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INTEGREVIEW IRB
DECEMBER 21, 2018

INFORMED CONSENT DOCUMENT
AGREEMENT TO BE IN A RESEARCH STUDY

NAME OF SPONSOR COMPANY:	Pfizer Inc
NUMBER AND NAME OF STUDY:	B4541023**;** "A PHASE 1, OPEN-LABEL, RANDOMIZED, TWO-WAY, SINGLE-DOSE, CROSSOVER STUDY IN HEALTHY VOLUNTEERS TO ASSESS THE BIOEQUIVALENCE OF MORPHINE FOLLOWING ADMINISTRATION UNDER FASTING CONDITIONS OF PF-06412528 (EMBEDA®) 60 MG/2.4 MG CAPSULES MANUFACTURED AT COATING PLACE COMPARED WITH CAPSULES MANUFACTURED AT ACTAVIS"
NAME OF PERSON IN CHARGE OF THE RESEARCH STUDY (STUDY INVESTIGATOR):	Mary Powell-St. Louis, M.D., MPH
TELEPHONE NUMBER 24 HOURS:	203-401-0300

INTRODUCTION

You are here today as a possible volunteer in a drug research study sponsored by Pfizer Inc. Whether or not you are in this study is strictly up to you. You may refuse to take part in this research study. The study staff will be available to answer questions before, during, and after the study.

The sponsoring company (the company paying for this study), Pfizer Inc, employs the study investigator conducting this study.

If you are not completely honest about your health history, you may be harmed by being in this study.

INFORMATION ABOUT THE STUDY DRUG

PF-06412528 (Embeda®) will be referred to as "the study drug" in the rest of this document.

The study drug is a marketed drug approved by the Food and Drug Administration (FDA) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment. It is approved in adults only for use for when other treatments are not adequate. The study drug is a combination of morphine sulfate and naltrexone hydrochloride (HCl). The study drug is designed to slowly release morphine sulphate where as naltrexone HCl is released only when the drug is manipulated. Morphine is a strong narcotic pain reliever. Naltrexone HCl counteracts or blocks the actions of morphine, such as drug-liking and feelings of well-being, which can lead to addiction. Capsules of study drug containing up to 100 mg/4 mg (morphine sulfate/naltrexone HCl) are marketed for prescription to patients with severe pain. In this study, a 60 mg/2.4 mg dose will be used. Study drug will be given orally (by mouth) as a capsule to be swallowed whole.

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The study drug is currently being made at a location in New Jersey (Actavis). The manufacturing process is being moved to a new location in Wisconsin (Coating Place). This study is being done to show that the study drug manufactured in the new location acts in the same way in the body as the study drug made at the current location. This is done by measuring the amount of morphine and naltrexone in the blood after dosing.

The study has two periods. Up to 30 subjects are planned for the study. If you are accepted into the study you will receive a single oral dose of study drug in each period. In one period you will receive the study drug made at Actavis. In the other period you will receive the study drug made at Coating Place. The order in which you receive each dose will be randomly assigned, like the flip of a coin.

In this document, you may see the terms "medication", "treatment", and "treatment period". These are terms used in research studies as mentioned above. This does not mean that you will be receiving medical treatment for any condition. These terms apply to the investigational study drug and parts of the study where you will be receiving it.

The study investigator or sponsor may decide to remove you from the study at any time if it seems you are having a significant reaction to the study drug.

PURPOSES OF THE STUDY

There are 5 purposes of this study:

1. To assess the bioequivalence of morphine after single oral doses of intact study drug capsules manufactured at Coating Place and Actavis when given under fasting conditions in healthy volunteers
   - Bioequivalence means that the morphine in the capsules at each manufacturing location has the same effects within and on your body
2. To measure the amount of morphine in your blood after single oral doses of intact study drug capsules manufactured at Coating Place and Actavis when given under fasting conditions in healthy volunteers
3. To see how the study drug is tolerated, if there are significant side effects, and how people feel after taking it
4. To measure the amount of naltrexone and 6-β-naltrexol (a by-product of naltrexone) after single oral doses of intact capsules manufactured at Coating Place and Actavis when given under fasting conditions in healthy volunteers
5. To collect exploratory samples for biobanking
   - Biobanking is the collection and storage of blood samples for possible future testing

HOW LONG THE STUDY WILL LAST AND HOW MANY PEOPLE WILL BE IN THE STUDY

You will be in this study up to about 44 days. This does not include the time between screening and dosing, which can be up to 28 days.

This study involves:

- 2 dosing periods (during one continuous admission)
- 12 overnight stays
- 1 follow-up phone call (between 28 and 35 days after the last dose of study drug)

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There will be at least 7 days between each dose.

Up to 30 healthy male and female subjects between the ages of 18 and 55 will be in this study.

WHEN ARE YOU ELIGIBLE TO PARTICIPATE IN ANOTHER DRUG STUDY?

The decision for when you are eligible to screen for another study is based on information from the previous studies and this study. You may be eligible to dose in another study as soon as 30 days after the last dose of study drug. This information is true for most drugs. Some drugs may be present in your body longer and that may mean you may have to wait longer before entering into another study. These results are usually known after your last regularly scheduled blood sample is tested. We will always tell you this as soon as possible. We will let you know if there is a longer than usual period of time that you should not be in another drug study after this one. Our goal is to keep you from doing anything that might potentially harm you. Your safety while in these studies is our main concern.

The half-life of the study drug is about 29 hours. The half-life of a drug is the time it takes for the amount of the drug in the body to decrease by half. It is expected that very little, if any, study drug will remain in your body after 6 days.

TO BE IN THE STUDY

You cannot screen for this study if you are currently in another research study. This includes being in the follow-up visit period of another research study.

To be in this study, your medical history and screening test results must be acceptable. Also, you must meet each of the following conditions:

- You must be a healthy male or female between the ages of 18 and 55 at the time of screening
- Females unable to have children must meet one of the following criteria:
  - Postmenopausal (at least 12 consecutive months without a period with no other medical cause and a blood test confirming that you are unable to have children)
  - Uterus and/or both ovaries removed (documented)
  - Medically confirmed ovarian failure
- You must have a body mass index (BMI) between 17.5 and 30.5 and weigh more than 50 kg (110 lbs)
- You must have signed and dated this consent form
- You must be willing and able to comply with scheduled visits, the study plan, lab tests, and other study procedures
- You must not have evidence or a history of blood, kidney, glandular, lung, stomach, intestine, heart, blood vessel, liver, psychiatric, nerve, or allergic disorders (including drug allergies)
  - Untreated seasonal allergies without symptoms are allowed
- You must not have any condition that might affect your body's ability to absorb drugs (for example, gastric bypass surgery)
- You cannot be in this study if you are using/taking any drugs of abuse. A urine test will be done to check for drugs of abuse
- While on this study please do not eat anything that contains poppy seeds, as they may cause a positive drug test

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- You must not have a history of excessive alcohol use within 6 months before screening
  - Females must not drink more than 7 alcoholic drinks a week
  - Males must not drink more than 14 alcoholic drinks a week
  - A drink is defined as 12 oz. of beer, 5 oz. of wine, or 1.5 oz. of hard liquor
- Study staff may check your breath for the presence of alcohol. If alcohol is detected, you will not be allowed to be in this study
- You must not have taken any investigational drugs for at least 30 days before the first dose of this study
  - You must not be in another drug study at any time during this study
- Your screening blood pressure while lying down must be less than or equal to 139/89 mm Hg
- Your screening ECG (electrocardiogram that measures the electrical activity of the heart) must be normal
- You must not have any of the following laboratory test abnormalities:
  - Liver enzymes (indicate how your liver is working) greater than or equal to 1.5 times the upper limit of normal
  - Total bilirubin greater than or equal to 1.5 times the upper limit of normal, or a direct bilirubin (for subjects with Gilbert's syndrome – a harmless mild liver condition in which the liver does not properly process bilirubin) greater than the upper limit of normal
- Female subjects must not be pregnant or breastfeeding
- Male subjects must not have a pregnant or breastfeeding partner
- Male subjects able to father children and female subjects able to have children must be able and willing to use a highly effective method of birth control (detailed later in this document) for the duration of the study through at least 28 days after the last dose of study drug
- You may not take any prescription or nonprescription drugs, or nutritional (dietary) supplements for at least 7 days before the first dose or at any time during this study
  - Tylenol® (acetaminophen) may be used at doses of less than or equal to 1,000 mg a day
    - Its use must first be approved by the study investigator
    - Other nonprescription medicines that are not thought to affect your safety or the overall study results may be allowed on a case-by-case basis if first approved by the study investigator
- You may not take herbal supplements (including St. John's Wort) within 28 days before the first dose or at any time during this study
- Hormone replacement therapy and hormonal methods of birth control are allowed
- You must not have donated (such as at a blood bank) a unit of blood (except plasma donations) for at least 60 days before dosing
- You must not donate any blood or blood products at any time during this study and for at least 4 weeks after your last blood draw
- You must not have a history of sensitivity to heparin (a substance that stops blood from clotting) or of low platelets (cells that help with blood clotting) as a result of heparin
- You must not have a history of allergy or hypersensitivity to morphine, naltrexone, or any components of Embeda®
- You must not have a history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C or a positive result for any of the following blood tests: HIV, hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb)

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- You must be willing and able to comply with the activity and diet restrictions of the study (detailed later in this document)
- You must not be a staff member of the Clinical Research Unit (CRU) directly involved in the study, a relative of a staff member at the CRU directly involved in the study, a staff member of the CRU supervised by the study investigator, or a Pfizer employee, including family members, directly involved with the study
- You must not have any medical or psychiatric condition, including recent (within the past year) or active suicidal thoughts or behavior, or lab abnormality that could increase your risk of being in the study or receiving the study drug
  - You must not have any condition or lab abnormality that could interfere with the interpretation of the study results and, in the judgment of the study investigator, make you an inappropriate subject for this study
- During the study, it is required that all male subjects use condoms to prevent the potential transfer of drug through the semen to their partner beginning with the first dose of study drug through the duration of the study and for at least 28 days after the last dose, as the effects of the study drug on sperm are unknown
- Male subjects must not donate sperm for the duration of the study through at least 28 days after the last dose

WHAT WILL HAPPEN DURING THE STUDY

Screening:

Before the study starts, you will be asked to:

- Sign this consent form
- Review the study entry criteria
- Give your race, age, gender, and ethnicity
- The use of appropriate birth control will be reviewed
- Give your medical history
  - If you are not completely honest with your medical history, you may be harmed by being in this study
- Give your drug, alcohol, and tobacco use history
- Tell the study staff if you have taken in the past 28 days, or are taking, any over-the-counter or prescription drugs, vitamins, or dietary or herbal supplements
- You will be asked "How do you feel?"

As part of screening you must complete all of the items listed below:

- Vital signs (blood pressure, heart rate, and breathing rate) while lying down
- Height and weight
- Safety lab tests (blood and urine)
  - Includes blood tests for HIV, HepBsAg, HepBcAb, and HCVAb
- Urine to test for drugs of abuse (illegal and prescription)
  - If this test is positive, you will not be allowed in the study
  - Urine collection may be monitored by a staff member of the same sex
  - You have the right to refuse to be monitored, but may be disqualified from the study
- The study investigator may decide to do an alcohol breath test

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- ECG
- Complete physical exam. This may be done at screening or when you check-in for Period 1 of the study
- Females able to have children will have a blood pregnancy test
- Females who have not had a period for at least 12 consecutive months will have a blood hormone test that will confirm they cannot have children

HIV and Hepatitis Testing:

As required by this study, and if anyone is exposed to your blood, you will have your blood tested for the hepatitis viruses and for HIV. HIV is the virus that causes acquired immune deficiency syndrome (AIDS). If you have a positive HIV or hepatitis test, you cannot be in/remain in the study.

If the HIV test is positive, a follow-up test will be done. If the follow-up test is also positive, you will be told in private and you will also be told about counseling.

It may take weeks or months after being infected with HIV for the test to be positive. The HIV test is not always right.

Positive results for HIV or hepatitis tests or for other infections, or possibly having certain infections, may have to be reported to the State Department of Health. If you have any questions about what information is required to be reported please ask the study investigator or study staff.

Although this testing is intended to be private, complete confidentiality cannot be guaranteed. For example, it is possible for a court of law to get health or study records without your permission.

During the Study:

During the study you will complete all of the items listed below:

- Before being brought to the second floor of the clinic for your in-house stay, your belongings will be thoroughly searched
  - You will be asked to empty your bags and set all of your belongings on the table so the staff can go through them
  - You will be asked to empty your pockets, remove your shoes and hat, if you are wearing one, and you will be patted down
  - You will be scanned with a metal detector wand
- Review the study entry criteria (Period 1 only)
- Updates to your medical history, including drug, alcohol, and tobacco use (Period 1 only)
- Updates in any medications used since screening
- Blood and urine samples will be collected at various times throughout the study
  - The blood and urine samples will be used for safety labs
    - Any leftover blood from the samples collected for safety labs may also be used for exploratory safety biomarkers (natural substances present in your body that can be used to indicate how your body works) or unexpected safety findings
    - Samples to be used for this purpose will be kept for up to 1 year following completion of this study

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  - Blood samples will also be used to measure the levels of morphine, naltrexone, and 6-β-naltrexone
    - As part of understanding how your body absorbs, distributes, and gets rid of morphine, naltrexone HCl, and 6-β-naltrexol, the samples may also be used for metabolite identification (by-product(s) or end product(s) of a drug produced as the body processes a drug) and/or evaluation of the laboratory test(s) used to measure morphine, naltrexone HCl, and 6-β-naltrexol, as well as for other internal exploratory purposes
- A sample of your blood will be collected to study your biology (such as deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, and metabolites). This is in order to understand your responses to the study drug (such as safety findings or drug levels)
  - This sample is called a "Banked Biospecimen"
    - A blood sample will be taken before the first dose
    - The Banked Biospecimen may be kept by Pfizer in a Pfizer-approved facility for as long as it is useful for scientific research
      - This may be for many years (no time limit)
    - The facility may be in a different country from where you have given the sample
- Females will have a blood pregnancy test done at check-in, Day -1, and discharge from the CRU
- Urine samples to test for drugs of abuse will be collected at the time of check-in and may be collected at various times throughout the study
  - If this test is positive, you will not be allowed to enter/continue in the study
  - Urine collection may be monitored by a staff member of the same sex
  - You have the right to refuse to be monitored, but may be disqualified from the study
- The study investigator may decide to do an alcohol breath test at check-in and at any time during the study
- A complete physical exam will be done at study check-in, if it was not done at screening
  - A limited physical exam may be done at various times throughout the study at the discretion of the study investigator
- The use of proper birth control will be confirmed/reviewed at check-in, discharge from the CRU, and at the time of the follow-up phone call
- Blood pressure, heart rate, and breathing rate will be measured while you are lying down at various times throughout the study
- A monitor will be placed on a finger to sense the amount of oxygen in the blood before each dosing through 12 hours after each dose
  - A single measurement will be done before you are discharged from the CRU
- Body temperature will be measured at check-in
- You will be asked "How do you feel?" each day
- An intravenous (IV) catheter may be placed in a vein in one of your arms for blood collection
- ECGs (single measurement) will be done before the first dose and at the time of discharge from the CRU
  - It may be necessary to shave your chest so that the patches for the ECGs will stick to your skin
  - Your chest may be marked with a pen to identify the correct areas for ECG patch placement
- You will receive a follow-up phone call between 28 and 35 days after the last dose of study drug

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A. Dosing Schedule:

Dosing is planned as follows:

DOSING SEQUENCE	NUMBER OF SUBJECTS	STUDY PERIOD	
		1	2
1	15	Treatment A	Treatment B
2	15	Treatment B	Treatment A

Treatment A: 60 mg/2.4 mg capsule (morphine/naltrexone HCl) manufactured at Actavis
Treatment B: 60 mg/2.4 mg capsule (morphine/naltrexone HCl) manufactured at Coating Place

On Day 1 of each period, you will receive a single oral dose of study drug as a capsule. You will fast overnight (nothing to eat or drink except water) for at least 10 hours before each dose.

Each dose will be taken with about 8 oz. (1 cup) of water. Capsules must be swallowed whole. Doses must not be chewed or crushed. We will check your mouth after each dose to make sure the study drug has been completely swallowed.

There will be at least 7 days between each dose.

Both you and the study staff will know which of the above you are receiving.

This is a research study. The study drug will be given to you only during this study and not after the study is over.

B. Blood Samples:

During the study, blood samples will be taken by individual needlesticks or by a catheter put directly into a vein in your arm. The catheter procedure consists of putting a small tube in your arm to take blood when required. Catheters are used at the judgment of the study investigator or when required by the study plan. Catheters are not used at the request of the subject.

There will be about 42 blood draws. The total amount of blood drawn during the study will be about 287 mL. This is equal to about a little more than 9½ oz. or a little less than 1¼ cups. For comparison, the standard blood donation is about 16 oz. (2 cups), once in any 56-day period.

As with all studies with blood draws, adequate rest and good eating habits are recommended.

Blood loss in this amount may lead to a low red blood cell count (anemia). Anemia can make you tire more easily.

YOUR RESPONSIBILITIES

Activity Restrictions:

- You will be confined to the CRU for 12 days starting with check-in
  - If a prolonged drug effect is noted and your safety is a concern, you may need to remain in the CRU longer
  - The study investigator or study staff will decide when you can leave the CRU

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- You must not do any strenuous exercise (for example, heavy lifting, weight training, calisthenics, or aerobics) for at least 48 hours before each blood collection for safety labs
  - Walking at a normal pace is allowed
- You must call the CRU at the 24-hour phone number listed on the first page of this consent form for approval before taking any drugs other than the study drug
  - You must report all such drugs taken during the study to the study staff
- You must not use tobacco or nicotine-containing products for at least 24 hours before dosing and while confined to the CRU
- Lying down is not allowed for 4 hours after dosing, unless needed for any study assessments

Diet Restrictions:

- You must not eat or drink anything, except water, for at least 10 hours before the collection of the pre-dose blood sample for study drug and 4 hours after each dose
- You must not eat or drink anything, except water, for at least 4 hours before each safety laboratory test
- Except for 1 hour before and 1 hour after each dose, you may drink water freely
- You must not eat or drink anything with alcohol for 24 hours before check-in through the collection of the last blood sample for study drug
- You must not eat or drink anything with caffeine from 24 hours before dosing through collection of the last blood sample for study drug
  - Food and beverages with caffeine include, but are not limited to, chocolate, coffee, tea, cola, Dr. Pepper®, and Mountain Dew®
- You must not eat or drink anything containing grapefruit or grapefruit-related citrus fruits (for example, Seville oranges, pomelos), including smoothies, from 7 days before the first dose through collection of the last blood sample for study drug
- You must be willing to eat all of the food offered on Day 1 of each study period
- Lunch will be served about 4 hours after dosing
- Dinner will be served about 9 to 10 hours after dosing
- Evening snacks may be allowed at appropriate times
- Meals will be provided as appropriate on the days you are not dosed

POSSIBLE SIDE EFFECTS AND RISKS OF THE STUDY DRUG AND PROCEDURES
STUDY DRUG

Any research has some risks, which may include things that could make you sick, make you feel uncomfortable, or harm you. You might experience negative effects related to the study drug while participating in the study. All research participants taking part in the study will be watched carefully for any negative effects; however, the study team does not know all the effects that the study drug may have on you. The study team may give you medicines to help reduce negative effects. These effects may be mild or serious. In some cases, these effects might be long-lasting, or permanent, and may even be life-threatening.

Embeda® is the drug you will take in this study. It contains morphine sulfate and naltrexone HCl. The compound naltrexone HCl is sequestered. This means that it is a closed off ingredient of the study drug. It will not be released if the study drug is taken as instructed (swallowed whole and not chewed or crushed). As long as the capsule is taken as directed, only side effects related to morphine may occur.

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Morphine sulfate:

The most common side effects related to morphine (seen in greater than or equal to 10% of people taking it) include:

- Constipation
- Nausea
- Somnolence (sleepiness)

Common side effects related to morphine (seen in between 1% and 10% of people taking it) include:

- Vomiting
- Indigestion
- Headache
- Excessive stomach gas
- Dizziness
- Sweating
- Tremor
- Stomach discomfort
- Restlessness
- Itching
- Anorexia (loss of appetite)
- Hot flush
- Muscle spasm
- Dry mouth
- Depression
- Diarrhea
- Sedation (drowsiness)
- Joint pain
- Fatigue
- Insomnia (inability to fall asleep or to remain asleep)
- Anxiety
- Chills
- Abdominal pain
- Lethargy (tired, lack of energy)
- Edema peripheral (fluid retention in lower extremities)
- Decreased appetite
- Irritability

This drug can cause a number of side effects that could affect your mental and physical abilities. Until you know how the drug will affect you and/or if you experience any of these type of side effects, you should use caution by:

- Avoiding stairs
- Not driving a car
- Not swimming or bathing in a tub
- Not working with machinery or at heights

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General Precautions with Opioids such as Morphine sulfate:

- Taking morphine sulfate for a long period of time may cause your body to become dependent (physical dependence). Physical dependence is not the same as drug addiction
- You should not stop taking morphine sulfate or other opioids without talking to your healthcare provider about how to slowly stop your medicine
  - You could become sick with uncomfortable withdrawal symptoms described above because your body has become used to these medicines
- There is a chance of abuse or addiction with morphine sulfate. The chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems
- Morphine sulfate and other opioids should be used with caution if you have a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g. major depression)
- There is a risk that morphine sulfate may slow the rate of breathing. This could be life-threatening. The risk of slowed breathing might be greatest when starting morphine sulfate when the dosage is increased, and may occur even at recommended dosages. Accidental ingestion, especially by children, may result in slowed breathing that can also be life-threatening. Combining morphine sulfate with alcohol or with medications that also act on the brain, such as anti-anxiety medications (like benzodiazepines), may lead to additive effects on breathing that can also be life-threatening. Morphine sulfate should not be used together with alcohol, or with these other medications that act on the brain, unless supervised by a healthcare provider
- Morphine sulfate may cause failure of the adrenal glands, or may cause these organs to not work properly, and this could be a potentially life-threatening condition. Nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, and low blood pressure may be signs that your adrenal glands are not working properly, and you should contact your study doctor immediately
  - The adrenal glands are found above each of your kidneys and produce hormones, including adrenaline and some steroids
- A rare but potentially life-threatening condition known as Serotonin Syndrome (symptoms such as agitation; hallucinations [imagines seeing, hearing, or sensing something when it is not present]; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea) could occur when morphine sulfate is taken together with certain other drugs that work on a chemical called serotonin. Examples of these other drugs include some antidepressants. Be sure to tell your doctor if you are taking or plan to take any other medications

Naltrexone HCl:

The side effects of naltrexone were reported with the marketed formulation of naltrexone (Revia®).

The most common negative effect related to naltrexone is liver injury. Liver injury can occur at doses higher than what will be given in this study. Liver injury can cause increases in liver enzymes (indicate how the liver is working).

Other side effects occurring in more than 10% of subjects that were reported when naltrexone was given to opioid-dependent subjects include:

- Difficulty sleeping

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- Anxiety
- Nervousness
- Abdominal pain/cramps
- Nausea
- Vomiting
- Low energy
- Headache
- Joint/muscle pain

Common side effects (occurring in between 1% and 10% of subjects) include:

- Loss of appetite
- Constipation
- Increased thirst
- Increased energy
- Feeling down
- Irritability
- Dizziness
- Skin rash
- Delayed ejaculation
- Decreased potency
- Chills

All drugs have a potential risk of an allergic reaction. If not treated promptly, it could become life-threatening. You should get medical help and contact the study investigator right away if you think you have any of the following symptoms of a serious allergic reaction:

- Trouble breathing
- Wheezing
- Difficulty swallowing
- Swelling of the face, mouth, lips, gums, tongue, or neck

Other allergic reactions may include:

- Itchiness
- Rash
- Hives
- Blisters
- Palpitations (racing heart)
- Chest discomfort/tightness
- Muscle pains/stiffness

At times, the following may also be symptoms of an allergic reaction:

- Diarrhea
- Nausea
- Vomiting
- Abdominal pain

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There may be rare and unknown side effects. This includes reactions that may be life-threatening. It is important that you report all side effects that you experience as soon as they happen, regardless of whether or not you believe they are caused by the study drug.

Any subject who experiences a significant side effect during the study may have the following additional procedures done:

- A heart monitor may be attached to the chest for a continuous reading of heart rhythm and rate
- Vital signs, including blood pressure, may be measured often
- A monitor may be placed on a finger to sense the amount of oxygen in the blood
- A catheter may be inserted into a vein in your arm so that you may be given IV fluids and/or medications
- Other tests or treatment may be given as necessary for your safety including, but not limited to, additional blood draws, collection of urine, stool, or other bodily fluids
    - Depending on the severity of your symptoms, you may be referred to outside medical providers or a hospital for additional evaluation and/or treatment
    - The study investigator may notify your emergency contact, as appropriate, in the event of an emergency while you are taking part in the study

If you are not honest about any side effects you have during the study, you may be harmed by staying in the study.

ADDITIONAL RISKS OR DISCOMFORTS

The long time you have to spend at the study site may make you uncomfortable.

Testing of DNA and/or RNA:

This research may involve studying your biology and the likelihood that a particular biological feature (including genes) may increase the chance of developing a disease. Genes are pieces of DNA that, through material called RNA, give instructions for building the proteins that make our bodies work. These instructions are stored in the form of a code. This is the code that you inherit from your parents and that you pass on to your children. DNA, RNA, and proteins can be studied as part of genetic research. The sponsor and researchers will put measures in place to minimize the possibility for the results from this research being linked to you, but there is always the remote possibility that information from your participation in the research may be disclosed.

Genetic Information Nondiscrimination Act (GINA):

A Federal law, called the GINA, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law will generally protect you in the following ways:

- Health insurance companies and group health plans may not ask for your genetic information that we get from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums

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- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

You should know that this Federal law does not protect you from genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Blood Samples and IV Catheter (if used):

Possible side effects of having your blood drawn or an IV catheter inserted into a vein in your arm include:

- Bleeding at the site of the needle puncture
- Bruising
- Feeling faint
- Rarely infection or blood clot
- Redness of the vein and/or pain

If you feel faint, tell one of the study staff immediately.

ECG:

Possible side effects from having an ECG include:

- Irritation or rash from the adhesive on the patches

A rash may result in a long lasting discoloration of your skin. If it is necessary to shave the area where the patches need to be, irritation from shaving may occur.

Other:

For a short time following the study you may test positive for drugs of abuse.

BIRTH CONTROL, DANGERS OF PREGNANCY AND BREASTFEEDING

The effects of the study drug on the following are not known:

- Sperm
- Pregnancy
- Unborn child
- Nursing child

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If you are currently pregnant, planning to become pregnant or breastfeeding a child, you should not join this study. If you are male whose partner is currently pregnant or plan to father a child, you should not join this study.

If you are pregnant or become pregnant during the study, your unborn baby may be exposed to the study drug. The effects of the study drug on an unborn or breastfed baby are unknown and may involve unforeseeable risks.

Prolonged use of opioids during pregnancy can result in physical dependence in the neonate (new born) and the development of neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as:

- Irritability
- Hyperactivity and abnormal sleep pattern
- High pitched cry
- Tremor
- Vomiting
- Diarrhea
- Failure to gain weight

PREGNANCY RELATED RISKS / USE OF BIRTH CONTROL

FOR FEMALES

Women in this study not able to get pregnant include:

- Women who have had no period for at least 12 consecutive months with no other medical cause plus have a blood hormone level confirming that you cannot get pregnant
- Women who have had their uterus and/or both ovaries removed (documented)
- Women who have ovarian failure, confirmed by your personal doctor

It is very important that men do not make women pregnant during this study. The only sure way to prevent pregnancy is to not have sex. If you are a man able to father children and choose to have sex with a woman who is able to have children, you and your partner must use a highly effective method of birth control. This is in addition to using a condom (see below). The method must be used consistently and correctly from the start of dosing (earlier for hormonal contraception) through the duration of the study and for at least 28 days after the last dose of study drug.

If the chosen method of birth control is changed or discontinued, you should inform us immediately.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly beginning with the first dose of study drug and continuing for the duration of the study and for at least 28 days after the last dose.

Men must not donate sperm for the duration of the study and for at least 28 days after the last dose.

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Highly effective methods of birth control for this study include:

FOR MALES

ONE of the following methods:

- Abstinence (completely and persistently refraining from all heterosexual intercourse), only if this is your preferred lifestyle
- Consistent use of a male condom used WITH a separate spermicide product (foam, gel, film, cream, or suppository)
- Male sterilization (vasectomy with confirmation of absence of sperm)
- Female partner with one of the following:
  - Hormonal method of birth control (must remain the same throughout the study and have been in use long enough to ensure its effectiveness)
    - Birth control pills
    - Inserted hormonal intrauterine device (IUD)
    - Injectable progesterone
    - Subdermal (under the skin) implant
    - Transdermal (applied on the skin) patch
    - Vaginal ring
  - Correctly placed copper-containing IUD
  - Bilateral tubal ligation (tubes tied)
  - Bilateral salpingectomy (both fallopian tubes removed)
  - Bilateral tubal occlusive procedure (tubes blocked), confirmed by personal doctor

If abstinence (not having sexual intercourse at all) is your usual and preferred lifestyle and both you and your study investigator agree that it is your selected method of birth control, you must continue not to have sexual intercourse or you may become pregnant/make your partner pregnant.

Birth control methods, even when used properly are not perfect. If you or your partner becomes pregnant during the study, or you want to stop your required birth control during the study, you should tell the study investigator immediately. You may be withdrawn from the study if you stop using birth control or you become pregnant.

Pregnancy Follow-up:

If you/your partner become pregnant during the study or within at least 28 days after you have stopped taking the study drug, please tell the study investigator immediately. Please also tell the doctor who will be taking care of you/your partner during the pregnancy that you took part in this research study. The study investigator will ask if you/your partner or your pregnancy doctor is willing to provide updates on the progress of the pregnancy and its outcome. If you/your partner agree, this information will be collected for safety monitoring follow-up.

POSSIBLE BENEFITS OF THE STUDY

You will get no medical benefit from being in the study. Information from this study may benefit persons in need of severe pain management in the future.

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ALTERNATIVES TO PARTICIPATING IN THIS STUDY

Since this study is for research only, the only other choice would be not to be in the study.

RELEASE OF YOUR MEDICAL RECORDS AND PRIVACY (CONFIDENTIALITY)

The clinic staff will record:

- Your medical history
- The dose(s) you receive
- The results of exams and tests done during the study

Your name will not appear in the study data. Instead you will be identified by a subject-identification number. The information from the study data may be shared with others.

Your clinic records may include:

- Health information about you
- Documents that directly identify you

People from the groups listed below may need to look at your clinic records to make sure that the study information is correct and that the study was run as it should have been.

These reviews may take place during the study or after the study is over.

Your study information may be shared with the following people or groups:

- Pfizer Inc or its representatives, including its auditors and companies it hires to provide study-related services
- IntegReview IRB, the institutional review board (IRB) that approved this study, and any other committees responsible for overseeing the research
- Researchers who are conducting this study at other study centers
- Government health agencies (such as the FDA) in the United States (US) or other countries
- Accrediting agencies

People from these groups may get information from your study data. Or, they may review your clinic records. Because of the need to share information with these people, it may not be possible to keep your identity a secret.

Pfizer will use and share your information only for research or legal reasons or to write research reports. In addition, Pfizer may:

- Look at the study data at a later date
- Add your information to information from other studies for other research reasons

However, your name will never appear in any reports, or in any future communication by Pfizer.

By signing this consent form, you agree to allow the use of your study information even after you leave the study.

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Please note the following information regarding the delivery of push notifications and text messages:

- The Sponsor, or a company working for the Sponsor, occasionally may send push notifications and text messages using an automated system to remind you of upcoming appointments, medication reminders and missed doses, or other study-related information
- To discontinue receiving text messages, please contact the Pfizer New Haven CRU at 800-254-6398
- Standard text messaging rates apply to all text messages. Message rates differ from carrier to carrier, so please contact your wireless phone provider to inquire about the details of your plan
- The contact information you have provided will be used for the sole purpose of communicating with you about the research study
- The push notifications or text messages received through this program may appear on your mobile phone screen as soon as they are received, even when the phone is locked. These messages could be seen and read by others who are near your phone when the message is received

PAYMENT FOR INJURY RELATED TO THE STUDY

If you experience a research injury, the clinic will arrange for medical treatment at no cost to you. Pfizer will cover the costs of this treatment. A research injury is any physical injury or illness caused by being in this study. There are no plans to offer you payment for such things as:

- Lost wages
- Expenses other than medical care
- Pain and suffering

To help avoid injury it is very important to follow all study directions. You can get more information about medical treatment for research injuries from the study investigator or study staff.

Remember that you must call the study investigator listed on the first page of this consent form immediately if you experience a research injury. A 24-hour answering service is available.

If you are treated for a research injury that is paid for by Pfizer, Pfizer or its representative will collect your Medicare Health Insurance Claim Number or Social Security Number to determine your Medicare status. If you are a Medicare beneficiary, Pfizer will report the payment and information about the study you are in to the Centers for Medicare & Medicaid Services (CMS), in accordance with CMS reporting requirements. Pfizer will not use this information for any other purpose.

LEGAL RIGHTS

You will not lose any of your legal rights by signing this consent form.

WHOM TO CONTACT

For answers to questions about this research or to report a research related injury, contact:

Mary Powell-St. Louis, M.D., MPH
Call the 24-hour Clinic Telephone Number
203-401-0300

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If you are unable to reach anyone at the number listed above and you need medical attention please go to the nearest emergency room.

You will receive a card with information about this study. This information includes:

- The name or number of the study
- The clinic 24-hour phone number

You should keep this card with you in case you have a medical emergency. You can give this card to any doctor or healthcare professional, if they need more information about the research study to provide the best treatment for you.

If you do not want to talk to the study investigator or study staff, if you have concerns or complaints about the research, or to ask questions about your rights as a study subject you may contact IntegReview.

IntegReview's policy indicates that all concerns/complaints are to be submitted in writing for review at a convened IRB meeting to:

Mailing Address:	OR	Email Address:
Chairperson IntegReview IRB 3815 S. Capital of Texas Highway, Suite 320 Austin, Texas 78704		integreview@integreview.com

If you are unable to provide your concerns/complaints in writing or if this is an emergency situation regarding subject safety, contact our office at:

512-326-3001 or
toll-free at 1-877-562-1589
between 8 a.m. and 5 p.m. Central Time

IntegReview has approved the information provided in this informed consent form and has given approval for the study investigator to do this study. This does not mean IntegReview has approved your personal participation in this study. You must consider the information in this consent form for yourself and decide whether or not you want to be in the study.

PAYMENT FOR BEING IN THE STUDY

Valid proof of a Social Security Number is required before any payment is released.

The amount of payment is based on a number of things including the length of the study.

Study payments will be paid in US dollars. Compensation may be provided on a loadable debit card or by paper check. Pfizer New Haven CRU reserves the right to determine method of payment.

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You will be paid $175.00 for travel expenses to and from screening. You will receive this payment within 2 weeks of screening. If you test positive for drugs of abuse, or if you leave the screening early, you will not be paid the $175.00. Travel pay for this study has been included in the subject payment. Additional travel pay is not available for this study.

Further, if you test positive for drugs of abuse:

- You will not be allowed to be in this study
- You will not be allowed to be in any future studies
- You will be removed permanently from our active database

The payment for completing the entire study will be up to $3,400.00. If you do not follow instructions your payment may be less.

If we ask you to return for additional tests, you will be paid $250.00 for each trip to the clinic. During times that you are confined to the clinic, you will not be paid more for repeat or added tests.

If you discontinue from the study, or if you are taken out of the study early, you will be paid for the time you completed. You will not be given the study completion bonus if you drop out of the study early.

If total payment by Pfizer is $600.00 or more in a calendar year, your payment will be reported to the Internal Revenue Service in accordance with Federal tax law.

Pfizer may use information resulting from the study or samples collected in the study to develop products or processes from which it may make a profit. There are no plans to pay you or provide you with any products developed from this research. Pfizer will own all products or processes that are developed using information or samples from the research study.

The decision to admit you into the study is based upon results of pre-study requirements. No one is assured a place in the study until the first dose is complete. Sufficient numbers of subjects will be brought in to be sure we fill the study.

<u>Study Subjects</u>:

- If you successfully complete this study, the total amount you will be paid will be up to $3,400.00 ($2,800.00 plus $600.00 completion bonus)
- If you do not follow instructions (including those listed in the New Haven CRU House Rules), if you are late for blood draws, or if you miss procedures, your payment will be reduced
- If you choose to leave or are withdrawn from the study before finishing all visits, your payment will be based on how much of the study you completed
    - This pay will be based on $200.00 for each overnight stay (12), $250.00 for each follow-up visit to the clinic (none are planned), and $100.00 per week for the time between discharge from the CRU and the follow-up phone call (about 4 weeks)
- Partial payments may be made during the study. Details will be provided at screening
- A final payment will be provided to you about 2 weeks after you finish the study

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Back-up Subjects:

- If you are a back-up subject who is required to stay in the CRU overnight, you will be paid $250.00 per night that you stay
- If you are not required to stay overnight, you will be paid $190.00

You will be paid a pro-rated amount based on the extent of your participation if:

- You are not able to complete the study
- You choose to leave the study
- You are withdrawn from the study early by the study investigator for non-safety related issues
- The study is stopped early
- You are qualified but not chosen to participate

YOUR DECISION TO BE IN THE STUDY

Whether you are in this study is entirely up to you. You cannot be forced to be in this study. You may not want to be in this study. You may leave the study at any time without penalty or loss of any benefits. Your future medical care will not be affected. The study investigator, Pfizer Inc, IntegReview IRB, or the FDA may take you out of the study without your permission at any time for the following reasons:

- You do not follow the instructions of the study investigator
- We find out you should not be in the study
- The study is stopped
- The study becomes harmful to your health
- You do not follow the New Haven CRU House Rules

If you leave the study or if you are taken out of the study for any reason, you may be asked to return to the clinic for a final visit. You may have some end of study evaluations or tests at this visit. This is to ensure your safe exit from the study. Also, the data collected to the point of your withdrawal remains part of the study database and may not be removed.

If you are withdrawn from the study, or decide to stop the study, you can ask that any unused samples that were collected be destroyed, by contacting the study investigator.

ADDITIONAL COSTS

There will be no charge to you for taking part in this study. The study drug, study-related procedures, and study visits will be provided at no charge to you or your insurance company.

NEW FINDINGS

If there is new information about the safety of the study drug or changes in the study tests, we will tell you. You can then decide if you still want to be in the study.

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THE REASON FOR INSTITUTIONAL REVIEW BOARDS AND INFORMED CONSENT

What is a consent form?
The informed consent document contains information required by federal regulations. The informed consent document must be reviewed and approved by an Institutional Review Board (IRB). You can tell the IRB has approved this study by dated information at the top of each page.

What is an Institutional Review Board (IRB)?
An Institutional Review Board (IRB) is a group of people that reviews research studies. The main goal of this review is to protect the rights and well-being of the human subjects participating in research studies.

IntegReview, the IRB for this study
IntegReview is an IRB. Its board members provide services in the US, Japan, and Latin America.

To meet the requirements of the federal regulations, the IntegReview Board currently includes:

- Doctors
- Pharmacists
- Nurses
- Toxicologist (people who study the harmful effects of chemicals)
- Other specialists
- Others who do not have a background in science or medicine

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AGREEMENT TO BE IN THE STUDY **PIMS # _____**

This consent form contains important information to help you decide if you want to be in the study. If you have any questions that are not answered in this consent form, ask one of the study staff.

By checking each of the following, you are agreeing that the statements below are true:

		Please Check
A.	This consent form is written in a language I understand.	
B.	I understand the information in this consent form.	
C.	I have been given enough time to ask questions and talk about the study.	
D.	All of my questions have been answered completely.	
E.	I think I have received enough information about the study.	
F.	I agree that I was not pressured by the study investigator or the study staff to be in this study.	
G.	I know that I can leave the study at any time without giving a reason and without affecting my healthcare.	
H.	I know that my health records from this study may be reviewed by Pfizer Inc and by government officials.	
I.	I know that I can't be in another study while I am in this study.	
J.	I have received the HIV, Hepatitis A, B, and C pamphlets and reviewed the information in them.	

IF YOU DID NOT CHECK THE BOX NEXT TO ANY OF THE ABOVE QUESTIONS, OR YOU ARE UNABLE TO ANSWER ANY OF THE ABOVE QUESTIONS, YOU SHOULD NOT SIGN THIS CONSENT FORM.

- You will get a copy of this signed and dated Informed Consent Document for your records
- You agree to participate in this study
- It is your responsibility to tell the study investigator about all changes in your physical or mental health during the study

_____
Printed Name of Adult Study Subject

_____
Signature of Adult Study Subject Date

_____
Printed Name or Initials of Person Explaining Informed Consent

_____
Signature or ALPHA NUMERIC CODE of Person Explaining Informed Consent Date

You will receive a signed and dated copy of this consent form to keep.

THIS IS AN IMPORTANT DOCUMENT - KEEP FOR FUTURE REFERENCE

VERSION CONTROL
bgb/12-7-17 jbm/1-2-18 jm/3-6-18 mjc/12-21-18

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ADDITIONAL CONSENT REQUEST

USE OF BANKED BIOSPECIMENS FOR ADDITIONAL RESEARCH
(OPTIONAL FOR SUBJECTS)

In the main part of this consent document, you were told about providing a Banked Biospecimen for research to understand your response to the study drug (such as safety findings or drug levels).

- This is an optional request and you do not have to agree to it even if you are providing a Banked Biospecimen
- This additional use of your Banked Biospecimen sample is called "Additional Research"
- If you decide to take part in this Additional Research, you do not have to provide any new samples because some of the Banked Biospecimen you gave in the main drug study will be used for this Additional Research

1. WHAT IS THE PURPOSE OF THIS ADDITIONAL RESEARCH?

This additional consent asks for your permission to use this Banked Biospecimen and the information (results or data) generated from such a sample to design and conduct further research. This is in order to gain an understanding of other diseases and to advance science, including development of other medicines for patients.

- This Additional Research involves studying your biology (such as DNA, RNA, proteins, and metabolites)
- The Additional Research includes exploratory research
  - It may not be possible to link the results of the exploratory research to individuals, including you
  - Pfizer does not plan to return information from this Additional Research to you or your study investigator
- Pfizer may share the Banked Biospecimen and data from it with other researchers and collaborators
  - Further information about this is explained in the privacy section below

The Banked Biospecimen may be kept by Pfizer in a Pfizer-approved facility for as long as it is useful for scientific research. This may be for many years (no time limit). The facility may be in a different country from where you have given the sample.

2. WHAT ARE THE RISKS OF TAKING PART IN THIS ADDITIONAL RESEARCH?

There is always the remote possibility that information from your taking part in the Additional Research may be disclosed. Pfizer and researchers have measures in place to minimize the chance that results from this Additional Research could be linked to you.

3. WHAT ARE POSSIBLE BENEFITS OF PARTICIPATING IN THIS ADDITIONAL RESEARCH?

This additional use of your Banked Biospecimen and data is for research purposes only. There is no direct benefit to you from taking part. Information learned may help other people in the future and help in the development of new medicines.

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4. CAN I WITHDRAW MY PERMISSION?

You can change your mind at any time about allowing your Banked Biospecimen to be used for Additional Research. However, any data already generated from the Banked Biospecimen will be kept to preserve the value of the research. If you withdraw or are taken out of the drug study, any Banked Biospecimen you have given will continue to be stored. It may be used by Pfizer for Additional Research unless you tell the study investigator you do not want any more Additional Research performed on this sample.

5. WHAT WILL I HAVE TO PAY FOR IF I TAKE PART IN THIS ADDITIONAL RESEARCH?

There will be no charge to you for allowing your Banked Biospecimen to be used for this Additional Research.

6. WILL I BE PAID IF I CONSENT TO THIS ADDITIONAL RESEARCH?

You will not be paid for taking part in this Additional Research.

Pfizer may use information from this Additional Research to develop products or processes from which it may make a profit. There are no plans to pay you or provide you with any products developed from this Additional Research. Pfizer will own or have rights to all products or processes that are developed using information from your Banked Biospecimen.

7. IF I TAKE PART IN THIS ADDITIONAL RESEARCH, HOW WILL MY PRIVACY BE PROTECTED?

All information about the confidentiality, use, and disclosure of your information found in the main consent form for the drug study applies to this consent as well.

The Banked Biospecimen will be handled in a way that protects your privacy and confidentiality. It will be assigned your study identification code (ID) at the site. The data generated from this Banked Biospecimen will also be labeled with this ID. The key between your ID and your personally identifying information (for example, name and address) will be held at the study site. Before Pfizer shares your Banked Biospecimen (or information from it) with others, additional measures will be taken to minimize the risk that you could be identified.

It is possible that results from the Additional Research may be included in:

- Further applications to government agencies to market other medicines or devices
- Ethics committees/IRBs involved in research

8. CONTACT INFORMATION

The study team will answer your questions or concerns before, during, and after the drug study.

The main consent has contact information if you need to reach the study team or wish to speak with someone not involved with the drug study.

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9. SIGNATURES:

- I have read the information about this Additional Research
- I have been given enough time and opportunity to ask about the details of the Additional Research and to decide whether or not to participate
- I do not give up any of my legal rights by signing this consent document
- I have been told that I will receive a signed and dated copy of this document

Please make your choice and check the box next to one of the statements below:

☐ I VOLUNTARILY AGREE TO ALLOW MY BANKED BIOSPECIMEN TO BE USED FOR ADDITIONAL RESEARCH

OR

☐ I **DO NOT** AGREE TO ALLOW MY BANKED BIOSPECIMEN TO BE USED FOR ADDITIONAL RESEARCH

_____
Printed Name of Adult Study Subject

_____
Signature of Adult Study Subject Date

_____
Printed Name or Initials of Person Explaining Informed Consent

_____
Signature or ALPHA NUMERIC CODE of Person Explaining Informed Consent Date