DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
ADULT
Phase 1, Randomized, Double-Blind, Active and Placebo Controlled, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of EXPAREL Administered via a Single Intrathecal Injection to Healthy Volunteers

CONCISE SUMMARY

You are being asked to take part in this research study because you are a healthy adult who is interested in being a participant in a clinical trial. The purpose of this study is to assess the safety and tolerability of EXPAREL (the study drug) given as a single intrathecal (spinal) injection, and to look at what the body does to the drug and how the drug works. The study drug is a liposome (surrounded in fat molecules) injection of bupivacaine, (an FDA approved drug used for pain). Bupivacaine acts by numbing the body area around where it is given, decreasing pain and other sensations. If you choose to participate, you will be randomized (chosen by chance—like drawing numbers from a hat) into one of the 3 study groups: You will receive (1) the study drug, (2) bupivacaine, or (3) placebo (for example, saline) by injection into the spinal region.

If you choose to participate, you will stay in the Duke Early Phase Research Unit (DEPRU) following study drug administration until 6 days after study drug administration, at which point you will be discharged. You will be asked to return to DEPRU on 3 days after discharge for a follow-up visit. You will also receive a follow-up phone call on Day 30.

The study drug (or bupivacaine or placebo) will be given as a single injection into your spine. On the day of drug administration, you will have several assessments done, including several blood samples, urine and cerebral spinal fluid (CSF) samples taken. Taking a CSF sample is similar to the way blood is taken from your vein. The difference is the fluid taken is CSF (not blood) and it is taken from your spinal column (not a vein). Other assessments include a 3-lead electrocardiogram (ECG) that measures your heart's electrical activity, a neurological questionnaire, sensory and motor tests, vital signs and comprehensive neurological assessment up to three hours before you receive the study drug. Risks of the study drug include spinal headache, restlessness, anxiety, blurred vision, ringing in the ears and tremors. Risks of other study activities, like the blood and CSF samples, include skin irritation, site infection, and systemic infection.

You will not receive any immediate direct benefits from being in this study. However, we hope the knowledge obtained from the results of this study may be of benefit to you or others in the future.

If you are interested in participating in this study please continue reading below.

You are being asked to take part in this research study because you are a healthy adult who is interested in being a participant in a clinical trial. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any

words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.
Please tell the study doctor or study staff if you are taking part in another research study.
David MacLeod, MD will conduct the study and it is funded by Pacira Pharmaceuticals, Inc. The sponsor of this study, Pacira, will pay Duke University to perform this research, and these funds may reimburse part of Dr. MacLeod's salary.

Two of the members of Dr. MacLeod's study team, Drs. Jeffrey Gadsden and William Michael Bullock, have received personal compensation from Pacira Pharmaceuticals, Inc. in the past for consulting and/or speaking engagements and may receive such compensation in the future.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. MacLeod will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to assess the safety and tolerability of EXPAREL (the study drug) administered as a single intrathecal injection in healthy volunteers. An intrathecal injection is an injection into a space in the spinal column.
The study drug is a liposome (surrounded in fat molecules) injection of bupivacaine, (an FDA approved drug used for pain). Bupivacaine acts by numbing the body area around where it is given, decreasing pain and other sensations.

Pacira is conducting this research to study the safety and tolerability of the study drug for intrathecal injection. Another purpose of this study is to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profile of the study drug administered as a single spinal (intrathecal) injection in healthy volunteers. Pharmacokinetics and pharmacodynamics, respectively, look at what the body does to the drug and how the drug works.

The study drug has been approved by the U.S. Food and Drug Administration (FDA) to control postsurgical pain in adult subjects by injecting around the surgical area and around nerves in the shoulder. However, study drug used this way is considered an investigational drug. An "investigational drug" is not approved by the United States by the Food and Drug Administration (FDA). In this study, the study drug will be used as an intrathecal (spinal) injection.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 60 subjects will be asked to take part in this study at Duke.

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WHAT IS INVOLVED IN THE STUDY?
If you choose to participate, you will be randomized (chosen by chance—like drawing numbers from a hat) into one of the 3 study groups: You will receive (1) the study drug, (2) bupivacaine, or (3) placebo (for example, saline) by injection into the spinal region.

There are 4 sets (also referred to as "cohorts") in this healthy adult (aged 18-50 years) study. Each cohort will enroll approximately 10 healthy adults. Each cohort will have six subjects receiving the study drug, two subjects receiving bupivacaine and two receiving placebo via a single intrathecal (spinal) injection. If you are randomized to receive the study drug, you will also be randomized to either provide a cerebrospinal fluid (CSF, fluid found within the spinal column) sample (four subjects will be randomized to this subgroup) or not provide a CSF sample (two subjects will be randomized to this subgroup). You will not know if you will be providing a CSF sample or not in this group. If you receive bupivacaine or placebo, you will provide a CSF sample.

Cohort 1 includes adults who will receive 1mL (less than ¼ of a teaspoon) of the study drug, Cohorts 2, 3 and 4 will receive 2mL, 3mL and 4mL (a little less than 1 tsp) of the study drug respectively, through injection into the spinal region. After Cohort 1 has completed enrollment, the safety, pharmacokinetic and sensory/motor information will be reviewed for the study before enrollment continues in Cohort 2. Cohorts 3 and 4 will also enroll sequentially following the review of safety information from the previously completed cohort.

Neither you nor the study staff will know which study drug you will be receiving. The study doctor can find out immediately what you are receiving in an emergency, if the information is necessary to treat the emergency.

<u>Screening Visit</u>
At this visit, you will be asked to read this informed consent form (ICF) and, if you agree to be in the study, you must sign and date this informed consent form before any study procedures can be done. You are strongly encouraged to review this informed consent form thoroughly and make sure that all of your questions/concerns are answered by your study doctor prior to signing this form. Once the informed consent form is signed and dated by you and the study staff member reviewing this informed consent form with you, then you will be provided a copy of the informed consent form for your records.

Also during this visit, the study staff will conduct the following assessments:
- Review the requirements of the study
- Explain the study purpose and procedures
- Answer any questions you might have relating to your taking part in the study
- Ask you to sign the consent form
- Record your relevant medical/surgical history

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- Complete a physical examination
- Record vital signs (such as heart rate, blood pressure, cardiac output, respiratory rate, end tidal carbon dioxide [CO_2] and oxygen [O_2] saturation of your blood)
- Complete a 3-lead electrocardiogram (ECG, which reads the electrical activity of your heart)
- Conduct an alcohol breath test and urine drug screen
- Conduct a urine pregnancy test for women of childbearing potential
- Complete clinical laboratory tests (hematology and chemistry). This will require 8.5mLs (or about 2 tsp) of blood.
- Ask you answer questions for a neurological history questionnaire
- Record any medical conditions that you experience once the ICF is signed

Day of Study Drug Administration (Before Administration)

Before you receive any study drug, the study staff and study doctor will check to see if you are still able to continue to take part in the study. They will ask you questions about any medication changes and how you are feeling. You will be asked to not to consume any solid food for 6 hours and can consume clear fluids until 2 hours prior to drug administration.

At this time, the study team will do the following:

- Access vital signs (heart rate, blood pressure, respiratory rate, cardiac output, end tidal CO_2 and O_2 saturation) (up to 3 hours before you receive study drug) and continue monitoring (every 15 minutes for two hours after study drug administration) and until you leave the EPRU
- Conduct a 3-lead electrocardiogram (ECG) up to 3 hours before you receive study drug
- Re-confirm urine pregnancy test for women of child bearing potential (if day of administration not the same day as screening)
- Record changes to any medications you are or have taken since screening
- Record any adverse (bad) events and any treatment(s) for these events
- Perform sensory and motor tests up to three hours before you receive study drug
- Record responses to neurological history questionnaire (up to 3 hours before you receive study drug)
- Complete comprehensive neurological assessment (up to 3 hours prior to drug administration) which would include assessment of proprioception, tone, coordination, vibration, gait, sensory/motor tests, and reflexes (knee, ankle and plantar).
- Obtain blood sample up to 30 minutes before you receive study drug
- Ask you to void urine up to 30 minutes before you receive study drug
- Confirm that you will be able to participate in the study based on the participation criteria

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Study Drug Administration

On the day of study drug administration, the study team will collect a CSF sample (3mL or about ½ teaspoon) except if you were randomized to a particular subgroup of the cohort. You will not know which subgroup you are in. This will be done up to five minutes before study drug injection. Taking a CSF sample is similar to the way blood is taken from your vein. The difference is the fluid taken is CSF (not blood) and it is taken from your spinal column (not a vein).

Following this, study drug will be administered by injection into the spinal area. The injection would be provided after ultrasound confirmation of the location. Neither you nor the study doctor or study staff will know what you will receive as you will be randomized in the study.

Blood samples will be taken at various time points after you receive study drug. Blood samples will be taken to assess the amount of study drug in your system at different time points in order to evaluate how long it lasts. This will be done up to thirteen (13) times following drug administration and one (1) time prior to drug administration.

Blood and CSF samples will be collected over the course of the first six (6) days of the study.

Blood samples will be taken to assess the amount of study drug in your system at different time points in order to evaluate how long it lasts. At each of the time points, approximately 2ml (1 teaspoon) of blood will be collected. These samples will be shipped to the United Kingdom for testing. These samples will be kept up to two (2) years after study results are published. The samples may be re-analyzed or utilized in future research. The samples may be used to re-assess the amount of drug in your system or to measure other biomarkers in your blood, indicative of your body function. You may decline to consent to future use and still participate in the main study.

After Study Drug Administration

The following will take place throughout your stay in DEPRU:

- On Day 1, sensory and motor tests will be performed every 15 minutes (+15 minutes) for two hours after you receive study drug
    - If onset of sensory/motor block is noted after the initial 2 hours post study drug administration, the sensory and motor assessments will continue every 15 min (±15 min) until recovery of sensory and motor block is noted on 2 consecutive assessments
    - If there is no onset of sensory/motor block after the initial 2 hours post study drug administration, assessments will be conducted every 2 hours (±30 min) until 10pm
- Complete motor assessments, recording when you are allowed to sit up from laying position and from sitting to standing position.
- Sensory and motor tests will be performed Day 2 through Day 5 (from 6AM to 10PM)

  - If continuation or onset of either sensory or motor block is observed, the assessments will be conducted every 2 hours (±30 minutes) until full sensory and motor recovery is seen on two consecutive assessments.
  - In the absence of sensory and motor block, assessments will be conducted every 4 hours (±1 hour) until 10pm.
- Sensory and motor tests will be performed at night from Day 1 through Day 5 (from 10 PM to 6 AM):
  - If any motor block is noted at the last assessment of the day, repeat motor assessments will be conducted every 2 hours (±30 minutes) throughout the night
  - If no block or only sensory block is noted at the last assessments of the day, sensory and motor assessments will be conducted every 4 hours (±1 hour)
- Sensory and motor tests will also be performed on Day 6 (at DEPRU discharge), Day 9 follow-up visit, and in the event of an adverse event.
- Recording of your responses to the neurological history questionnaire (up to Day 30)
- Continuous collection of vitals and 3-lead ECG (every 15 minutes) for 2 hours after study drug administration, and once daily around noon (±4 hours)
- Following the first 2 hours, we will collect specific vital signs (blood pressure, heart rate, oxygen saturation), and an ECG in combination with every sensory and motor assessments (up to Day 6 – DEPRU discharge). In addition, all vitals will be measured once a day throughout the course of your stay in the DEPRU. Your heart rate, blood pressure and oxygen saturation will be monitored overnight.
- Recording of any adverse events and any treatment for the events
- Monitoring of vital signs and ECG (up to Day 6 – DEPRU discharge)
- Bladder function monitoring will be performed every 4 hours (±30 minutes) Day 1 through Day 6 (at DEPRU discharge)
- CSF samples (3mLs or about ½ tsp each) will be collected three times: at 24 hours (±6 hours), 48 hours (±6 hours), and 96 (±6 hours) after you receive study drug.
- Blood samples will be taken 12 times after drug administration: at 5 min (±5 min), 1(±1 hr.), 3(±1 hr.), 6(±1 hr.), 12(±1 hr.), 15(±1 hr.), 20(±1 hr.), 24(±1 hr.), 30(±4 hr.), 42(±4 hr.), 96 (±4 hr.) and 120(±6 hr.) hours after you receive study drug.
- Complete a neurological assessment (this will include sensory and motor function tests, as well as bilateral (both sides) symmetrical reflex assessments) Day 6 (at DEPRU discharge)
- IV fluids may be provided as needed

Sensory test: ability to tell whether the skin sensation feels normal or numb (sensory loss) when tested with a needle

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Motor test: ability to move muscle groups of the lower extremity (e.g. push your foot down on the gas, bend your knee off the bed) and ability to stand and perform simple movements (e.g. pick items off the floor, turn without losing balance).

Bladder function monitoring: bladder function responses, collection of date and time of bladder scans, urinary catheterization (a procedure of inserting a long thin tube into the urinary bladder), and urine volumes.
The total amount of blood drawn for this study will not exceed 78.5mL (about 5½ tablespoons). Blood samples will be drawn from a catheter (IV) placed in your arm. If these blood samples cannot be drawn from the placed catheter, additional sticks (venipunctures) may be needed to obtain the study samples.

At the time of discharge from DEPRU, you will be asked for your responses to the neurological history questionnaire, as well as perform sensory and motor tests.

The total amount of CSF drawn for this study will not exceed 12mLs (about 2 ½ teaspoons).

Follow-Up Visits
Your study doctor or the study staff will ask you to come back to the clinic on Day 9, and answer questions by phone at the Day 30 visit. During these visits, you will be asked to do the following:

- At Day 9 and Day 30, provide responses to the neurological history questionnaire
- At Day 9 and Day 30, complete motor and sensory tests
- At Day 9, tell the study staff if you have had any adverse events, and any treatments for the events
- At Day 30, tell the study staff if you have had any admissions to the hospital, emergency department visits, office visits, or phone calls to a physician.

Please tell your regular health care providers and any emergency care providers that you are participating in this research study.

HOW LONG WILL I BE IN THIS STUDY?
If you choose to participate in this study, the screening period will last for up to 30 days prior to study drug administration. You will be followed up for up to 30 days after you receive treatment. You will stay in the Duke Early Phase Research Unit (DEPRU) following study drug administration until Day 6 when you will be discharged. You will be asked to return to DEPRU on Day 9 for a follow-up visit. You will also receive a follow-up phone call on Day 30. Your participation in this study will be complete after your 30-day phone call (±3 days). Therefore, you may participate in the study for up to 63 days.

You will have as much time as you need to read, sign, and return this informed consent form to your study doctor. Providing you with this form for information on the study, allowing you to read the form

and ask question, and having you sign this form will all take place prior to any study-related procedures take place.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT WOULD PREVENT ME FROM BEING ALLOWED TO TAKE PART IN THIS STUDY?

Anyone taking part in this study must meet certain conditions. If you do not meet all of these conditions, you will not be allowed to take part in this study. Your study doctor can explain these conditions in detail. In general, you cannot be in this study if you:

- Have an allergy, hypersensitivity, intolerance, or contraindication to any of the study medications for which an alternative is not available per the study (e.g., amide-type local anesthetics, opioids, bupivacaine, NSAIDs, spinal anesthesia).
- Have impaired renal or hepatic (liver) function (e.g., 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 >1.5 times the upper limit of normal [ULN], or serum alanine aminotransferase [ALT] level >1.5 times the ULN).
- Are at an increased risk for bleeding or have a coagulation disorder (defined as platelet count less than 80,000 × 103/mm3).
- Have concurrent painful physical condition that may require analgesic treatment (such as long-term, consistent use of opioids) in the post-dosing period for pain and which may confound the post dosing assessments.
- Are a woman of childbearing potential and do not have a documented negative pregnancy test at screening which must be confirmed on the day of drug administration. However, if you are postmenopausal, you must have a documented follicle stimulating hormone (FSH) test confirming menopause at screening.
- Are currently pregnant, nursing, or planning to become pregnant during the study or within 30 days after completion of the study.
- Have a positive serology (blood) test result for human immunodeficiency virus (HIV), Hepatitis B virus, or Hepatitis C virus.

- Have a clinically significant abnormal ECG (electrocardiogram, or reading of your heart's electrical activity) that in the opinion of the investigator would preclude the subject from participation in the study.
- Have previously participated in a study sponsored by Pacira.
- Have a history of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s), or alcohol within the past 2 years.
- Have received administration of an investigational drug within 30 days or 5 elimination half-lives such a study 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. (The half-life of a drug is the time it takes about half of the drug to leave the body after it has been taken.)

If any of the above conditions apply to you, you may not participate in this study.

WHAT ARE THE RISKS OF THE STUDY?
It will be important to inform your study doctor and study staff of any changes to your health and any complications that you notice while participating in this study.

Risks of EXPAREL (the study drug)
The study drug contains an FDA-approved drug known as bupivacaine. Bupivacaine is one of the commonly used, longer-acting numbing drugs (anesthetics). The effect of bupivacaine (immediate release formulation) or other anesthetics is limited to usually no more than 12 hours and the effect of the study drug (extended release of bupivacaine) lasts approximately 72-96 hours when injected around the area of the incision during surgery or by nerve block. Serious side effects related to bupivacaine are not common but may occur if too much is given or if it is injected into a blood vessel instead of under the skin or around the nerves (Local Anesthetic Systemic Toxicity).

Side effects may involve the central nervous system (the brain and spinal cord) such as:
- restlessness
- anxiety
- dizziness
- tinnitus (ringing in the ears)
- blurred vision
- tremors (shaking), possibly leading to convulsions

Reaction to bupivacaine given near the spinal cord is very rare but may include
- Urinary retention and bladder distension
- Back pain radiating to the legs (Transient Neurological Symptoms)

- Paralysis, coma, respiratory and cardiovascular distress (total spinal anesthesia)
- Tingling or weakness in legs, lower back pain, sensory disturbances in the genital area, bowel or bladder disturbances (Cauda Equina Syndrome)

When too much bupivacaine is given or when bupivacaine is injected in a blood vessel by accident, these include side effects such as:

- low heart rate or abnormal heart rhythm
- decreased blood flow
- low blood pressure

A numbing sensation caused by bupivacaine may be persistent, with slow, incomplete, or no recovery. Sometimes, a tingling sensation may appear in the area injected with bupivacaine. When injected next to a large nerve, bupivacaine may cause weakness or paralysis.

Allergic reactions to bupivacaine are rare, but may include:

- rash, itching, and redness of the skin
- a fast pulse
- sneezing
- wheezing
- having a hard time breathing
- inability to breathe without assistance
- swelling around the eyes and mouth, or swelling of the throat
- nausea
- vomiting
- a sudden drop in blood pressure (causing dizziness or fainting)
- sweating
- a feeling of dread
- fever
- loss of joint cartilage (chondrolysis)
- impaired oxygen release to tissues (methemoglobinemia)
- low blood pressure (hypotension)

If you have any of these symptoms or any other side effects during the study, you should get medical help and then call your study doctor.

The safety of the study drug has been studied in previous local infiltration studies where the study drug doses were evaluated at 66mg up to 532mg. Adverse reactions reported in all local infiltration studies were:

Most common (incidence greater than or equal to 10%, or 10 in 100 people experience):
- nausea
- constipation
- vomiting

Common (incidence greater than or equal to 2% to less than 10%, or less than 2 and up to 10 people in 100 experience):
- fever (pyrexia)
- dizziness
- excess fluid in the body (edema peripheral)
- low red blood cell count (anemia)
- low blood pressure (hypotension)
- itching (pruritus)
- headache
- low red blood cell count (anemia postoperative)
- muscle spasms
- low red blood cell count (hemorrhagic anemia)
- back pain
- deep sleepiness (somnolence)
- post-surgery pain (procedural pain)
- insomnia

The less common/rare (incidence less than 2%, less than 2 in 100 people experience):
- chills
- skin inflammation (erythema)
- joint inflammation (arthralgia)
- joint swelling
- low heart rate (bradycardia)
- loss of joint cartilage (chondrolysis)
- anxiety
- urinary retention
- pain
- excess fluid (edema)
- shaking (tremor)
- tingling (paresthesia)
- fainting (syncope)
- muscular weakness
- neck pain
- pale skin (pallor)

- rash and itching (pruritus)
- excessive sweating (hyperhidrosis)
- cold sweat
- palpitations
- irregular heartbeat (atrial and ventricular arrhythmias)
- high blood pressure (hypertension)
- confusion
- depression
- agitation
- restlessness
- hives (urticarial)
- low oxygen (hypoxia) suspended breathing (apnea)
- respiratory depression
- respiratory failure
- oxygen saturation decreased
- leaky bladder (urinary incontinence)
- blurry vision
- ringing in the ears (tinnitus)
- drug reaction (hypersensitivity)
- vocal cord spasm (laryngospasm) cardiac arrest

Side effects that affect the central nervous system with an occurrence greater than or equal to 1% (greater than 1 in 100 people) following study drug administration were:

- dizziness
- headache
- deep sleepiness (somnolence)
- numbness (hypoesthesia)
- tiredness (lethargy)

Side effects that affect the heart with an occurrence greater than or equal to 1% (greater than 1 in 100 people) following study drug administration were:

- high heart rate (tachycardia)
- low heart rate (bradycardia)

Please tell the study doctor or study staff right away if you have any of these side effects or any not listed. Even if you have told the study doctor or study staff, tell them if any side effects become get worse or become serious.

Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these problems are related to the study drug.

It is possible that receiving study drug or bupivacaine may change how your regular medications, vaccines, or supplements work. It is very important that you tell the study doctor about any medications, supplements, or vaccines before you take them during the study.

Risks of Procedure and Cerebral Spinal Fluid (CSF) Draw

The administration of study drug will be through intrathecal injection, in which a needle is used to inject the study drug into the spinal canal so that it reaches the cerebrospinal fluid. You may also be required to provide CSF samples depending on the group that you have been randomized to. You will also provide blood samples, regardless of your randomization. You may have pain, bleeding or bruising at the site where the injection is given (or sample is taken). You may feel dizzy or you may faint. For most people, needle punctures for injections do not cause any serious problems. Sometimes people complain of discomfort and/or pain at the site of the injection. Rarely, injections may cause skin and/or soft tissue infections.

There is a low risk that germs could enter into the blood system when a needle is inserted into the blood vessel, which could cause a serious infection. There is a low risk of this (<0.5%, that is it occurs in less than 1 in 200 people), and is associated with the size of the needle used. The smallest needle will be used in this study. When CSF fluid is removed from the body, the risks include headache, brain herniation and infection. Each of these risks are very uncommon except for headache, as this may appear from hours to up to a day after a CSF fluid is removed from the body. If the headache is severe then the anesthesiologist can perform an 'epidural blood patch', which has a high rate of success in reducing or eliminating the headache.

Reproductive Risks

The risks to the embryo, fetus, or infant from exposure to the study drug are unknown. Some drugs cause premature (early) birth or birth defects. For these reasons, women who are pregnant, planning a pregnancy, or breastfeeding are not allowed to participate in this study.

If you are a woman who could possibly become pregnant and you have a partner who is able to father children, urine pregnancy tests will be performed at study visits as described above. Please talk to the study doctor about methods of birth control. You should use an effective method of birth control for the duration of the study and for 30 days after the completion of the study.

If you suspect that you have become pregnant while participating in the study, tell the study doctor immediately.

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Risk of Loss of Confidentiality
There is a risk of loss of confidentiality of your information. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

Risks of Blood Draws
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
You will not receive any immediate direct benefits from being in this study. However, we hope the knowledge obtained from the results of this study may be of benefit to you or others in the future.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests and procedures may be reported to Pacira and its affiliates. In addition, your study and/or medical records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives and affiliates of Pacira, the Duke University Health System Institutional Review Board (IRB), and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain tests and/or procedures performed. These test results may be recorded in your medical record or shared with your physician(s) and will be reported to the representatives and affiliates of Pacira.

The study results will be retained in your research record for at least six years after the study is completed. At that time the research information may be destroyed or information identifying you will be removed from such study results.

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This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

Your medical and study information may be used for the following purposes:

- As information in this research study.
- Publication or other sharing of study results, data, and other information (such as in professional writings, at professional meetings, and in the sponsor's product information and/or advertising or other promotional materials) in a manner that will not reveal your personal identity. Your name will not be disclosed, and your personal information will be treated confidentially.
- Study results submitted to regulatory authorities, such as the FDA, for approval to commercially market or approve of uses for the study drug.
- To fulfill the regulatory authorities' reporting requirements or other requirements by federal law or by the sponsor's policies or procedures regarding clinical research.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS (Duke University Health System), we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

Your blood and CSF samples will not be labeled with your name or other directly identifying information. Your samples will have a code (your subject number and initials) instead. The list that matches the code with your name and information will be stored separately from your samples. If you refuse to have your samples kept for future potential analysis, this will not affect your participation in the study or care provided to you by your doctor and staff.

If you change your mind later, be aware that your samples may not be withdrawn from the research.

If you choose not to authorize this use and sharing of your information to the groups identified above, this will not affect your right to regular medical care, but you cannot be in this research study and you should not sign this form.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
ADULT
Phase 1, Randomized, Double-Blind, Active and Placebo Controlled, Dose Escalation Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of EXPAREL Administered via a Single Intrathecal Injection to Healthy Volunteers

This authorization to use and share your information expires in 50 years.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT OTHER OPTIONS DO I HAVE?
You do not have to participate in this study. This study is not designed to diagnose, treat or prevent any disease. Your alternative is to not participate.

WHAT ARE THE COSTS TO YOU?
There will be no cost to you for the study procedures and supplies related to this study.
The study sponsor Pacira has agreed to pay for services and procedures that are done solely for research purposes. Please talk with the PI/study team about the specific services and procedures that the sponsor will pay for.

We will monitor your DUHS care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

At the end of the study, or if you decide to withdraw from the study before it ends, the study doctor may request that you return for a checkup and may ask you to complete the tests that would ordinarily occur when a person completes the study.

WHAT ABOUT COMPENSATION?
You will be reimbursed up to $2,000 for your expenses related to your participation (parking, gas, and time): Screening $25, Day1-6 $200 per day (up to $1200), Day 9 $275, Day 30 $500. You will also receive parking passes for your Screening and Day 9 visits. If you decide to withdraw from the study, you will be paid for the portion of the study you have completed.

Additional travel reimbursement (parking, gas, and hotel) might be available for subjects living outside of the local Raleigh/Durham area and could be considered per PI discretion.

Payment received as compensation for participation in research is considered taxable income to the research subject. If payment to an individual exceeds $600 in any one calendar year, Duke University is required to report this information to the Internal Revenue Service (IRS). Research subject payments to a non-employee of Duke University exceeding $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

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WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physician to provide monetary compensation or free medical care in the event of a study-related injury.

If you are injured as a direct result of the study drug or a protocol procedure that you would not have had but for your participation in the study, the study sponsor, Pacira Pharmaceuticals, Inc., will reimburse for reasonable and necessary medical care expenses incurred for diagnosis and treatment, provided all aspects of the study protocol have been properly performed and your injuries are not due to the natural progression of an underlying or pre-existing condition or events, unless exacerbated by participating in the study.

For questions about the study or research-related injury, you should contact Dr. David MacLeod at (919) 812-3201 during regular business hours and by pager at (919) 970-7963 after hours and on weekends and holidays.

CAN MY PARTICIPATION IN THIS STUDY BE STOPPED?
Yes. Your participation in this study may be stopped by the study doctor, the IRB, the FDA, or the sponsor without your consent for any of the following reasons:
- If the study procedures appear to be medically harmful to you.
- If you fail to follow directions.
- If it is discovered that you do not meet the study requirements.
- If the study is canceled.
- If it is determined to be in your best interest.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. MacLeod in writing and let him know that you are

withdrawing from the study. His mailing address is 5695 HAFS Building, 2301 Erwin Road, Durham, NC, 27710.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your samples and data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.
The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. MacLeod at 919-812-3201 during regular business hours and at 919-970-7963 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

USE OF SAMPLES FOR FUTURE RESEARCH
Please initial one of the following to indicate:

_____ I agree to allow my samples to be kept up to two (2) years after study results are published. The samples may be re-analyzed or utilized in future research.

_____ I do not agree to allow my samples to be kept up to two (2) years after study results are published, and re-analyzed or utilized in future research.

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STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____
Printed Name of Subject

_____ _____ _____
Signature of Subject Date Time

_____
Printed Name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time