribing information for Exparel indicates that bupivacaine HCl and Exparel may be administered simultaneously in the same syringe, and that bupivacaine HCl may be injected immediately before Exparel as long as the ratio of the milligram dose of bupivacaine HCl solution to Exparel does not exceed 1:2.¹ The total dose of bupivacaine HCl is 10 mg and the total dose of Exparel® is 53.2 mg. This dose does not exceed the 1:2 ratio noted in the prescribing information (10 mg bupivacaine HCl / 53.2 mg Exparel = 0.1879). Therefore, 2 mL of the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) may be administered on each side followed by 2 mL of Exparel bupivacaine liposome suspension 1.3% (13.3 mg/mL) on each side for patients randomized to the treatment group.

6.1.1.3 Study Agent Accountability Procedures

The coordinator will record and distribute the participant's study group assignment to key personnel prior to surgery per current institutional best practices. Prior to the surgery the IDS pharmacist will prepare the study drug for delivery to the Outpatient Surgical Center Operating Room PYXIS medication station refrigerator. The IDS pharmacist will clearly

label the study drug for use exclusively in the post-tonsillectomy pain management clinical trial with the patient's name, date of birth, and the clinical trial IRB study number. Exparel will be used on the day of surgery only for a patient randomized to the adjunct Exparel treatment arm of the study.

The IDS pharmacist will maintain an accurate log of study drug receipt, dispensing, and use. The drug log will be updated upon each use of the study drug.

The IDS pharmacist will appropriately dispose of any unused, unopened, or expired study drug remaining at the close of study in accordance with institutional policy. A copy of the study drug log will be maintained in the Inpatient Pharmacy IDS records.

6.1.2 Study Agent/Intervention #2

The standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) will be administered to both the adjunct Exparel treatment and standard care groups. The standard of care drug will be purchased commercially by the SJMAA Inpatient Pharmacy as a formulary item for this study. It will be held in Pharmacy inventory until needed for the supply to the Outpatient Surgery Center Operating Room PYXIS drug dispensing system.

6.1.2.1 Formulation, Packaging, and Labeling

The standard of care agent is an aminoacyl local anesthetic containing bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL). It is available in single and multiple dose vials. Single dose vials will be used in this study.

6.1.3 Preparation, Administration, Storage, and Dosage of Study Agent(s)/Intervention(s)

After removal of the tonsils and prior to extubation, the principal investigator will collaborate with the nursing staff to access, prepare, and administer the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) to participants in both arms of the study. The principal investigator/surgeon will infiltrate 0.5 mL of bupivacaine HCl into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx for a total volume of 2 mL bupivacaine HCl (total dose of 5 mg) with epinephrine (total dose of 10 mcg) on each side

Bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) will be stored unrefrigerated at controlled room temperature of 68°F to 77°F as standard of care in PYXIS Drug Storage.

Unused portions of bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) will be disposed of as pharmaceutical waste in accordance with Pharmacy Medication

Use Policy #506, via sink. Empty bupivacaine HCl 0.25% with epinephrine (5 mcg/mL) drug vials will be disposed of as solid waste in the trash.

6.1.2.3 Study Agent Accountability Procedures

Bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) will be commercially obtained via standard of care SJMAA Inpatient Pharmacy procurement procedures. Standard Pharmacy drug accountability procedures will be used to track bupivacaine.

6.2 Assessment of Participant Compliance with Study Agent(s)/Intervention(s)

This section is not applicable to this clinical trial. The principal investigator will administer the study agent only once to the treatment group Arm 1.

6.3 Concomitant Medications and Procedures

All procedures and medications used during pre-operative preparation, tonsillectomy surgery, and postoperative recovery prior to discharge are routine or standard of care for adult patients except that lidocaine rinse is to be avoided for a possible drug interaction with Exparel.

6.4 Precautionary and Prohibited Medications and Procedures

Bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) and other amide-containing products should be used with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional change associated with prolongation of AV conduction produced by these drugs or products. Multiple injections of bupivacaine products may cause an increase in plasma concentration with each repeated dose resulting in slow accumulation of the drug or slow metabolic degradation. Additionally, patients with severe hepatic disease are at greater risk of developing elevated or toxic plasma concentrations of the drug because amide-type local anesthetics are metabolized in the liver.

Patients with known clinically significant cardiovascular, hepatic, and kidney comorbidities will be excluded from the study per study criteria. All patients will be closely monitored throughout surgery and recovery for any cardiovascular and neurologic issues.

6.5 Prophylactic Medications and Procedures

The patient will receive standard of care pre-operative Percocet (10 mg oxycodone and 650 mg acetaminophen) by mouth prior to surgery. Post tonsillectomy pain and symptom management standard of care treatment for all patients will include the following components. The study participant will document use of pain medication in the Postoperative Diary.

Discharge Medications commonly prescribed to patients include the following. However no standard medication will be required or withheld for the purposes of this study.

Pain medication

Narcotic for moderate to severe pain (Prescription)

- Oxycodone liquid (5 mg / 5 mL)
 - Dose—10 mg or 10 mL by mouth every 4 – 6 hours as needed
 - May take for 10 – 14 days

Over-the-counter for mild to moderate pain

- Acetaminophen liquid (160 mg / 5 mL)
 - One dose = 960 mg (about 30 mL or one ounce) by mouth every 6 hours as needed (Limit dose to 4000 mg/day or about 4 doses in 24 hours)
 - May take for 10 – 14 days

Nausea/Vomiting (Prescription)

- Ondansetron ODT (4 mg. / 5 mL)
 - Dose—4 mg every 6 hours as needed for nausea/vomiting

Bowel Regimen (Over the counter)

- MiraLax (17 grams powder)
 - Mix one packet with 4 – 8 ounces of liquid
 - Take daily while taking Oxycodone liquid

7. STUDY PROCEDURES/EVALUATIONS

Clinical evaluation—medical history, physical examination, laboratory, and any other required preoperative procedures—will be conducted by the appropriate medical staff as part of routine or standard of care MOSA assessments prior to tonsillectomy surgery. All procedures used prior to surgery, during anesthesia and removal of palatine tonsils; and after surgery during the recovery period are routine or standard of care for adult patients undergoing tonsillectomy and not part of study procedures. Abstraction of any information from the patient's EMR will occur after obtaining informed consent to participate in the clinical trial. The patient will be blind to randomization assignment. There are no projected sub-studies associated with this clinical trial.

8. STUDY SCHEDULE

The study schedule is displayed in [Table 1 in the Appendices](#)

8.1 Recruitment

Eligible participants will be sought from the MOSA clinic at or around the time of a pre-operative assessment or scheduling for tonsillectomy. A HIPAA waiver of authorization for pre-screening will be obtained in order to conduct an initial review of the clinical

schedule and available medical record. With participant satisfaction in mind, consenting may take place in the clinic during the appointment or at a later time.

8.2 Screening

After an appropriate informed consent process has been completed, a copy of the signed document will be given to the participant and MOSA clerical staff. MOSA clerical staff will file a copy of the informed consent document in the participant's medical record and will include a copy of the informed consent in the package for the Outpatient Surgery Center. The primary coordinator will maintain the original informed consent document in the study file. Eligibility will then be confirmed based on a thorough review of the medical history as provided by the participant and/or available through the medical record. If not eligible, the participant will be considered a screen failure.

8.3 Enrollment

Once eligibility has been confirmed each participant will receive the randomized assignment into Arm 1 or Arm 2 as described in section 6.1.1.3 Study Agent Accountability Procedures.

8.4 Surgery Day 0

Confirmation of study arm and availability of Exparel, as appropriate, will take place prior to the surgical procedure. Administration will occur as described in 6.1.1.2 Preparation, Administration, Storage, and Dosage of Study Agent(s)/ Intervention(s). In the PACU follow up will occur as dictated by standard care. Data from this period will be abstracted from the medical record.

8.5 Follow-up

After discharge home, participants will complete Postoperative Diary entries on Day-1, -2, -3, -5, and -10. The information will include pain ratings; medication use; fluid and food intake; activity; and unanticipated events. Participants will receive reminders by phone to complete this step. As available, patients will be able to complete the diary on paper or via the secure REDCap Surveys system.

8.6 Final Study Visit

About two weeks after surgery, the participant will return to MOSA for a standard of care postoperative tonsillectomy assessment visit. At this visit, the study participant will be seen by the principal investigator and asked to evaluate satisfaction with treatment, to make a conjecture about which medication was administered at the end of surgery, and to reflect on whether there were any unreported unanticipated events during the postoperative period. The participant will also return the paper copy of the Postoperative Diary at the two-week postoperative visit if not completed via REDCap.

8.7 Early Termination Visit

If a participant voluntarily withdraws from the study at any point, the individual will be asked to continue with the routine or standard of care post-tonsillectomy recommended medications for pain control; instructions regarding fluid intake, diet, and activity; and two-week postoperative follow-up visit to MOSA. The individual will be asked if he/she is willing to return any of the of the Postoperative Diary entries completed before withdrawing from participation. Additionally, the withdrawing participant will be reminded that study related information already submitted or obtained will be included anonymously in the report of study results.

8.8 Unscheduled Visits

We do not anticipate any unscheduled visits for clinical, laboratory, or safety evaluations to occur within the two-week period between surgery and the postoperative follow-up visit. If the participant experiences an unanticipated event after receiving the study intervention and being discharge from the Outpatient Surgery Center, the study participant will be instructed to contact the PI or in the case of an emergency to go to the nearest Emergency Department for immediate care.

9. ASSESSMENT OF SAFETY

Examining the effectiveness of Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/ mL) as an adjunct to standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain management after tonsillectomy compared with administration of bupivacaine HCl 0.25% with epinephrine alone is the primary outcome measure of this clinical trial. Acute emergencies from local anesthetics are generally related to high plasma concentrations encountered during therapeutic use of local anesthetics or to unintended intravascular injection of the local anesthetic solution.¹ The safety and effectiveness of Exparel and bupivacaine products depend on proper dosage, correct administration technique, appropriate precautions, and adequate preparation for emergencies. Exparel and bupivacaine HCl 0.25% with epinephrine will be administered only in the SJMAA Outpatient Surgery Center where trained personnel and emergency equipment as well as rescue medications are available to promptly treat patients who show evidence of unanticipated problems, such as cardiac or neurologic toxicity.

9.1 Specification of Safety Parameters

Tonsillectomy surgery will be performed in a fully equipped Outpatient Surgery Center operating room with participating anesthesiologists and/or certified nurse anesthetists, registered nurses, and certified technicians in attendance to carefully monitor the patient and surroundings. The patient's cardiovascular and respiratory status will be monitored consistently according to standard procedures during surgery and administration of the study drug. The dose of Exparel® to be used in this trial is considered adequate to provide postoperative analgesia and is well below the maximum dose.

Bupivacaine HCl administered together with Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/ mL) may impact the pharmacokinetic and/or physicochemical properties of Exparel, and this effect is concentration dependent. The prescribing information for Exparel indicates that bupivacaine HCl and Exparel may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before Exparel as long as the ratio of the milligram dose of bupivacaine HCl solution to Exparel does not exceed 1:2.¹ The total dose of bupivacaine HCl is 10 mg and the total dose of Exparel is 53.2 mg. This dose does not exceed 1:2 ratio noted in the prescribing information (10 mg bupivacaine / 53.2 mg Exparel® = 0.1879). Therefore, 2 mL of the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) may be administered on each side followed by 2 mL of Exparel bupivacaine liposome suspension 1.3% (13.3 mg/mL) on each side for patients randomized to the treatment group.

After removal of the tonsils and before extubation, all study participants will receive the standard of care medication-bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL), 0.5mL infiltrated into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx for a total volume of 2 mL bupivacaine HCl (total dose of 5 mg) with epinephrine (total dose of 10 mcg) on each side. Afterward, participants assigned to the adjunct Exparel® treatment group will receive the study drug Exparel bupivacaine liposome suspension 1.3% (13.3 mg/mL), 0.5 mL infiltrated into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left sides of the oropharynx for a total volume of 2 mL of Exparel (total dose of 26.6 mg) on each side of the oropharynx.

During infiltration of Exparel®, the principal investigator will aspirate frequently to avoid intravascular injection of the drug. The patient's cardiovascular, respiratory, and neurologic status will be monitored constantly during surgery in the Outpatient Surgery Center operating room and after administration of the study drug in the Outpatient Surgery Center post anesthesia care area (PACU). Continued monitoring will occur in PACU by physicians and nurses, until the patient is stable, alert, assessed as adequately recovered, and able to swallow without aspiration prior to discharge. If the patient experiences a toxic reaction to Exparel, the appropriate liposomal rescue medication available in the Outpatient Surgery Center will be administered to the patient and the patient may be admitted to the hospital for additional monitoring.

9.2 Definition of an Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered Study Agent(s)/Intervention(s) and that does not necessarily have a causal relationship with the study treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) Study Agent(s)/Intervention(s), whether or not related to the medicinal (investigational) Study Agent(s)/Intervention(s). (SJMHS Clinical Trials Template)

The most common adverse reactions to Exparel® are nausea, constipation, and vomiting. These adverse reactions also are associated with the use of routinely prescribed narcotic pain medications. Symptom control of these common adverse reactions may be attenuated by the routine standard of care medications (ondansetron and MiraLax) prescribed for patient use at home after discharge.

All adverse responses will be graded in the following manner (SJMHS Institutional Review Board(s) Policy: Unanticipated and Adverse Event Reporting, 2016).

- Grade 1 (Mild): Events require minimal or no treatment and do not interfere with the patient's daily activities.
- Grade 2 (Moderate): Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Grade 3 (Severe): Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Grade 4 (Life threatening): Any adverse drug experience that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.
- Grade 5 (Death).

9.3 Definition of a Serious Adverse Event (SAE)

A Serious Adverse Event is defined as an AE meeting one of the following conditions: (SJMHS Institutional Review Board(s) Policy Unanticipated and Adverse Event Reporting, 2016).

- Death during the period of protocol defined surveillance.
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event).
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance.
- Results in congenital anomaly or birth defect.
- Results in a persistent or significant disability/incapacity.

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above (SJMHS IRB Clinical Trials Template)..

9.4 Methods and Timing for Assessing, Recording, Analyzing, Managing Safety Parameters

In the Outpatient Surgery Center operating room, as standard of care, the participant will be assessed by the surgeon, anesthesiologist and/or nurse anesthetist, and nursing staff for

any cardiovascular, respiratory, or neurologic adverse events on standard of care parameters throughout post-anesthesia extubation and patient arousal. At transfer to the Outpatient Surgery Center post-anesthesia care area, the patient will be monitored at routine intervals varying from 5-minutes to 30-minutes until cardiovascular, respiratory, and neurologic systems are stable and the patient is awake and completely responsive.

9.4.1 Methods and Timing for Assessment

As standard of care the nurses in the post-anesthesia recovery area will monitor and record in the electronic medical record the patient's vital signs, level of consciousness, pain ratings, and any adverse event until the patient is stabilized. Adverse events of interest during this perioperative period are cardiac arrhythmias, neurologic problems, inability to swallow, allergic reaction, vomiting, aspiration, and return to the operating room.

All participants will be given contact information in the Post-Operative Diaries in order to report adverse events in the 2-week follow period as needed.

At the final study visit participants will be queried on adverse events not previously reported.

9.4.1.1 AE/SAE Grading and Relationship Assignment

The following adverse events and serious adverse event grading are designated in the SJMHS Institutional Review Board(s) Policy on Unanticipated and Adverse Event Reporting (2016).

- Grade 1 (Mild): Events require minimal or no treatment and do not interfere with the patient's daily activities.
- Grade 2 (Moderate): Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Grade 3 (Severe): Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Grade 4 (Life threatening): Any adverse drug experience that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, (that is, it does not include a reaction that had it occurred in a more severe form, might have caused death).
- Grade 5 (Death).

The principal investigator will assess the relationship of adverse event/serious adverse event to the study agent using the following terms defined in the SJMHS Institutional Review Board(s) Policy on Unanticipated and Adverse Event Reporting (2016).

Definitely Related

There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to

administration of the study agent/intervention and cannot be explained by concurrent disease or other drugs or chemicals.

Probably Related

There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time sequence to administration of the study agent/intervention, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Possibly Related

There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event, for example, the subject's clinical condition or other concomitant events. Although an adverse event may be identified only as "possible" soon after discovery, the event can be identified as requiring more information and later be upgraded to probable or definitely related, as appropriate.

Unlikely

A clinical event in which the temporal relationship to administration of the study agent/intervention makes a causal relationship improbable. That is the event did not occur within a reasonable time after administration of the trial medication, and during a period in which other drugs or chemicals or underlying disease provides plausible explanations.

Not related

The adverse event is completely independent of administration of the study agent/intervention, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.4.2 Recording/Documentation

Complete description of all adverse events occurring during care in the Outpatient Surgery Center will be noted in the patient's electronic medical record. Any other adverse event occurring after discharge could be documented in the Postoperative Diary, MOSA medical record, or reported to the study team through other means such as a phone call.

Regardless of source, all adverse events occurring while participating in the study will be documented by the study team and assessed by the PI for 1) expectedness 2) relatedness 3) severity and 4) change in risk.

Any medical condition that does not meet exemption criteria and is present at the time that the patient is screened will be considered as baseline and not recorded as an adverse event. If the condition deteriorates at any time during the study it will be recorded and reported as an adverse event. Changes in the severity of an adverse event will be documented to allow an assessment of the duration of the event. Adverse events characterized as intermittent will require documentation of the onset and duration of each

episode. Any changes in assessment of the relationship of the event to the study agent/intervention will be documented.

9.4.3 Analysis/Management

If a serious side effect occurs in the Outpatient Surgery Center after administration of the study drug and before discharge, the nursing staff, anesthesiologist, and surgeon/principal investigator/PI, will provide appropriate emergency care.

Participants are instructed and a written reminder will be in the Postoperative Diaries to contact the PI for any questions or concerns regarding adverse events which do not require immediate medical attention. In an emergency they are to bring the consent and/or Diary with them and go to the nearest Emergency Center, notify the staff of the study, and contact the PI as soon as possible afterwards.

9.5 Reporting Procedures

This study will follow the SJMHS IRB policy on Unanticipated Problems and Adverse Event Reporting, version 11-14-2016 or any updates as available. The PI will also notify the FDA about the unanticipated events using the FDA Adverse Events Reporting System (FAERS).

9.5.1 Specific Serious Adverse Event Requirements

All serious adverse events will be:

- Recorded on the appropriate study complications case report form.
- Reported to the IRB on the SJMHS IRB Internal Adverse Event and Unexpected Problem Reporting Form or the SJMHS IRB Internal/External Adverse Event and Unexpected Problem Summary Form as required by SJMH IRB policy.
- Reported to the FDA through FAERS electronic submissions.
- Followed through resolution by the PI.

The principal investigator will complete an Expedited or Serious Adverse Event Form within the following timelines:

- All deaths and immediately life threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and electronically communicated within 24 hours of site awareness.
- All reportable adverse events will be followed until satisfactory resolution or until the principal investigator deems the event to be chronic or the participant to be stable.

9.6 Reporting of Pregnancy

Any women known to be pregnant, planning to become pregnant, and/or lactating are not eligible for study inclusion. These parameters will be explained to the potential participants during recruitment and enrollment. Women will be encouraged to make every effort to avoid pregnancy during the period between enrollment and the end of the

study participation at the 2-week postoperative follow-up. If a woman becomes pregnant, she will be encouraged to report use of Exparel® as pain management for tonsillectomy to her obstetrician. The pregnancy will be reported as an unexpected event on the SJMHS IRB Internal Adverse Event and Unanticipated Problem Reporting Form in alignment with the SJMHS Institutional Review Board(s) Unanticipated Problems and Adverse Events Reporting Policy (within 3 days of study team awareness).

9.7 Type and Duration of the Follow-up of Participants after Adverse Events

During the study period, the patients will be followed until the reportable adverse event is resolved or considered stable by the principal investigator. If additional treatment is required, beyond the study period, the patient's care will be transferred to the patients' primary care physician.

9.8 Modification of Study Agent(s)/Intervention(s) for a Participant

There is no planned modification of the study agent intervention to be used in this clinical trial.

9.9 Halting Rules for the Protocol

Safety findings that would be of concern to investigators which may be the basis for temporarily suspending enrollment and/or study agent administration include participants' inability to swallow, aspiration, allergic reaction, and death. An ad hoc safety review would be conducted by the SJMAA Exparel® RCT Safety Monitoring Committee. Committee members will recommend whether the study should continue per protocol, proceed with caution, undergo further investigation, be discontinued, or be modified and then proceed.

9.10 Stopping Rules for an Individual Participant/Cohort

The principal investigator may stop an individual's study participation if a clinical adverse event or other medical condition or situation occurs in which continuing in the study would not be in the best interest of the patient. If able, patients would be expected to complete the follow-up visit at the scheduled two-week postoperative period or as soon as possible after the adverse event is resolved or stabilized.

9.11 Premature Withdrawal of a Participant

At enrollment, participants will be informed that they may voluntarily withdraw consent to participate in the study at any time. If a participant voluntarily withdraws prematurely from the study prior to the follow-up study visit, the patient will be asked to complete the two week postoperative follow-up visit. Any data that had been collected prior to withdrawal will be used in data analysis. However, the information from the time after withdrawal will be excluded from data analysis.

10. CLINICAL MONITORING STRUCTURE

This section will describe the study monitoring to be conducted to ensure that the safety and conduct of the study complies with 45 CFR 46.

10.1 Site Monitoring Plan

Site monitoring for safety will be conducted to ensure the human subject protection, study procedures, administration of the study agent/intervention, and data collection processes are of high quality and meet regulatory guidelines.

An internal study site monitoring plan will assure adherence to the established protocol. Staff from the Academic Research Department will be appointed to conduct monitoring and will document the results in a monitoring table. During the first four months of the study, the monitor will review all informed consent documents, study participant case report forms, source documents, and adverse events reports on a monthly basis. Afterward, the monitor will continue to review documents quarterly in a similar fashion. The principal investigator may delegate responsibility to the primary coordinator to ensure that monitor findings are addressed.

10.2 Safety Monitoring Plan

The principal investigator queried the Food and Drug Administration (FDA) regarding the status of this small scale single site clinical trial; whether a study of the marketed drug Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/ mL) falls within the exemption under § 312.2(b)(1) (21 CFR 312.2(b)(1)). The FDA rendered the decision that the study was exempt from Investigational New Drug (IND) regulations. The principal investigator identified the potential risk to participants in this clinical trial as minimal. Therefore internal safety monitoring will be conducted on a quarterly basis by the Exparel RCT Safety Monitoring Committee appointed by the principal investigator. The Exparel RCT Safety Monitoring Committee will review data on enrollment, internal study monitoring result, study procedures, forms completion, data quality, losses to follow up, and adverse events/unanticipated problems. The Exparel RCT Safety Monitoring Committee will document meeting discussion and decisions in a formal report of minutes. The report will be submitted to the principal investigator and study team. The principal investigator will submit the report to the IRB.

11. STATISTICAL CONSIDERATIONS

The study statistician will use SAS® software (SAS Institute Inc., Cary, NC) for data analysis. Patient demographics and pre-operative clinical variables will be summarized using means and percentages, as appropriate. Difference in characteristics between the experimental and standard care group will be tested for statistical significance by either two sample *t*-test for continuous variables or *chi-square* test for categorical variables.

With respect to the outcomes, the mean pain rating for average pain and maximum pain at each time point will first be summarized and graphed for visualization. Two-sample *t*-

test will be used to formally compare the statistical differences in the primary study outcome average pain score during the first 3 days after surgery. Furthermore, longitudinal mixed model analysis (SAS: PROC MIXED)¹⁶ will be used to model the trajectory of pain rating, dosage of narcotic use, and fluid intake over time and to compare across 2 or more time points using CONTRAST statement. Time to change in food intake and physical activity will be graphed by Kaplan-Meier survival curves and statistical significance in the difference will be tested by the log rank test. The incidence of adverse events will be descriptively summarized by the group assignment. All tests will be two sided and p values less than 0.05 will be considered as statistically significant.

A power analysis was conducted for the primary outcome of interest, average pain rating during the first 3 days after surgery, corresponding to the time period during which Exparel® is expected to act. Using two sample t-test, we estimated that a sample size of 34 patients (17 in each group) would be needed to achieve 80% power to detect a statistically significant difference of 1 in pain rating (standard deviation = 1) with $\alpha=0.05$. Cases will be replaced until the minimum sample size of 34 is met.

11.1 Overview and Study Objectives

The goal of this study is to examine post tonsillectomy outcomes in adult patients who receive post-excision Exparel® as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain management, compared with adults who receive standard of care post-excision bupivacaine HCl alone.

The primary objective is to examine post tonsillectomy pain ratings in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) 0.25% MARCAINE with Epi for pain control, compared with adults who receive the post-excision standard of care bupivacaine HCl with epinephrine alone.

The secondary objective is to examine post tonsillectomy pain medication requirements in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone.

The exploratory objective is to examine post-tonsillectomy recovery outcomes (Day-5 and Day-10 pain ratings and pain medication taken; Day-1, -2, -3, -5, and -10 fluid and food intake; resumption of activity; and adverse events) in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care bupivacaine HCl with epinephrine alone.

11.2 Study Population

The study population will be composed of adult patients from the MOSA office. Patients will be 18 years of age and older in need of bilateral palatine tonsillectomy for recurrent tonsillitis or obstructive pathologies. After surgery and before extubation, all participants will receive the standard of care post tonsillectomy medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) infiltrated into the superior and inferior poles of the anterior and posterior tonsillar pillars on the right and left side of the oropharynx. The duration of effect of bupivacaine HCl with epinephrine is relatively short, extending up to 6 hours, as a bridge to use of outpatient narcotic and over the counter pain control medications. Patients randomized to the treatment arm will receive the study drug Exparel® (bupivacaine liposome suspension 1.3%, 13.3 mg/mL) as adjunct to the standard of care local anesthetic bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) infiltration into the upper and lower poles of the anterior and posterior tonsillar pillars on the right and left side of the oropharynx after tonsillectomy for pain management. The average duration of action of action for Exparel is 72 hours and it may extend up to 96 hours. Patients treated with Exparel may report a greater difference in pain ratings during the 3-day postoperative period and thereafter, from those treated with post-excisional bupivacaine HCl with epinephrine alone.

11.3 Description of the Design

This is a single site, post marketing, open label, randomized clinical trial with two arms. There will be 19 participants in each arm with parallel assignment to the arms. In Arm 1, the treatment arm, the participant will receive the study drug Exparel® (bupivacaine liposome suspension 1.3%, 13.3 mg/mL) after the standard of care drug, bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL). In Arm 2, the standard of care arm, the participant will receive the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone. Participants will be blind to the study group assignment. The principal investigator, coordinator, anesthesiologist or nurse anesthetist, and nurses working with the study patients in the Outpatient Surgery Center will not be blind to patient study assignment and will not will not disclose this information to the participant.

Study data will be collected and managed by the primary coordinator using REDCap electronic data capture tools hosted at St. Joseph Mercy Ann Arbor.²¹ REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

11.4 Measures to Minimize Bias

To minimize selection and accidental bias, subjects will be randomly allocated to Arm 1 treatment with the post-excision standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) followed by adjunct Exparel® bupivacaine liposome suspension 1.3% 13.3 mg/mL or Arm 2 standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) using block randomization assignment. A block randomization schedule will be prepared by the statistician.

The study participants will be blind to group assignment. The principal investigator will become aware of the patient's group assignment prior to surgery. Masking the principal investigator regarding patient group assignment will not be possible because Exparel® is a liposomal emulsion with a cloudy appearance, which will be evident to the principal investigator on drug preparation and administration. Likewise for anesthesia staff, masking of group assignment will not be possible because the study drug will be administered prior to extubation. Planned unmasking of randomization will occur at the final postoperative follow-up visit when the principal investigator asks participants to guess which study intervention they received. Unplanned breaking of the randomization code may occur if a patient requires Emergency Services for an allergic or life threatening adverse event.

11.5 Appropriate Methods and Timing for Collecting Outcome Measures

The primary objective is to examine post tonsillectomy pain ratings in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

After receiving the study drug on the day of surgery (Day-0), study participants will maintain a Postoperative Diary of pain ratings on Day-1, -2, and -3.

Timing for Collecting Outcome Measures

Patients will record pain ratings on Day-1, -2, and -3 in the Postoperative Diary. The day after surgery and each designated following day the primary coordinator will provide a reminder telephone call to the patient about recording information in the Postoperative Diary

The secondary objective is to examine post tonsillectomy pain medication use in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to standard of care bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive standard of care post-excision bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

Timing for Collecting Outcome Measures

On Day-1, -2, and -3, study participants will maintain a Postoperative Diary of pain medications used. The day after surgery and each designated following day the primary coordinator will provide a reminder telephone call to the patient about recording information in the Postoperative Diary

The exploratory objective is to examine post-tonsillectomy outcomes (Day-5 and Day-10 pain ratings and pain medication taken; Day-1, -2, -3, -5, and -10 fluid and change in food intake; resumption of activity outside of the home; and adverse events) related to the recovery process in adult patients who receive post-excision Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) as an adjunct to standard of care bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control, compared with adults who receive the post-excision standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

Timing for Collecting Outcome Measures

On Day-1, -2, -3, -5 and -10, study participants will maintain a Postoperative Diary of pain ratings, medication use, fluid and food intake, activity, and unexpected or unanticipated events. The day after surgery and each designated following the primary coordinator will provide a reminder telephone call to the patient about recording information in the Postoperative Diary

The primary and secondary variables are continuous variables and will be summarized using means. Patient demographics as well as preoperative and postoperative clinical variables will be summarized using percentages. Difference in characteristics between the experimental and control group will be tested for statistical significance by either two sample *t*-test for continuous variables or *chi-square* test for categorical variables. Time to change in food intake and first physical activity outside of the home will be graphed by Kaplan-Meier survival curves. Longitudinal mixed model analysis will be used to demonstrate the trajectory of pain rating, dosage of narcotic use, and fluid intake over time and will be compared across 2 or more time points.

11.6 Study Hypotheses

Null Hypothesis 1: There will be no decrease in pain ratings in adult patients receiving post-tonsillectomy adjunct Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) following the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after tonsillectomy during the 3-day period after surgery, compared with patients receiving standard care of post-excision bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

Alternative hypothesis 1: There will be a decrease in pain ratings in adult patients receiving post-tonsillectomy adjunct Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) following the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after tonsillectomy during the 3-day period after surgery, compared with patients receiving standard care of post-excision

bupivacaine with epinephrine alone, with the most significant reduction reported during the 3-day period after surgery.

Null Hypothesis 2: There will be no decrease in narcotic requirements in adult patients receiving post-tonsillectomy adjunct Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) following the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after tonsillectomy during the 3-day period after surgery, compared with patients receiving the standard care of post-excision bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone.

Alternative Hypothesis 2: There will be a decrease in narcotic requirements in adult patients receiving post-tonsillectomy adjunct Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) following the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after tonsillectomy, compared with patients receiving the post-excision standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) alone, with the most significant reduction reported during the 3-day period after surgery.

Null Hypothesis 3: There will be no decrease in time to resumption of eating, drinking, and activity in adult patients receiving post-tonsillectomy Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) following the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after tonsillectomy compared with adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone.

Alternative Hypothesis 3: There will be a decrease in time to resumption of eating, drinking, and activity in adult patients receiving post-tonsillectomy Exparel® bupivacaine liposome suspension 1.3% (13.3 mg/mL) following the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL) for pain control after tonsillectomy compared with adults who receive the post-excision standard of care medication bupivacaine HCl with epinephrine alone, with the most significant decreases reported during the 3-day period after surgery.

11.7 Sample Size Considerations

A power analysis was conducted for the primary outcome of interest, average pain rating during the first 3 days after surgery, corresponding to the time period during which Exparel® is expected to act. Using two sample *t*-test, we estimated that a sample size of 34 patients (17 in each group) would be needed to achieve 80% power to detect a statistically significant difference of 1 in pain rating (standard deviation = 1) with $\alpha=0.05$.

All analyses will be conducted after the last randomized participant has completed the final study follow-up visit. Data from patients who withdraw from the study will be analyzed according to the intervention to which they were randomized (intention to treat) to minimize the risk of attrition bias when participants are excluded from the analysis. SAS (SAS Institute, Cary, NC) will be used for data analysis.

11.8 Maintenance of Trial Treatment Randomization Codes

The statistician will provide a block randomization schedule, allocating participants to group assignment.

Arm 1: post-excision adjunct Exparel® bupivacaine liposome injectable suspension 1.3% (13.3 mg/mL) following the standard of care medication bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5 mcg/mL).

Arm 2: post-excision bupivacaine HCl 0.25% (2.5 mg/mL) with epinephrine (5mcg/mL) alone.

The coordinator will maintain the cross walk file that links the patient, the study number, and the clinical trial group assignment in a secure password protected shared drive and such information that will be entered into REDCap.

11.9 Participant Enrollment and Follow-Up

The estimated study accrual period will be about 12 months, given enrollment of 3 – 4 patients per month. The expected duration of commitment from the study participant after providing voluntary informed consent will extend from the day of surgery through completion of the two week postoperative follow-up visit and final Postoperative Diary reporting. Some patients may enroll several weeks prior to surgery due to their individual schedules. Patients will be considered active from the day of surgery until the follow-up visit to MOSA after surgery.

12. QUALITY CONTROL AND QUALITY ASSURANCE

This clinical trial will be conducted only at SJMAA in the Outpatient Surgery Center with pre-operative assessment and postoperative follow-up at MOSA. The research team will periodically monitor data and safety indicators verifying that the clinical trial is being conducted and that data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. At the outset of the trial, internal monitoring will occur on a monthly basis for three months, then quarterly thereafter. Any missing data or data anomalies will be communicated to the principal investigator for clarification/resolution. Reports of internal monitoring will be submitted to the principal investigator who will forward them to the Exparel RCT Safety Monitoring Committee for review. The principal investigator will then forward the report of the Exparel RCT Safety Monitoring Committee to the SJMHS IRB on completion of monitoring activities.

All clinical trial regulatory documents will be maintained in an e-binder on the Academic Research shared drive, with limited password protected access by study team members, and limited authorization to make entries and revisions to designated team members only. The investigational site will provide direct access to all trial related de-identified source data/documents, and reports for the purpose of monitoring and auditing by the Exparel

RCT Safety Monitoring Committee and inspection by local and regulatory authorities, as required by policy or law.

All data collected from study participants will be entered into the REDCap system. All paper copy files that pertain to patient data (e.g., signed consent forms, patient contact information, randomization schedule, patient identifier file, case report forms, etc.) will be kept in locked files within the secure SJMAA Academic Research Department. Only the principal investigator, and study team will have access to identifiable data. Information from patients' Postoperative Diaries collected during and at the completion of the final visit will be recorded in REDCap by the primary coordinator and verified through internal monitoring. Study team members will return to source documents to verify any discrepancies or inconsistencies in data. Patient identifiers will be redacted from data collection tools and a study number (identified at enrollment) will be applied to the CRF data collection tools.

All study related data will be maintained for at least seven years after the completion of the research in compliance with SJMAA and Trinity Health policies.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Institutional Review Board/Ethics Committee

The principal investigator will submit this clinical trial protocol, along with the associated clinical trial informed consent document to the SJMHS IRB for review and approval prior to implementing the protocol. In addition, any amendment to the protocol or consent materials will be submitted to the IRB for review and approval before the revisions are placed into use.

13.2 Informed Consent Process

The informed consent process will be completed prior to any study intervention and data collection. The principal investigator and/or the primary coordinator will engage in explaining the study to the individual and the individual's family members before and throughout the individual's study participation. The informed consent process will include discussion of risks and possible benefits of the study therapy, as well as the individual's rights and responsibilities regarding the study and study processes/procedures. The participant will also be informed about the option to withdraw consent at any time throughout the course of the trial. The rights and welfare of the participant will be protected by emphasizing that the quality of medical care will not be adversely affected if the individual declines to participate in this study. After all of the potential participant's questions about the study have been answered to the individual's satisfaction, he/she will be asked to verify understanding and agreement to voluntarily participate in the study by signing an informed consent document. A copy of the informed consent document will be given to the participant for reference. The study coordinator will maintain the original in the study file and will provide a copy for the patient's electronic medical record.

Patients without obvious exclusion characteristics will be identified for potential recruitment. The principal investigator in collaboration with the primary coordinator will complete the screening and recruitment process, educate the patient about the study, and obtain informed consent. In addition, the primary coordinator will maintain a screening and recruitment log, recording the outcome of each patient's decision to participate, as well as the rationale regarding the decision. Further, the primary coordinator will provide a copy of the informed consent document and the Postoperative Diary that will be used by the patient for follow-up documentation and reporting of pain ratings, medications, oral intake, activity, and adverse or unanticipated events. MOSA office staff will include a copy of the informed consent document in the patient's medical record for reference.

Participants will be approached at time of clinical evaluation at MOSA for recruitment into the study. In conjunction with the principal investigator, the primary coordinator will review whether a patient meets inclusion and exclusion criteria under waiver of informed consent to help determine eligibility. The members of the study team understand that the protection of human subjects is absolutely essential. All study personnel involved in patient screening, consent, enrollment, and collection of study data will be fully trained in all study and IRB relevant procedures and mechanisms: This includes required CITI certification. The informed consent processes will take place in a private location in the MOSA clinical setting or in a private office in the Academic Research Office by the primary coordinator.

13.3 Participant Confidentiality

All study staff will follow study specific procedures for maintaining participant confidentiality. All study team members will receive training in maintain the confidentiality of patient protected health information and securing study information provided by participants. Study identification numbers, rather than written names or other personal identifying information, will be used to identify and track paper copy data forms containing patient information. Patient identifiers will be redacted when necessary, and the study number will be substituted for the personal identifiers. Patient identifying information to data will be kept safeguarded using secure technology on password-protected SJMAA computers.

The study protocol, documentation, data and all other information generated from the study will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval.

Authorized representatives of the Sponsor / principal investigator may inspect all documents and records required to be maintained by the principal investigator including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management Responsibilities

The principal investigator is responsible for complete and accurate documentation for the entire clinical trial. Data collection is the responsibility of the clinical trial staff under the supervision of the principal investigator. In addition the principal investigator will review all adverse. The principal investigator will delegate responsibility for daily management of study documentation to the primary coordinator.

The primary coordinator will collect information on case report forms, using content from source documents in patients' electronic medical records, MOSA office records, direct report, Postoperative Diary, and other sources as needed and will enter data into the REDCap System. The primary coordinator is responsible for maintaining all regulatory documents, trial materials, and reports in an electronic e-binder file, as well as paper copies as needed of case report forms and source documents for each participant. The study statistician will be responsible for data cleaning and data analysis. The statistician will produce tables and chart for displaying data and written interpretation of the analysis. The principal investigator and study team will review the analysis report and make recommendations for clinical application based on the analysis. Under the direction of the principal investigator, the study team will prepare a final summary report of the results of the clinical trial and clinical recommendations for the SJMAA Research Committee (study funding source), the SJMHS IRB, and ClinicalTrials.gov registry.

14.2 Data Capture Methods

Patients will record pain rating variability, medications used, fluid intake, time to change in food intake, time to first physical activity outside of the home, and any unusual/adverse events on Day-1, -2, -3, -5, and -10 in the Postoperative Diary. The day after surgery and each designated following day the primary coordinator will provide a reminder telephone call to the patient about recording information in the Postoperative Diary. The primary coordinator will be responsible to enter or transfer data into the REDCap system. All study case report forms, and returned patient Postoperative Diaries will be stored in locked files in the Department of Academic Research with restricted access to study team members only.

14.3 Types of Data

The patient will record information about pain ratings, medication use, fluid and food intake, activity, and any adverse events in the Postoperative Diary. The Diary information will be used as outcomes data. The primary coordinator will record demographic, history information, and hospital experience data after the patient has returned for the follow-up visit. Adverse events will be reported in aggregate in study results as well as separately to the SJMHS IRB.

14.4 Source documents and Access to Source Data/Documents

Source documents will include information from selected patient hospital records such as operative reports; clinical and office records such as current history; pharmacy dispensing records; and patient Postoperative Diary recordings.

All study staff will follow study specific procedures for maintaining participant confidentiality. All study team members will receive training in maintain the confidentiality of patient protected health information and securing study information provided by participants.

Only the principal investigator and study team will have access to the patients' medical records for this trial. This study site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory, and institutional requirements for the protection of confidentiality of participants. This site will permit authorized representatives of the sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

14.5 Timing/Reports

History and demographic information will be collected by the primary coordinator from clinical/office records after obtaining patient informed consent. Data analysis will be performed by the study statistician after all data has been collected from the last study participant enrolled in the study.

14.6 Study Records Retention

All study related data will be maintained for at least seven years after the completion of the research in compliance with SJMHS and Trinity Health policies. Afterward the electronic and paper records will be destroyed.

14.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, and/or Good Clinical Practice (GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. The principal investigator in collaboration with the primary coordinator will report major protocol deviations to the IRB when discovered and minor deviations at continuing review using the SJMAA protocol deviation template. With the report of a protocol deviation, the principal investigator and primary coordinator will create a plan of corrective action to assure that a similar deviation may be avoided.

15. PUBLICATION POLICY

The investigators express interest in publishing the results of this clinical trial at the completion of the investigation. The principal investigator will register this clinical trial in the ClinicalTrials.gov public trials registry as a qualifying study and in compliance with the recommendations of International Committee of Medical Journal Editors

(ICMJE) policy as a condition for publication. In addition, the investigators will incorporate CONSORT (CONsolidated Standards of Reporting Trials) 2010 guidelines in reporting trial results.

16. SCIENTIFIC REFERENCES

1. Exparel® [package insert]. San Diego, CA: Pacira Pharmaceuticals, Inc; 2015.
https://www.exparel.com/sites/default/files/EXPAREL_Prescribing_Information.pdf.
Accessed June 12, 2017.
2. Marcaine™ [package insert]. Lake Forest, IL: Hospira, Inc; October 2011.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022046s004lbl.pdf.
Accessed June 12, 2017.
3. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. Natl Health Stat Report. 2009;(11):1–25. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19294964>. Accessed December 5, 2014.
4. Grainger J, Saravanappa N. Local anaesthetic for post-tonsillectomy pain: a systematic review and meta-analysis. Clin Otolaryngol. 2008;33(5):411–419. doi:10.1111/j.1749-4486.2008.01815.x.
5. Bhattacharyya N, Kepnes LJ. Revisits and postoperative hemorrhage after adult tonsillectomy. Laryngoscope. 2014;124(7):1554–1556. doi:10.1002/lary.24541.
6. Stelter K, Hiller J, Hempel JM, et al. Comparison of two different local anaesthetic infiltrations for postoperative pain relief in tonsillectomy: a prospective, randomised, double blind, clinical trial. Eur Arch Otorhinolaryngol. 2010;267:1129–1134. Doi: 10.1007/s00405-009-1200-8.
7. Arikan OK, Ozcan S, Kazkayasi M, Akpinar S, Koc C. Preincisional infiltration of tonsils with ropivacaine in post-tonsillectomy pain relief: double-blind, randomized, placebo-controlled intraindividual study. J Otolaryngol. 2006;35(3):167–72. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16929992>. Accessed December 21, 2014.
8. Diakos EA, Gallos ID, El-Shunnar S, Clarke M, Kazi R, Mehanna H. Dexamethasone reduces pain, vomiting and overall complications following tonsillectomy in adults: a systematic review and meta-analysis of randomised controlled trials. Clin Otolaryngol. 2011;36(6):531–42. doi:10.1111/j.1749-4486.2011.02373.x.
9. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal Formulations in Clinical Use: An Updated Review. Pharmaceutics. 2017 Mar 27;9(2). pii: E12. Doi: 10.3390/pharmaceutics9020012.
10. Tamm-Daniels, Inge. *Liposomal Bupivacaine: What Is All The Fuss?* University of Wisconsin School of Medicine and Public Health Madison, 5 Nov 2014-video Department of Anesthesiology grand Rounds <https://videos.med.wisc.edu/videos/56752>.
11. Tong YCI, Kaye AD, Urman RD. Liposomal bupivacaine and clinical outcomes. Best Pract Res Clin Anaesthesiol. 2014;28(1):15–27. doi:10.1016/j.bpa.2014.02.001.

12. Pacira Pharmaceuticals, Inc. Pharmacokinetic Evaluation of EXPAREL in Adults Undergoing Tonsillectomy. Available from: <https://clinicaltrials.gov/ct2/show/results/NCT02199574>
13. Olson MD, Moore EJ, Price DL. A Randomized Single-Blinded Trial of Posttonsillectomy Liposomal Bupivacaine among Adult Patients. *Otolaryngology--Head And Neck Surgery: Official Journal Of American Academy Of Otolaryngology-Head And Neck Surgery*. 2018;159(5):835-842. doi:10.1177/0194599818791773
14. Kamarauskas A, Dahl MR, Hlidarsdottir T, Mainz J, and Ovesen T. Need for better analgesic treatment after tonsillectomy in ear, nose and throat practices. *Dan Med J*. 2013 May;60(5):A4639.
15. Hu D, Onel E, Singla N, Kramer WG, and Hadzic A. Pharmacokinetic profile of liposome bupivacaine injection following a single administration at the surgical site. *Clin Drug Investig*. 2013 Feb;33(2):109-15. Doi: 10.1007/s40261-012-0043-z.
16. SAS Institute Inc. SAS® Carey, NC: 2014 .
17. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res* 2009;18:873-880
18. Yost KJ, Cella D, Chawla A, Holmgren E, Eton DT, Ayanian JZ, West DW. Minimally important differences were estimated for the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument using a combination of distribution- and anchor-based approaches. *J Clin Epidemiol* 2005;58:1241-1251
19. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol* 2008;61:102-109
20. Cohen, J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
21. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, *J Biomed Inform*. 2009 Apr;42(2):377-381. Available at <https://www.project-redcap.org/resources/citations/>. Accessed June 12, 2017.

APPENDIX A: SCHEDULE OF EVENTS

	Screen	Enroll	Day 0	Day 1	Day 2	Day 3	Day 5	Day 10	Day 14
Informed consent	X								
Abstract medical history & physical information	X								
Randomization		X							
Study intervention after routine/standard of care tonsillectomy			X						
Standard PACU Pain surveillance & management			X						
Postoperative Diary entries (± 1 day) paper or REDCap Survey				X	X	X	X	X	
MOSA Follow-up visit									X
Satisfaction survey									X