PCPC Study (Post Cesarean Section Pain Control)

PROTOCOL TITLE: Post Cesarean Section Analgesic Safety and Efficacy of EXPAREL (Liposomal Bupivacaine) Infiltration Locally Versus Transversus Abdominis plane Infiltration

VERSION DATE: 12-04-2017

PROTOCOL TITLE:
Post-cesarean section analgesic safety and efficacy of EXPAREL (Liposomal Bupivacaine) infiltration locally versus Transversus Abdominis plane Infiltration

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REVISION HISTORY

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<td>1</td>
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<td>NA</td>
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ABBREVIATIONS/DEFINITIONS

AE  Adverse event
ANOVA  Analysis of variance
ASA  American Society of Anesthesiology
C-section  Cesarean section
CI  Confidence interval
Cmax  Maximum plasma concentration
CV  Coefficient of variation
CRF  case report form
FDA  Food and Drug Administration
ICF  Informed consent form
IRB  Institutional Review Board
LC-MS  Liquid chromatography-mass spectrometry
NRS  Numeric rating scale
NSAIDs  Non-steroidal anti-inflammatory drugs
OBAS  Overall benefit of analgesia score
OR  Operating room
PACU  Post-anesthesia care unit
PO  Oral
PRN  as needed
PTAE  Pretreatment adverse event
q4h  Every 4 hours
q6h  Every 6 hours
QoR-15  Quality of recovery 15-item questionnaire
SAE  Serious adverse event
Transversus Abdominis Plane: TAP
PROTOCOL TITLE: Post Cesarean Section Analgesic Safety and Efficacy of EXPAREL (Liposomal Bupivacaine) Infiltration Locally Versus Transversus Abdominis plane Infiltration

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STUDY SUMMARY

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<tr>
<th>Study Title</th>
<th>Post-cesarean section analgesic safety and efficacy of EXPAREL (Liposomal Bupivacaine) local wound infiltration versus Transversus Abdominis Plane Infiltration</th>
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<tbody>
<tr>
<td>Study Design</td>
<td>Prospective, randomized, partially-blinded</td>
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<tr>
<td>Primary Objective</td>
<td>Total postsurgical opioid consumption (in morphine equivalents) through 72 hours post-operatively or until discharge</td>
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</tbody>
</table>
| Secondary Objective(s) | 1. Time to first rescue opioid pain medication  
2. Percentage of opioid-free subjects through 24, 48, and 72 hours.  
3. Quality of recovery questionnaire [Time frame: through 72 hours post-op or at discharge]  
4. Patient’s satisfaction [Time frame: through 72 hours post-op or hospital discharge]  
5. VAS pain scores [Time frame: 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery]  
6. Overall benefit of anesthesia score questionnaire [Time frame: through 72 hours post-op or discharge]  
7. Related and unrelated A.E to EXPAREL [Time frame: through 72 hours post-op]  
8. Liposomal Bupivacaine related adverse events [time frame: through day 14]  
9. Allergic reactions attributable to local anesthetic use (rash, hives, anaphylaxis) [ Time frame: through day 14]  
10. Wound complications [Time frame: through day 14]  
11. Hospital length of stay |
**PCPC Study (Post Cesarean Section Pain Control)**

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| **Research Intervention(s)/Investigational Agents** | Name of Finished Products: EXPAREL (bupivacaine liposome injectable suspension)  
Name of Active Ingredients: Bupivacaine, 1.3%, 13.3 mg/mL |
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<tr>
<td><strong>IND/IDE # (if applicable)</strong></td>
<td>None</td>
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<tr>
<td><strong>Study Population</strong></td>
<td>Women undergoing elective cesarean section delivery.</td>
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<tr>
<td><strong>Sample Size (number of participants)</strong></td>
<td>Approximately 80 subjects are planned for enrollment into the study.</td>
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<tr>
<td><strong>Study Duration for Individual Participants</strong></td>
<td>Participation will begin upon signing of the ICF. No more than 7 days should pass between signing the ICF and surgery. Patient’s evaluation will continue till 3 days after surgery so duration of patient’s involvement in the study will be for a maximum of 14 days.</td>
</tr>
</tbody>
</table>
1.0 Objectives

1.1 Primary objective: The primary objective of this study is to compare total opioid consumption through 72 hours following EXPAREL+bupivacaine HCl infiltration into the transversus abdominis plane (TAP) after spinal anesthesia to EXPAREL+bupivacaine infiltration into the abdominal incision (fascia and subcutaneous tissue) in subjects undergoing an elective cesarean section (C-section).

1.2 Secondary objective:

1. Time to first rescue opioid pain medication
2. Percentage of opioid-free subjects through 24, 48, and 72 hours.
3. Quality of recovery questionnaire [Time frame: through 72 hours post-op or at discharge]
4. Patient’s satisfaction [Time frame: through 72 hours post-op or hospital discharge]
5. VAS pain scores [Time frame: 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery]
6. Overall benefit of anesthesia score questionnaire [Time frame: through 72 hours post-op or discharge]
7. Related and unrelated A.E to EXPAREL [Time frame: through 72 hours post-op]
8. EXPAREL related adverse events [time frame: through day 14]
9. Allergic reactions attributable to local anesthetic use (rash, hives, and anaphylaxis) [Time frame: through day 14]
10. Wound complications [Time frame: through day 14]
11. Hospital length of stay
2.0 Background

The adequate management of postoperative pain is central to surgical and anesthetic practice. A near-infinite number of different pain management methods have been tried - and are in current use [1]. These range from the administration of various different opioids, combinations of opioids and other medications (e.g NSAIDS, sedatives, anxiolytics, and many more) and the use of multi-modal non-opioid based regimens to various central (e.g. spinal, epidural and caudal) and peripheral nerve blocks (e.g. lumbar plexus, paraspinous, erector spinae and more) as well as local infiltration and field blocks. No method has been universally successful, either due to limited efficacy or due to treatment related side effects.

The treatment of postoperative pain in patients who have undergone a cesarean section poses some unique problems for the simple fact that new mothers must be able to quickly care for (and often nurse) their newborns [2-5]. Many of the aforementioned analgesic regimens are incompatible with these needs, either because they render the mother incapable of providing adequate care (due to their sedating effects) or because the medications are transferred to the child via breast milk. This is particularly true of opioids. The goal of nearly all providers involved in the care of cesarean-section patients is therefore to minimize opioid doses (and the duration of their use) -and ideally to eliminate the use of these drugs altogether. This is most commonly done by using neuraxial anesthesia (spinal or epidural) for the surgery itself, and then either continuing the neuraxial anesthetic (via a catheter in the epidural space) into the postoperative period, or by providing some other form of "local or regional anesthesia" in combination with non-opioid analgesics - with opioids used only for "rescue purposes" [6-9].

At the University of Minnesota, cesarean sections are routinely done with a spinal anesthetic, followed (after delivery of the baby) by the performance of an ultrasound guided transversus abdominis plane (TAP) block using the long-acting liposomal bupivacaine mixture EXPAREL[10-15]. [This block is done while the spinal anesthetic is still active and hence results in no patient discomfort.] Patients subsequently receive a standard regimen of acetaminophen, ibuprofen and ketorolac - with oxycodone given as needed for "rescue" purposes. The goal is to minimize the amount of oxycodone - and to avoid discharging patients with opioid prescriptions. While this approach is quite successful, it is not "generalizable". The limiting factor is the technology and expertise needed to perform TAP blocks; these are not available to the great majority of obstetrical patients either in the US or around the world. There would therefore be substantial value in a simpler - and yet comparably effective- method for achieving high quality postoperative analgesia.

The EXPAREL mixture used currently for TAP blocks is also approved by the FDA for the direct infiltration of surgical wounds prior to or after closure and such infiltration have been shown in several surgical settings to provide longer analgesia than bupivacaine alone [16-23]. Such infiltration can easily be performed by the operating surgeon during surgery and requires no unique skills. Our goal, therefore, is to determine whether the postoperative analgesia achieved by direct surgical wound infiltration is equivalent (in terms of postoperative pain control) to that achieved with TAP blocks, using total postoperative opioid consumption (in morphine equivalents) as our primary outcome variable.
3.0 Study Endpoints/Events/Outcomes

3.1 Efficacy measurements

Date, time of administration, and amount of all postsurgical opioid rescue medication taken through 72 hours post-surgically.

Pain intensity scores using the VAS at rest at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours.

Subject satisfaction with postsurgical pain control (using a 5-point Likert scale) at 72 hours (or prior to hospital discharge) and at day 14.

Quality of Recovery 15-item questionnaire at 72 hours (or prior to hospital discharge).

OBAS questionnaire at 24, 48, and 72 hours.

3.2 Efficacy endpoints

The primary efficacy endpoint is the total postsurgical opioid consumption in morphine equivalents through 72 hours or hospital discharge.

The secondary efficacy endpoints include:

- Time to first postsurgical opioid rescue medication
- The VAS pain intensity scores at rest from 0 to 72 hours (6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery)
- Percentage of opioid-free subjects through 24, 48, and 72 hours.
- Overall assessment of the subject’s satisfaction with postsurgical pain control (using a 5-point Likert scale) at 72 hours after surgery (or at hospital discharge if earlier than 72 hours) and on day 14.
- Responses to the QoR-15 questionnaire at 72 hours after surgery (or at hospital discharge if earlier than 72 hours).

3.3 Safety Assessments endpoint

Adverse events will be monitored from the time the ICF is signed through Day 3 post-operatively and EXPAREL related A.E till day 14.

Wound complication till day 14 (this is routine for all cesarean section patients)

Allergic reactions attributable to local anesthetic use including rash, hives, and anaphylaxis till day 14.

Comment: Appropriateness of Measures Endpoints selected for this study were based on well-established clinical measurements used in multiple peer-reviewed studies.
4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Indications EXPAREL is a liposomal suspension of the local anesthetic bupivacaine and was developed to extend the duration of action of bupivacaine, and thereby provide longer lasting analgesia than can be obtained with bupivacaine alone. EXPAREL is indicated and approved by the FDA for administration into the surgical site to produce postsurgical analgesia and for infiltration into the abdominal wall (as a TAP block) for the same purpose. Since the performance of a TAP block (the most commonly used form of postoperative analgesia in Csection patients at the UMN) requires substantial technology (ultrasound guidance) and provider expertise, there would be substantial advantages to being able to provide analgesia via simple, direct infiltration of the surgical wound prior to closure. Our goal, therefore, is to determine whether direct infiltration provides postoperative analgesia of comparable quality and duration to a TAP block.

4.2 Human Experience with EXPAREL

To date, there are more than 36 clinical studies involving over 1800 human subjects examining EXPAREL. Doses ranged from 2 to 655 mg injected via various routes, including local infiltration, subcutaneous infiltration or via TAP blocks. The product has been well tolerated and, in active comparator studies with plain bupivacaine, reported AEs occurred at a similar rate as the corresponding bupivacaine HCl controls. No adverse safety signal attributed to either the central nervous or cardiovascular systems was reported with EXPAREL. As of January 2017, it is estimated that more than 2.5 million patients have received EXPAREL.

4.3 Selection of Doses in the Study

Pharmacokinetic studies have shown that because EXPAREL releases bupivacaine gradually as the lipid structure breaks down, administration of EXPAREL 266 mg results in a maximum plasma concentration (Cmax) equivalent to that seen with 100mg of plain bupivacaine (a commonly used dose for local infiltration and nerve blocks). Clinical studies have shown that for wound infiltration a total dose of 266 mg (20 mL) of EXPAREL is safe and efficacious. Based on this experience, the FDA-approved marketed dose of 266 mg was deemed appropriate for this study.
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5.0 Procedures Involved

5.1 Inclusion and Exclusion criteria

Inclusion criteria:
1. Females 18 years of age and older at screening.
2. Term pregnancies of 37 to 42 weeks gestation, scheduled to undergo elective C-section.
3. ASA physical status 1, 2, or 3 are able to provide informed consent, adhere to the study visit schedule, and complete all study assessments

Exclusion criteria:
1. Age <18
2. BMI ≥ 40 or otherwise not anatomically appropriate to undergo a TAP block.
3. Planned general anesthetic
4. Cesarean delivery via vertical skin incision
5. Allergy, hypersensitivity, intolerance, or contraindication to any of the study medications.
6. Planned concurrent surgical procedure with the exception of salpingo-oophorectomy or tubal ligation.
7. Severely impaired renal or hepatic function (eg, serum creatinine level >2 mg/dL [176.8 µmol/L], blood urea nitrogen level >50 mg/dL [17.9 mmol/L], serum aspartate aminotransferase [AST] level >3 times the upper limit of normal [ULN], or serum alanine aminotransferase [ALT] level >3 times the ULN.)
8. Subjects at an increased risk for bleeding or a coagulation disorder (defined as platelet count less than 80,000 × 10³/mm³ or international normalized ratio greater than 1.5).
9. Concurrent painful physical condition that may require analgesic treatment (such as long-term, consistent use of opioids) in the postsurgical period for pain that is not strictly related to the surgery and which may confound the postsurgical assessments.
10. Clinically significant medical disease in either the mother or baby that, in the opinion of the investigator, would make participation in a clinical study inappropriate. This includes any psychiatric or other disease in the mother that would constitute a contraindication to participation in the study or cause the mother to be unable to comply with the study requirements.
11. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
12. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject’s participation in this study.
13. Previous participation in an EXPAREL study.

14. Any clinically significant event or condition uncovered during the surgery (eg, excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject’s postsurgical course.

15. Initiation of treatment with any of the following medications within 1 month of study drug administration or if the medication(s) are being given to control pain: selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin (Lyrica®), or duloxetine (Cymbalta®). If a subject is taking one of these medications for a reason other than pain control, she must be on a stable dose for at least 1 month prior to study drug administration.

16. Use of any of the following medications within the times specified before surgery: long-acting opioid medication, non-steroidal anti-inflammatory drugs (NSAIDs), or aspirin (except for low-dose aspirin used for cardioprotection) within 3 days, or any opioid medication or acetaminophen within 24 hours.

17. Patient membership in a vulnerable population such as a prisoner, mentally unable to provide direct consent etc.
**5.2 Study Design**

This is a randomized, partially-blinded, active-controlled equivalency study in approximately 80 adult subjects undergoing elective C-section.

**5.2.1 Screening**

Subjects will be screened within 7 days prior to surgery including the day of surgery. During the screening visit, subjects will be assessed for any past or present medical conditions that in the opinion of the investigator would preclude them from study participation. After the ICF is signed, a medical history, surgical history, physical examination, vital sign measurements.

**5.2.2 Randomization and Blinding**

Once a subject is identified as being qualified for the study in accordance with the eligibility criteria, a computer generated random number will be assigned, a sealed envelope will be given by the blinded study personnel will give it to the un-blinded surgical team (anesthesiologist and operating surgeon). The envelop to be opened after delivery of the fetus.

**5.2.3 Day of Surgery**

Eligible subjects will be randomized in a blinded 1:1 ratio to either:

- Group 1: EXPAREL+bupivacaine TAP infiltration following spinal anesthesia and closure of the c-section incision.
- Group 2: EXPAREL+bupivacaine infiltration into the fascia and skin incision following spinal anesthesia and closure of the uterine incision.

Note that, prior to the C-section, ALL subjects will receive a intrathecal injection (spinal anesthetic) consisting of 150 mcg morphine (eg, Duramorph®) in conjunction with single-shot spinal anesthesia (1.4-1.6 mL bupivacaine HCl 0.75%) plus 15 mcg intrathecal fentanyl. This is standard of care for C-section patients at UMN. A combined spinal epidural (CSE) anesthesia technique may also be used.

**TAP infiltration group (group 1):** After delivery of the baby and closure of the Pfannensteil incision, 2-point classic TAP block will be performed under ultrasound guidance within 1 hour (± 30 minutes) following skin incision closure of the C-section. Infiltration includes single 20-mL dose of EXPAREL 266 mg expanded in volume with 20 mL normal saline plus 20 mL 0.25% bupivacaine for a total volume of 60 mL, administered as 30 mL (10 mL EXPAREL, 10 mL 0.25% bupivacaine HCl, and 10 mL saline) on each side of the abdomen. A confirmatory ultrasound picture or video will be taken of each side of the abdomen after the TAP needle position has been established and after infiltration of study drug. This represent a standard TAP-block procedure.

**Fascia and skin incision infiltration group (group 2):**
5.2.4 Postsurgical Analgesia

As per our standard routines, the following multimodal pain regimen will be initiated immediately following the delivery of the baby:

- IV ketorolac 30 mg q6 hr for 24 hr after the procedure.
- Scheduled (PO) Acetaminophen 975 mg every 8 hours for up to 72 hours.
- Scheduled PO ibuprofen 600 mg q6h for up to 72 hours.
- Oral (PO) Oxycodone 5-10 mg q3hr prn up to 72 hours for breakthrough pain.

5.3 Study Procedures:

All assessments conducted after baseline will be timed from the delivery of the baby. Day 1 is defined as the day on which study drug is administered. The beginning of surgery is defined as the time of the first incision. The end of surgery is defined as the time of closure of the C-section wound. Postsurgical is defined as after the end of surgery. C-section patients at the UMN are typically hospitalized for 72 hours after surgery, but may be discharged earlier per the discretion of the attending OB physician. Postsurgical analgesia and collection of study data through hospital discharge will take place under the supervision of study staff.

5.3.1 Patient diary

The Patient Diary will be given to the subject at the first scheduled assessment (i.e., 6 hours) following surgery. While in the hospital, the subject will use the diary to record all scheduled VAS (i.e., at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours) and OBAS (i.e., at 24, 48, and 72 hours) assessments.

If a subject is discharged prior to any of the scheduled VAS assessments collected at 6 to 72 hours post-surgery or a scheduled OBAS assessment collected at 24 to 72 hours post-surgery, a member of the study site staff will telephone the subject at the appropriate scheduled times (i.e., the time of each assessment scheduled to be collected that occurs after hospital discharge) to remind him/her to complete the VAS and OBAS assessments and to record the scheduled assessments in the Patient Diary. This will ensure that for any subject discharged prior to 72 hours, all VAS and OBAS assessments required for calculation of the study endpoints are captured. These phone calls will only occur if a subject is discharged prior to 72 hours.

5.3.2 Pain Intensity Assessments

Pain intensity will be assessed at rest using the VAS (see Appendix 1) at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours.
To assess pain intensity (VAS) at rest, the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score.

5.3.3 Overall Benefit of Analgesia Score Questionnaire (OBAS)

The OBAS questionnaire will be completed at 72 hours (or hospital discharge, whichever occurs first; see Appendix 2).

5.3.4 Subject Satisfaction with Postsurgical Pain Control

The subject’s satisfaction with postsurgical pain control will be assessed at 72 hours (or hospital discharge, whichever occurs first; see Appendix 3) and on day 14 visit.

5.3.5 Quality of Recovery

The subject’s quality of recovery will be assessed using the QoR-15 questionnaire at 72 hours, (or hospital discharge, whichever occurs first; see Appendix 4).

5.3.6 Screening/Baseline Procedures

The following screening/baseline procedures should be performed prior to administration of study drug.

- Explain study purpose and procedures
- Obtain signed ICF
- Assess eligibility
- Record medical/surgical history
- Record prior and concomitant medications
- Record demographics and baseline characteristics
- Explain to the subject that she will be provided with a Patient Diary while in the hospital and that she will be expected to capture specific information in the diary till 72 hours after the procedure.
- Measure vitals (blood pressure and heart rate)
- Perform physical exam according to the investigational site’s standard of care
- Record AEs starting when the ICF is signed
- Record concomitant medications for treatment of AEs
- Randomize subject
- provide the Patient Diary, addressed and stamped envelope, and instructions for use
5.3.7 Post-operative assessment

**Day 1 - Prior to PACU Discharge**
- Record date, time in and out of the PACU
- Measure vital signs (blood pressure and heart rate)
- Record date, time, and dose of all postsurgical opioid and other pain medication.

**Days 1-3 (0-72 Hours After Surgery/Hospital Discharge)**
- Record scheduled VAS pain intensity scores (see Appendix 1) at rest at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours.
- Record date, time, and dose of all standardized multimodal pain medications administered
- Record an unscheduled VAS pain intensity score immediately before any postsurgical opioid medication while in the hospital.
- Record date, time, and dose of all postsurgical opioid and other pain medications administered through 72 hours. Note: Subjects should only receive opioid pain medication (morphine, hydromorphone [Dilaudid], oxycodone) upon request for breakthrough pain, PRN.
- Record OBAS (see Appendix 2) at 24, 48, and 72 hours
- Record overall rating of subject’s satisfaction with postsurgical pain control at 72 hours (or hospital discharge, whichever occurs first; see Appendix 3)
- Record QoR-15 data at 72 hours (or hospital discharge, whichever occurs first; see Appendix 4)
- Record date and time of hospital discharge
- Record any AEs or SAEs
- Record any concomitant medications for treatment of AEs

**Day 14:**
During the standard 2 weeks post-partum wound check. If the patient didn’t show up for the visit, then call the patient to collect the following
- Wound complications
- Allergic reactions attributable to local anesthetic use.
- EXPAREL use related A.E
- Patient satisfaction with pain control

**Follow-up:** See Above

**Individually Identifiable Health Information:**
Name and MR numbers will be collected initially in BOX; study data later will be coded for the statistical analysis.
6.0 Data and Specimen Banking

Data will be stored using BOX.

7.0 Sharing of Results with Participants

Data will not be shared with participants as they will be blinded.

8.0 Study Duration:

Participation will begin upon signing of the ICF. No more than 7 days should pass between signing the ICF and surgery. Patient’s evaluation will continue till 7 days after surgery so duration of patient’s involvement in the study will be for a maximum of 21 days. We are anticipate finishing recruitment in one year.

9.0 Vulnerable Populations

9.1 Vulnerable Populations: Identify which of the following populations will be involved in this study.
(You may not include members of the populations below as participants in your research unless you indicate this in your inclusion criteria above.)

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
Undervalued or disenfranchised social group
☐ Members of the military
☒ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☐ None of the above

Note: as explained previously, the study medication will not be given until the fetus is delivered and uterine incision is closed.

9.2 Adults lacking capacity to consent and/or adults with diminished capacity to consent:
Will be excluded

9.3 Additional Safeguards: NA

10.0 Total Number of Participants
80 subjects will be enrolled.

11.0 Local Recruitment Methods
11.1 Recruitment Process: participants will be recruited within 7 days of their scheduled cesarean section.
11.2 Source of Participants: patients who are planned to have their cesarean section at Fairview Riverside Hospital.

11.3 Identification of Potential Participants: Subjects scheduled to have an elective cesarean section are identified using EPIC cesarean section OR schedule.

11.4 Recruitment Materials: no materials will be used.

11.5 Payment: no payment will be used.

12.0 Withdrawal of Participants
If any clinically significant event or condition is uncovered during the surgery (e.g., excessive bleeding, acute sepsis) that might render the subject medically unstable or complicate the subject’s postsurgical course.

13.0 Data Management
A comprehensive statistical analysis plan (SAP) will be developed for this study. Demographic and baseline characteristics will be summarized descriptively by treatment group for all subjects who receive study drug. Efficacy endpoint analyses will be described in the SAP. Safety endpoints will be summarized descriptively by treatment group. Sample size for this study was based on Quale et al (2016). The coefficient of variation (CV) from this poster was approximately 60%. Assuming a log-
normal distribution for total opioid consumption with a 60% CV, 5% alpha, a 1:1 randomization ratio, and 80% power, a total of 72 subjects per treatment group will be sufficient to detect a 30% difference between treatments.

14.0 Confidentiality

14.1 Data Security:

All data will be stored in a secure data shelter available through the BOX. The data will be accessible only to study staff that has completed HIPAA compliance training through the University of Minnesota. The data shelter is password protected. All paper forms will be destroyed.

15.0 Provisions to Monitor the Data to Ensure the Safety of Participants

Safety will be monitored by both the investigator and the medical care team (Including staff attending, physician residents, and nurses).

AE will be monitored and recorded.

AE will be managed by the medical care team immediately as with the appropriate medical measures. Consult serviced will be obtained if needed depending on the severity of the AE.

16.0 Provisions to Protect the Privacy Interests of Participants

16.1 Protecting Privacy and access to participants:

- The consent process, asking questions will be done in a secluded private setting.
- Participants permission will be obtained to access their health record to obtain only the required related information to the study (any pain medication they received post-operatively, adverse events encountered postoperatively, discharge date, discharge pain medications)
- Allowing participants to refuse to answer any questions or complete any study tasks that they find objectionable.
- Refusing to participate in the study will not affect their care in any shape.
- Discussing the study with other investigators in a private setting.
- Assigning a specific code for every participant to de-identify them.
- Accessing minimal amount of health information
- Accessing the needed health information in a private setting.
- During follow up process after the cesarean section is done, patients will be evaluated in a private setting.
The follow up phone call on day 14 will be done in private setting as well.

If interpreter is needed during the process, subject’s permission will be obtained first to discuss study details using the interpreter.

17.0 Compensation for Research-Related Injury

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow up care as needed. Care for such injuries will be billed in the ordinary manner. No personal compensation will be provided.

18.0 Consent Process

18.1 Consent Process

The consent will take place within 7 days of the scheduled elective C-section.

It will take place either during their prenatal visit in the clinic privately or when they will present to L&D for their C-section in triage or L&D room in private setting

Consent document is attached in supporting documents.

18.2 Waiver or Alteration of Consent Process: NA

18.3 Non-English Speaking Participants:

After obtaining subject’s permission to discuss study details using an interpreter. Oral instructions will be explained via the interpreter; written instructions will be given in her language.

Written instructions will be translated to the desired language using certified interpreter.

The language of the investigator obtaining consent is English.

Interpreters hired by Fairview Riverside Hospital will be used for the interpretation process. Translated short forms are available on the UMN IRB website: https://www.research.umn.edu/irb/guidance/short-forms.html.

18.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

They are excluded from the study

18.5 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

They are excluded from the study

18.6 Adults Unable to Consent:

They are excluded from the study

19.0 Setting

19.1 Research Sites: Research will be conducted in Fairview Riverside Hospital. The subjects who will be recruited are scheduled for elective C-section in Riverside Hospital-Labor and Delivery unit.

19.2 Multi-Site Research: NA
19.3 Study-Wide Number of Participants: 80
19.4 Study-Wide Recruitment Methods: NA
19.5 Study-Wide Recruitment Materials: NA
19.6 Communication Among Sites: NA
19.7 Communication to Sites: NA

20.0 References

Appendix 1

**VAS (Visual Analogue Score) PAIN SCALE**

- Assess pain intensity (VAS) at **REST**, the subject should rest quietly in a supine or seated position that does not exacerbate her postsurgical pain for 3-5 minutes before entering the pain score.
- Assess your pain at **REST** at 6, 12, 18, 24, 30, 36, 42, 48, and 72 hours after surgery.

<table>
<thead>
<tr>
<th>No Pain</th>
<th>Moderate Pain</th>
<th>Worst Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

- No pain
- Mild, annoying pain
- Nagging
- Uncomfortable
- Troublesome
- Hurts little bit
- Hurts little more
- Distressing
- Miserable pain
- Hurts even more
- Intense
- Dreadful
- Horrible
- Hurts whole lot
- Excruitating
- Hurts worst
- Worst possible
- Unbearable
- Excruciating
- Hurts worst
Appendix 2

**Overall Benefit of Analgesia Score Questionnaire -OBAS**

- Please complete at 72 hours after surgery (or at hospital discharge, whichever occurs first)

<table>
<thead>
<tr>
<th>Question</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Please rate your current pain at rest on a scale between 0= minimal pain and 4= maximum imaginable pain</td>
<td></td>
</tr>
<tr>
<td>2. Please grade any distress and bother from vomiting in the past 24 h (0= not at all to 4= very much)</td>
<td></td>
</tr>
<tr>
<td>3. Please grade any distress and bother from itching in the past 24 h (0= not at all to 4= very much)</td>
<td></td>
</tr>
<tr>
<td>4. Please grade any distress and bother from sweating in the past 24 hours (0= not at all to 4= very much)</td>
<td></td>
</tr>
<tr>
<td>5. Please grade any distress and bother from freezing in the past 24 h (0= not at all to 4= very much)</td>
<td></td>
</tr>
<tr>
<td>6. Please grade any distress and bother from dizziness in the past 24 h (0= not at all to 4= very much)</td>
<td></td>
</tr>
<tr>
<td>7. How satisfied are you with your pain treatment during the past 24 h (0= not at all to 4= very much)</td>
<td></td>
</tr>
</tbody>
</table>

**Overall benefit of analgesia score**
Appendix 3

Subject Satisfaction with Postsurgical Pain Control - Likert Scale

- Please circle the number below that best describes your overall satisfaction with your pain control, pain management and treatment after surgery. (*Select one number only.*)
- To be conducted at 72 hours after surgery (or at hospital discharge, whichever occurs first)

1. Extremely dissatisfied
2. Dissatisfied
3. Neither satisfied nor dissatisfied
4. Satisfied
5. Extremely satisfied
Appendix 4

Quality of Recovery 15-item Questionnaire - The QoR-15

- To be conducted at 72 hours after surgery (or at hospital discharge, whichever occurs first).

**Part A:**

How have you been feeling in the last 24 hours? (0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1. **Able to breathe easily**
   - None of the time
   - All of the time

2. **Been able to enjoy**
   - None of the time
   - All of the time

3. **Feeling rested**
   - None of the time
   - All of the time

4. **Have had a good sleep**
   - None of the time
   - All of the time

5. **Able to look after personal toilet and hygiene unaided**
   - None of the time
   - All of the time

6. **Able to communicate with family or friends**
   - None of the time
   - All of the time

7. **Getting support from hospital doctors and nurses**
   - None of the time
   - All of the time

8. **Able to return to work or usual home activities**
   - None of the time
   - All of the time
9. Feeling comfortable and in control
None of the time All of the time

10. Having a feeling of general well-being
None of the time All of the time

Part B:
Have you had any of the following in the last 24 hours? (10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11. Moderate pain
None of the time All of the time

12. Severe pain
None of the time All of the time

13. Nausea or Vomiting
None of the time All of the time

3. Feeling rested
None of the time All of the time

14. Feeling worried or anxious
None of the time All of the time

15. Feeling sad or depressed
None of the time All of the time

Total score
### Appendix 5

**Time and events schedule of study procedures**

<table>
<thead>
<tr>
<th>Study procedure</th>
<th>Screen within 7 days of surgery</th>
<th>Day 1 (OR, PACU)</th>
<th>Hours after surgery</th>
<th>Hospital discharge</th>
<th>Day 14 call</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain study purpose and procedures; obtain signed ICF</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess/confirm eligibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record/confirm medical and surgical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record prior and current meds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record demographics and baseline characteristics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure vital signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explain Patient Diary</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomize subject</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer study drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record intra-op opioids and doses</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record VAS</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
## PCPC Study (Post Cesarean Section Pain Control)

**PROTOCOL TITLE:** Post Cesarean Section Analgesic Safety and Efficacy of EXPAREL (Liposomal Bupivacaine) Infiltration Locally Versus Transversus Abdominis plane Infiltration

**VERSION DATE:** 12-04-2017

| Record date, Time, dose of all post-op pain meds | x | x | x | x | x | x | x | x | x | x | x |
| Time to 1st post-op opioid pain med requested | x | x | x | x | x | x | x | x | x | x | x |
| Record date, time, and dose of all standards pain medication | x | x | x | x | x | x | x | x | x | x | x |
| Record OBAS | x | x | x | x | x | x | x | x | x | x | x |
| Record QoR-15 | x | x | x | x | x | x | x | x | x | x | x |
| Record satisfaction with post-op pain control | x | x | x | x | x | x | x | x | x | x | x |
| Record date and time of hospital discharge | x | x | x | x | x | x | x | x | x | x | x |
| Document whether the subject has made any 1. unscheduled pain related phone calls or office visits 2. experienced any ER visits or hospital readmission; 3. experience AEs 4. Experienced incisional allergic reaction | x | x | x | x | x | x | x | x | x | x | x |
| Record AEs/SAEs | x | x | x | x | x | x | x | x | x | x | x |
| Record meds used for treatment of AEs | x | x | x | x | x | x | x | x | x | x | x |

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Revised: April 19, 2017
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VERSION DATE: 12-04-2017