NCT NUMBER: NCT05374499

TITLE: Double-Blinded Randomized Controlled Study Investigating the Efficacy of Exparel (Liposomal Bupivacaine) for Postoperative Pain Relief in Mandibular Third Molar Extractions

STUDY PHASE: IV

STUDY ARMS: Experimental Group (Exparel)
Control Group (Bupivacaine)

PRINCIPAL INVESTIGATOR(S): NAME: JOHN COSTANDI, MD, DMD
ADDRESS 925 W 34TH STREET #201, LOS ANGELES, CA 90089
TELEPHONE (562) 533-2698

CO-INVESTIGATOR(S):
Felix Kyle Yip, MD, DDS
Simon Youn, DDS
Samuel Sheridan

SPONSOR: None

PARTICIPANTS/LOCATIONS: Herman Ostrow School of Dentistry

AMENDMENTS/REVISIONS: None

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1.0 BACKGROUND AND HYPOTHESES

- The most prevalent complaint after third molar extractions is pain. There have been many modalities and regimens developed to manage post-operative pain, such as modifications in surgical techniques, locally-applied medicaments, and oral analgesics. Recently, liposomal bupivacaine (Exparel) has been FDA approved for single-dose infiltration in the oral cavity in adults and children (6 years or older) to produce extended postsurgical local anesthesia. We hypothesize that the administration of liposomal bupivacaine (Exparel) at the end of third molar extractions will decrease postoperative pain and decrease narcotic use for pain management.

2.0 OBJECTIVES AND PURPOSE

- In this study, we will prospectively collect data from all patients receiving bilateral third molar extractions with Exparel versus 0.5% bupivacaine 1:200,000 epinephrine (standard bupivacaine) injections to determine the efficacy of Exparel in reducing postoperative pain. Outcomes measured will be pain intensity based on a numeric scale, date and time when pain completely subsides for each side, adverse events, use of NSAID or acetaminophen outside of prescribed pain regimen, and use of narcotics. The purpose of this research project is to evaluate the use and efficacy of Exparel in postoperative pain management in third molar extractions.

3.0 STUDY DESIGN

- All patients receiving bilateral mandibular third molar extractions at the Herman Ostrow School of Dentistry by an oral & maxillofacial surgery resident without any conflicts with our exclusion criteria will be eligible for our study. A screening visit will be conducted within 30 days before the procedure and include a comprehensive medical/surgical history, informed consent signature, eligibility worksheet, and a complete physical and dental examination. Patients will not be charged an additional fee to receive Exparel in this study.
- On the day of the procedure (day 0), a double-blinded randomization process will be used to preoperatively assign patient's left or right side to receive either Exparel (39.9 mg/3 mL) or standard bupivacaine (5 mg/mL). Each patient will be receiving both treatments, with one injection on each side. For the double-blinded randomization process, the number of patients receiving Exparel to the right and left sides will be equally distributed. Each patient, who will be identified by a unique study ID number, will be randomly assigned Exparel and standard bupivacaine to the right or left using statistical software. Standard bupivacaine will be diluted with normal saline (2:1 ratio of normal saline to 0.5% bupivacaine w/ 1:200,000 epinephrine) to permit equal volumes (3 mL) of Exparel and standard bupivacaine deposited. An envelope, which is identified by the patient specific study ID, will contain Exparel and standard bupivacaine syringes. The syringes will be masked and labeled left or right, depending on the randomization results. Designated dental assistants not associated with the study will receive the corresponding envelope to prepare the syringes. Syringes containing the solutions will be masked so that the operator would not be able to detect which solution is being infiltrated.
- Preoperatively, all patients will be anesthetized with 2% lidocaine w/1:100,000 epinephrine. For mandibular third molar extractions, all patients will receive inferior alveolar and long buccal nerve blocks. In addition, topical benzocaine or intraoperative nitrous oxide could be administered at the discretion of the investigator. Intraoperatively, patients will receive more local anesthetic as needed with the same techniques or periodontal ligament injections. The time and volume of each injection of local anesthetic will be recorded by the designated dental assistant. At the end of the procedure and at least twenty minutes following the most recent administration of 2% lidocaine with 1:100,000 epinephrine, all patients will receive one side of their mandibular infiltrations with 3mL of 1.3% Exparel and the other side with 3 mL of diluted 0.5% bupivacaine with 1:200,000 epinephrine (as noted above).
- Infiltration sites are illustrated in Figure 1; 3 mL of liposomal bupivacaine will be injected into one side of the mandible, according to the following guidelines: after readaptation or closure of the mucoperiosteal flap, the external oblique ridge will be palpated to identify the buccinator muscle attachment; 4 infiltration points (6–8 mm apart) will be selected along the buccinator muscle attachment line, and 0.5 mL of study drug solution will be infiltrated approximately 5 mm deep into the muscle at each infiltration point. Then, at the point of greatest subperiosteal reflection, just lateral to the third molar socket, 1.5 cm deep, 2 infiltrations of 0.5 mL each will be administered as the needle will be withdrawn. 3mL of diluted standard bupivacaine will be deposited on the other side of the mandible according to the same guidelines. (1)
- Following the procedure, patients will be assessed immediately for any adverse effects. Subjects will complete an at-home questionnaire daily for the subsequent four days. This questionnaire will assess pain level via a numerical rating scaling (0: no pain; 10: most pain), occurrence of any adverse events, date and time when pain completely

subsided for each side, and NSAID/Acetaminophen use (with a Likert-type scale indicating which side of the mouth the medication was intended to treat) for four days post-operatively. Pain monitoring assessment will be completed each morning and evening for four days following surgery, with subjects asked to record this data each day within two hours prior to sleeping and within two hours following waking up. If the patient requires additional pain medications, he/she will be prescribed oxycodone upon consultation with the oral surgeon. The date, time of administration, dosage, and quantity will be recorded for all pain medications for up to 96 hours following the procedure. Patients will be contacted over phone by investigators of this study to improve patient compliance and remind patients to complete the questionnaire each day. During their two week follow-up appointment, all subjects will return with their questionnaires and any questions will be answered.

4.0 DRUG INFORMATION

- Acetaminophen
  - Generic
  - Analgesic, antipyretic
  - Maximum daily dose: 4000 mg
  - Store at room temperature (68 to 77°F); out of direct sunlight in a tightly closed container and well ventilated room.
  - Stable under recommended storage conditions.
- 0.5% Bupivacaine with 1:200,000 epinephrine
  - Henry Schein
  - Anesthetic
  - Maximum dose: 3 mg/kg with total maximum dose of 225 mg
  - Store at room temperature (68 to 77°F) for up to 30 days out of direct sunlight in a tightly closed container and well ventilated room.
  - Stable under recommended storage conditions.
- Exparel
  - Pacira Pharmaceuticals
  - Anesthetic
  - Maximum daily dose: 266 mg/day
  - Store at room temperature (68 to 77°F) for up to 30 days out of direct sunlight in a tightly closed container and well ventilated room.
  - Stable under recommended storage conditions.
- Ibuprofen
  - Generic
  - NSAID, analgesic
  - Maximum daily dose: 3200 mg
  - Store at room temperature (68 to 77°F); out of direct sunlight in a tightly closed container and well ventilated room.
  - Stable under recommended storage conditions.
- 2% Lidocaine with 1:100,000 epinephrine
  - Henry Schein
  - Anesthetic
  - Maximum dose: 4.4 mg/kg with total maximum dosage of 500 mg
  - Store at room temperature out of direct sunlight in a tightly closed container and well ventilated room.
  - Stable under recommended storage conditions.
- Nitrous Oxide
  - Air Source Industries, Inc.
  - Maximum concentration: 70% nitrous oxide; 30% oxygen
  - Store as liquid nitrous oxide in a compressed gas cylinder at 745 psi.
  - Stable under recommended storage conditions.
- Oxycodone
  - Purdue Pharma
  - Analgesic, antipyretic, opioid.
  - Maximum daily dose:
  - Store at room temperature (68 to 77°F); out of direct sunlight in a tightly closed container and well ventilated room.

- Stable under recommended storage conditions.

- 10% Topical Benzocaine Gel
  - Centrix
  - Anesthetic
  - Store at room temperature (68 to 77°F) out of direct sunlight in a tightly closed container and well ventilated room.
  - Stable under recommended storage conditions.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

- Inclusion Criteria: All patients receiving bilateral mandibular third molar extractions at the Herman Ostrow School of Dentistry by an oral & maxillofacial surgery resident will be candidates for the study.
- Exclusion Criteria: Patient unable to complete form for four days postoperatively. Patient with severe hepatic disease, history of allergy or contraindication to amide-type LA or opioids, recent history of antibiotic use within the past thirty days. Patients with use of long-acting opioids, NSAIDs, aspirin, acetaminophen within 3 days prior to screening. Patients who are pregnant. Patients receiving additional mandibular teeth extractions.
- Withdrawal Criteria: Patients are allowed to withdraw at any point of the study without disclosing the reason. Treatment will be completed with or without the use of Exparel based on the patient's decision.

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

- Because patients will be given both the control (standard bupivacaine) and experimental (Exparel) drug, stratification factors will not play a role in our study.
- Patient's age, gender and ethnicity are descriptive factors we will take into account at the time of study analysis.
- We plan to conduct a double-blind study. Simple randomization scheme will be performed to determine which side receives bupivacaine versus liposomal bupivacaine. Double-blind procedure will include a coded label generated to keep operator and patient blind; labels will be sent to the data collection team to identify solutions deposited.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

- Preoperative anesthesia treatment plan: For mandibular third molar extractions, all patients will receive inferior alveolar and long buccal nerve blocks with 2% lidocaine w/1:100,000 epinephrine.

AGENT	DOSE	ROUTE	NOTES
2% lidocaine with 1:100,000 epinephrine	34 mg per quadrant	local injection	maximum cumulative dose 7 mg/kg maximum total dose of 500 mg/day

- Intraoperative anesthesia treatment plan: Patients will receive more local anesthetic as needed with the same techniques or periodontal ligament injections.
- Postoperative anesthesia treatment plan: All patients will receive half of their mandibular infiltrations with 1.3% liposomal bupivacaine (Exparel) and the other half with standard bupivacaine.

AGENT	DOSE	ROUTE	NOTES
1.3% liposomal bupivacaine	3 mL per mandibular quadrant	local injection	maximum cumulative dose 266 mg
0.5% bupivacaine 1:200,000 epinephrine	1 mL per mandibular quadrant	local injection	maximum cumulative dose 3 mg/kg maximum daily dose 225 mg

0.9% normal saline	2 mL per mandibular quadrant	local injection	

- Analgesic protocol: All patients will be prescribed ibuprofen and acetaminophen to take Q4-Q6 around the clock for three days.
    - Patients will be prescribed oxycodone for breakthrough pain.

AGENT	DOSE	ROUTE	DAY	NOTES
Ibuprofen	600 mg	PO Q6H	1-4	maximum daily dose 3200 mg
Acetaminophen	500 mg	PO Q4H	1-4	maximum daily dose 4000 mg
Oxycodone	5 mg	PO PRN Q6H	1-4	Schedule III

- A patient may always be removed from treatment whenever he/she wishes.

8.0 ASSESSMENT OF EFFICACY AND SAFETY

- All side effects/toxicities that will be monitored immediately following the injection of Exparel are allergic reactions, paresthesia, dysgeusia, nausea, vomiting, lightheadedness, diaphoresis, palpitations, fever, tinnitus, twitching, blurred vision and headache.
- Long-term toxicities to be monitored after completion of therapy are paresthesia, dysgeusia, nausea, constipation, fever, vomiting, lightheadedness, diaphoresis, palpitations, and headache up to 96 hours following the procedure.
- Unexpected toxicities will be reported via incident reporting form to Office of Clinical Affairs at the Herman Ostrow School of Dentistry, and life-threatening or fatal toxicities (myocardial infarction, cerebrovascular accident) will be reported to the Dental Board of California on the same day and must include the time, date, location, and events that preceded the incident.

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

Parameter	**Pre-Treatment**	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Comprehensive History & Complete Physical Examination	X				
Targeted History & Directed Physical Examination	X	X			
Postoperative Questionnaire		X	X	X	X

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

- The primary outcome will be cumulative pain rating (as assessed by the numerical pain scale area under the curve calculated by the trapezoidal rule), for the left and right sides of the mouth in the 0-94 hours after surgery. Secondary outcomes include: numerical pain scale area under the curve evaluated in the intervals of 0-24, 0-48, and 0-72 hours after surgery; and total dosage of NSAID/Acetaminophen use attributable to each side of the mouth. All eligible patients who begin treatment will be included in the analysis.
-

  Endpoint: Data collection will complete two weeks after the procedure, when patients return with their postoperative questionnaire

11.0 SPECIAL INSTRUCTIONS:

- Blood samples will not be taken for pharmacokinetics, pharmacodynamics, correlative molecular studies or other translational studies.

12.0 DATA COLLECTION AND MONITORING

- All data is encrypted. No patient names will be used on data collection forms. A code for medical record number with corresponding study ID will be kept on the server and then destroyed once study is completed. All procedure notes, including medical history, current medications, local anesthesia dosage, patient status, and other pertinent information will be recorded on Axium software according to Herman Ostrow School of Dentistry guidelines. Other recorded information will be obtained via the eligibility worksheet and postoperative questionnaire, which is listed in Appendix I & II. All data collected in the post-operative questionnaire will be considered valid if it is completed within two hours of the requested time after surgery (upon waking up and before sleeping).

13.0 STATISTICAL CONSIDERATIONS

- The purpose of this research project is to evaluate the use and efficacy of Exparel in postoperative pain management in third molar extractions.
- Anticipated accrual rate: 85% response rate after procedure
- Based on previous studies, we plan for 15% of patients lost to follow-up and an additional 40% non-compliance rate (including missing questionnaires and poor compliance to pain medication regimen).
- Under these assumptions, with an accrual goal of 80 patients, we will have a total intent-to-treat sample of 68 participants and a total per-protocol population of 40.
- A sample size of 40 will allow us to detect a minimum effect of $d=0.45$. In contrast, we would expect to see an effect size of $d=1.51$ for the comparison of NRS AUC in hours 0-96 if patients have a pain score of 2 on days 1-2 and if on days 3-4 they have an average pain score of 4 in the treatment group and 6 in the control group. Previous Studies (Lieblich & Danesi) have reported effect sizes of $d=1.72$ for the difference in NRS AUC in 0-48 hours after surgery when comparing Exparel to saline placebo in the intent-to-treat sample. In the per-protocol sample, this effect size is as high as $d=3.29$.
- Main objective: We will compare NRS AUC in hours 0-96 using a paired t-test with a 0.05 2-sided significance level.
- Other objectives (AEs, NSAID consumption, narcotic consumption, NRS AUC for 0-24, 0-48 and 0-72 hours): We will follow a similar approach as our main objective, using a paired t-test with a 0.05 2-sided significance level.
- For this study, we expect a significant decrease in pain level and consumption of pain medications in patients treated with Exparel. Any decrease in pain level or consumption of pain medications in patients treated with Exparel will be considered minimal difference of clinical interest.
- A statistician will be consulted following data collection prior to statistical analysis.

14.0 REGISTRATION GUIDELINE

- All patients are included in the experimental group, and the half of the mouth to receive either liposomal bupivacaine or bupivacaine infiltration will be randomized.
- Informed consent and eligibility worksheet will be the only forms needed for registration.

15.0 BIOHAZARD CONTAINMENT

- All biohazard materials will be disposed of in the designated red biohazard bins.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

- All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

17.0 REFERENCES

Journal: Lieblich, S., Danesi, H. Liposomal Bupivacaine Use in Third Molar Impaction: INNOVATIVE Study. Anesthesia Progress. 64(3): 127-135. 2017

Database: National Center for Biotechnology Information. Pubchem. 2022.

Website: Case Report Form Templates. University of Wisconsin Institute for Clinical and Translational Research. 2022.

APPENDICES

Appendix I: Informed Consent, Eligibility Worksheet
Appendix II: Postoperative Questionnaire, Local Anesthesia Report

Appendix I

Study Title: Double-Blinded Randomized Controlled Study Investigating the Efficacy of Exparel (Liposomal Bupivacaine) for Postoperative Pain Relief in Mandibular Third Molar Extractions

Principal Investigator: Dr. John Costandi, MD, DMD

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

You have been asked to participate as a subject in a medical experiment. Before you decide whether you want to participate in the experimental procedure, you have a right to the following information:

CALIFORNIA LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:

1. The nature and purpose of the study.
2. The procedures in the study and any drug or device to be used.
3. Discomforts and risks reasonably to be expected from the study.
4. Benefits reasonably to be expected from the study.
5. Alternative procedures, drugs, or devices that might be helpful and their risks and benefits.
6. Availability of medical treatment should complications occur.
7. The opportunity to ask questions about the study or the procedure.
8. The ability to withdraw from the study at any time and discontinue participation without affecting your future care at this institution.
9. Be given a copy of the signed and dated written consent form for the study.
10. The opportunity to consent freely to the study without the use of coercion.

I have carefully read the information contained above and I understand fully my rights as a potential subject in this study.

Date: _____ Time: _____

Signature: _____
(Research Participant)

Signature: _____
(Parent)

INFORMED CONSENT FOR RESEARCH

Study Title: Double-Blinded Randomized Controlled Study Investigating the Efficacy of Exparel (Liposomal Bupivacaine) for Postoperative Pain Relief in Mandibular Third Molar Extractions

Principal Investigator: Dr. John Costandi, MD, DDS

Department: Oral & Maxillofacial Surgery

24-Hour Telephone Number: 562-533-2698

INTRODUCTION

If you are reading this form as the parent/legal guardian of a participant, “you” also refers to your child. We invite you to take part in a research study. Please take as much time as you need to read the consent form. You may want to discuss it with your family, friends, or your personal doctor. If you find any of the language difficult to understand, please ask questions. If you decide to participate, you will be asked to sign this form. A copy of the signed form will be provided to you for your records.

KEY INFORMATION

The following is a short summary of this study to help you decide whether you should participate. More detailed information is listed later in this form.

1. Being in this research study is voluntary–it is your choice.

2. You are being asked to take part in this study because the most common complication of third molar extractions is pain. The purpose of this study is to evaluate the use and efficacy of Exparel in postoperative pain management in third molar extractions. Your participation in this study will last four days after the procedure. The procedure will include mandibular third molar extractions.

3. There are risks from participating in this study. The most common risks are nausea, constipation and vomiting. More detailed information about the risks of this study can be found under the “Risk and Discomfort” section.

4. The possible benefits to you for taking part in this study may include reduction in postoperative pain and use of other pain management modalities.

   It is also possible you may not receive any direct benefit from taking part in this study. However, your participation in this study may help us learn a new modality of pain management for third molar extractions.

5. If you decide not to participate in this research, your other choice will include the standard treatment and postoperative pain management without the use of Exparel.

DETAILED INFORMATION

PURPOSE

The purpose of this study is to evaluate the use and efficacy of Exparel in postoperative pain management in third molar extractions. Exparel has been FDA approved for single-dose infiltration in adults and children (6 years or older) to produce postsurgical local anesthesia. We hope to learn the difference in pain intensity, adverse events, and use of pain medications when patients are treated with Exparel versus bupivacaine after third molar extractions. You are invited as a possible participant because you are a patient receiving bilateral mandibular third molar extractions at the Herman Ostrow School of Dentistry by an oral & maxillofacial surgery resident. About 80 participants will take part in the study.

PROCEDURES

Third molar extraction with the use of a local anesthetic is done for standard of care. After the extractions, the injection or application of Exparel and bupivacaine is done solely for the research. The third molar extractions will take approximately 30 minutes, and the injection of Exparel and bupivacaine will take approximately 5 minutes. The patients will complete the survey/questionnaire for four days postoperatively.

If you decide to take part, this is what will happen:

- A screening visit will be conducted within 30 days before the procedure and include a comprehensive medical/surgical history and a complete physical and dental examination.
- On the day of the procedure, a double-blinded randomization will be used to preoperatively assign your left or right side to receive either liposomal bupivacaine or matching bupivacaine. Syringes containing the solutions will be masked so that the operator would not be able to detect which solution is being infiltrated. Double-blinded randomization means that you and the investigator will not know which side of the mouth received Exparel or bupivacaine. A placebo is a liquid without any study drug.
- Preoperatively, you will be anesthetized with a standard local anesthetic with standard injection techniques. The resident will extract the third molars when you are properly anesthetized. Postoperatively, you will receive Exparel injections on one side of your mouth and the other side with normal bupivacaine injections.
- Following the procedure, you will be assessed immediately for any adverse effects. You will complete an at-home questionnaire involving pain level via a numerical rating scaling (1: no pain; 10: most pain), occurrence of any adverse events, and NSAID/Acetaminophen use (With a likert-type scale to specify the side of mouth causing NSAID/Acetaminophen use) for four days post-operatively. Pain monitoring assessment will be completed every morning and evening for four days after surgery. Oxycodone will be permitted for breakthrough pain only. You will need to record the date, time of administration, and dosage for all pain medications for up to 96 hours following the procedure. During your two week

follow-up appointment, you will return with your questionnaires and any questions will be answered.

RISKS AND DISCOMFORTS

Possible risks and discomforts you could experience during this study include:

Exparel Use: All side effects/toxicities that will be monitored immediately following the injection of Exparel are allergic reactions, abnormal sensations such as tingling, change in taste, nausea, vomiting, lightheadedness, sweating, palpitations, fever, ringing in ears, twitching, blurred vision and headache. Long-term toxicities to be monitored after completion of therapy are abnormal sensations such as tingling, change in taste, nausea, constipation, fever, vomiting, lightheadedness, sweating, palpitations, and headache 24, 48, 72, and 96 hours following the procedure.

Surveys/Questionnaires: You can choose to skip or stop answering any questions you don't want to. The questions may feel repetitive for four postoperative days.

Breach of Confidentiality: There is a small risk that people who are not connected with this study will learn your identity or your personal information.

If enrolling USC Student Participants: There is a risk that people who are not connected with this study will learn your identity or your personal information. You will be asked questions about activities that if you are under 21 years old may be illegal and/or not in compliance with university policy. Although highly unlikely, if your information becomes public, it might result in the university taking action such as referring you to Campus Support and Intervention (CSI) or Trojans Care 4 Trojans (TC4T).

Reproductive Risks We do not know whether this drug might hurt an unborn baby. If you are pregnant, you cannot take part in this study. If you are breastfeeding and do not want to stop, you may not take part in this study.

Unforeseen Risks: There may be other risks that are not known at this time.

BENEFITS

The potential benefits to you may include less postoperative pain and less use of pain medications.

PRIVACY/CONFIDENTIALITY

We will keep your records for this study confidential as far as permitted by law. However, if we are required to do so by law, we will disclose confidential information about you. Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who are required to review this information. We may publish the information from this study in journals or present it at meetings. If we do, we will not use your name.

The University of Southern California's Institutional Review Board (IRB) and Human Subject's Protections Program (HSPP) may review your records.

Other people who provide medical care or who handle billing and payment at USC may review your research records and medical records, if necessary, to conduct the research.

Federal law provides additional protections of your medical records and related health information. These are described in the HIPAA Authorization document. You will be asked to sign a separate HIPAA Authorization for Research form authorizing the access, use, creation, and disclosure of your health information.

Your responses, which are also called "data' will be encrypted. No patient names will be used on data collection forms. Only personnel involved with the study will have access to the data. A code for the medical record number with corresponding study ID will be kept on the server and then destroyed once the study is completed.

Your data and/or specimens collected as part of this research will not be used or distributed for future research studies, even if all your identifiers are removed.

ALTERNATIVES

An alternative would be not to take part in this study and continue with your current care.

PAYMENTS / COMPENSATION

You will not be compensated for your participation in this research.

INJURY

If you are injured as a direct result of research procedures, you will receive medical treatment; however, you or your insurance will be responsible for the cost. The University of Southern California does not provide any monetary compensation for injury.

VOLUNTARY PARTICIPATION

It is your choice whether to participate. If you choose to participate, you may change your mind and leave the study at any time. If you decide not to participate, or choose to

end your participation in this study, you will not be penalized or lose any benefits that you are otherwise entitled to.

If withdrawal must be gradual for safety reasons, the study doctor will tell you. The study site may still, after your withdrawal, need to report any safety event that you may have experienced due to your participation to all entities involved in the study. Your personal information, including any identifiable information, that has already been collected up to the time of your withdrawal will be kept and used to guarantee the integrity of the study, to determine the safety effects, and to satisfy any legal or regulatory requirements.

WITHDRAWAL FROM STUDY INSTRUCTIONS

You are allowed to withdraw at any point of the study without disclosing the reason. Treatment will be completed with or without the use of Exparel based on the patient's decision.

PARTICIPANT TERMINATION

You may be removed from this study without your consent for any of the following reasons: you do not follow the study doctor's instructions and at the discretion of the study doctor. If this happens, the study doctor will discuss other options with you.

CONTACT INFORMATION

If you have questions, concerns, complaints, or think the research has hurt you, talk to the study doctor at 562-533-2698 (Dr. Costandi).

This research has been reviewed by the USC Institutional Review Board (IRB). The IRB is a research review board that reviews and monitors research studies to protect the rights and welfare of research participants. Contact the IRB if you have questions about your rights as a research participant or you have complaints about the research. You may contact the IRB at (323) 442-0114 or by email at irb@usc.edu.

STATEMENT OF CONSENT

I have read (or someone has read to me) the information provided above. I have been given a chance to ask questions. All my questions have been answered. By signing this form, I am agreeing to take part in this study.

Name of Research Participant	Signature	Date Signed (and Time*)

Minor/Youth Participant (Ages 14-17 years)

If your child agrees to participate, have your child sign here.

Name of Child	Child's Signature	Date Signed

(and Time*)

Name of Parent	Signature	Date Signed (and Time*)

LOSS OF CAPACITY TO PROVIDE CONSENT

In order to make your wishes known in the event you lose the capacity to provide consent to take part in this study, please indicate your preferences below.

☐ Yes, I wish to continue participating in the study if I lose the capacity to consent.

☐ No, I do not wish to continue participating in the study if I lose the capacity to provide consent.

☐ I do not wish to make a decision at this time.

We will notify your Legally Authorized Representative of your choice if you are no longer able to provide consent to take part in the study.

If you lose the capacity to consent and you indicated above that either you wish to continue or you did not wish to make a decision, we will ask your Legally Authorized Representative if they will allow you to continue in the study. We will also ask for your assent to continue in the study. You will continue in the study if your Legally Authorized Representative approves your continued participation and you indicate verbally or nonverbally that you wish to continue.

Person Obtaining Consent

I have personally explained the research to the participant using non-technical language. I have answered all the participant's questions. I believe that the participant understands the information described in this informed consent and freely consents to participate.

Name of Person Obtaining Informed Consent	Signature	Date Signed (and Time*)

Witness

A Witness is Required When: (1) the participant cannot see, read, write, or physically sign the consent form, or (2) the Short Form method is used to obtain consent. In these situations, the witness must sign and date the consent form.
If no witness is needed, leave this signature line blank.

Name of Witness	Signature	Date Signed

Dr. John Costandi, APP-22-00106, Double-Blinded Randomized Controlled Study Investigating the Efficacy of Exparel (Liposomal Bupivacaine) for Postoperative Pain Relief in Mandibular Third Molar Extractions

Subject ID ☐☐☐☐☐ **Date:** ☐☐ / ☐☐ / ☐☐
Month Day Year

Eligibility Criteria

Inclusion Criteria

Patients who meet *all* of the following criteria are eligible for enrollment as study participants:

	Yes	No
1. Patient is receiving bilateral mandibular third molar extractions at the Herman Ostrow School of Dentistry by an oral & maxillofacial surgery resident.		

Exclusion Criteria

Patients who meet *any* of these criteria are *not* eligible for enrollment as study participants:

	Yes	No
1. Patient has severe hepatic disease.		
2. Patient is unable to complete the questionnaire for four days postoperatively.		
3. Patient has a history of allergy or contraindication to amide-type local anesthesia or opioids.		
4. Patient has a history of antibiotic use within the past thirty days.		
5. Patient has used long acting opioids, NSAIDs, aspirin, or acetaminophen within 3 days prior to screening.		
6. Patient is pregnant.		
7. Patient is receiving additional mandibular teeth extractions.		

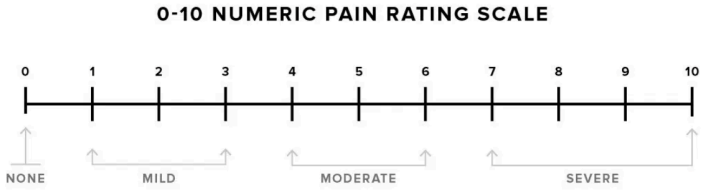
Form Completed by: _____ Date: _____
Site PI Signature: _____ Date: _____

Appendix II

Dr. John Costandi, APP-22-00106
Double-Blinded Randomized Controlled Study Investigating the Efficacy of Exparel (Liposomal Bupivacaine) for Postoperative Pain Relief in Mandibular Third Molar Extractions

Subject ID | | | | | | |

Pain Monitoring Report



On a scale of 0-10, with 0 being no pain at all and 10 being the most severe pain imaginable, please rate your pain on this scale.

Please complete within 2 hours of waking up and before sleeping following surgery for at least 4 days.

Time of Surgery:

		Right Side	Left Side
Date	Time	Pain (Rate 1-10; Write 0 when pain gone completely)	Pain (Rate 1-10; Write 0 when pain gone completely)

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[redacted]

Please indicate your reason for taking the medication according to the following scale:

1	2	3	4	5
Left side only	**Mostly left side Partially right side**	**Left & right sides evenly**	**Most right side Partially left side**	**Right side only**

NSAID & Acetaminophen Use Report

		Ibuprofen		Acetaminophen		Reason
Date	Time	Dose	Quantity	Dose	Quantity	Scale (1 - 5)

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Oxycodone Use Report

		Oxycodone		
Date	Time	Dose	Quantity	Reason for Use (Left side, Right side or Both)

Adverse Event Tracking Log

Check box if there were no adverse events to be recorded □

Please record any of the following symptoms 24, 48, 72, and 96 hours following surgery:

Abnormal sensation (tingling, prickling)
Change in taste
Nausea
Constipation
Fever
Vomiting
Lightheadedness
Diaphoresis
Palpitations
Headache
None

Date	Time	Symptom (See above)	Severity (1-10)	Duration	Resolve (Y or N)	Treatment (if any)

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Local Anesthesia Report

Please record the time, dosage, and location of local anesthesia administration
At least 20 minutes following most recent lidocaine injection required prior to administration of study drugs
Include administration of study drugs (time, quantity, right vs. left side)

Date	Time	Local anesthesia (ie. 2% lidocaine 1:100,000 epinephrine)	Location (ie. inferior alveolar nerve block)	Quantity (ie. 1.8 mL)