

Peninsula Pharmaceuticals, Inc. / Protocol Number DORI-05, Amendment 5

Initials: _____

**CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
AND
AUTHORIZATION TO DISCLOSE HEALTH INFORMATION**

Sponsor / Study Title: Peninsula Pharmaceuticals, Inc. "A Multicenter, Double-Blind, Randomized, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem and Levofloxacin in Complicated Lower Urinary Tract Infection or Pyelonephritis."

Protocol Number: Protocol DORI-05
Amendment 5, dated 15 September 2005

Principal Investigator: [Insert Full Name and Credentials]

Address: [Insert Complete Site Address and Facilities]

Telephone Number: [Insert Telephone Number of the Principal Investigator]

You are being invited to participate in a clinical research study. The following information describes the study and your role as a possible participant. Your doctor will answer any questions you may have about this information sheet and about the study. Please read this information carefully and do not hesitate to ask any questions about the study information provided below.

PURPOSE

This study involves an experimental treatment for two kinds of infections: complicated lower urinary tract infections and pyelonephritis. Pyelonephritis is a bacterial infection of the kidney which has symptoms including: frequent, irritating or painful urination that may look cloudy, smell bad, and/or contain blood; increased urination at night; fever, chills, nausea, vomiting, and/or pain in your lower back. A urinary tract infection is a condition where your urinary tract – the route urine takes from your kidneys to your bladder and then out of your body – becomes infected by bacteria. It is a common type of infection and more than one million patients are hospitalized annually with this disease. When a urinary tract infection occurs in someone who has one of a number of abnormalities in the urinary tract, doctors may refer to this as a complicated urinary tract infection. The abnormalities could include conditions such as retention of urine in the bladder, abnormal tissue in the lining of the tract, or a swollen prostate gland (in men). The abnormalities can hinder the normal flow of urine and make it harder for your body's natural defenses to clear out the bacteria. If you have these complications, your doctor will discuss them with you.

The standard treatment for both complicated urinary tract infections and pyelonephritis is the administration of antibiotic drugs. These drugs may be oral (taken by mouth and swallowed) or IV (intravenous, or "in the vein" which means injected into your vein). The purpose of this study, which involves research, is to determine if an investigational antibiotic drug, Doripenem (for IV injection) is safe and effective in the treatment of this disease, compared with another standard antibiotic drug treatment. An investigational drug is a drug that has not been approved by the US Food and Drug Administration (FDA). The standard treatment to be used in this study is

Levofloxacin. This is a medication that has already been approved by the FDA for the treatment of complicated lower urinary tract infections and pyelonephritis.

Doripenem has been tested previously in several studies with animals and humans. It is expected that approximately 750 subjects in 60 centers in North America, South America and Europe will be randomized in this study. Eligible subjects will be those who are currently hospitalized or will be hospitalized for treatment of a complicated lower urinary tract infection or pyelonephritis.

PROCEDURES

If you decide to participate in this study, you will be asked to undergo a number of procedures during your hospital stay. Additionally, when you have been discharged from the hospital you will be asked to return for two more study specific visits. Your overall participation will last approximately 6 to 8 weeks. Your study visits will be as follows:

Screening visit:

This first visit consists of a series of study procedures performed within the 48 hours prior to receiving study medication that will determine whether you are eligible to receive study drug:

- You are to provide written informed consent to participate in this study.
- Your medical history, current medication use, and current symptoms will be reviewed.
- You will be given a complete physical examination.
- Your vital signs (temperature, blood pressure, pulse rate, height, weight) will be taken.
- If you are a woman of child bearing potential a pregnancy test will be performed. If a urine pregnancy test is used, blood must also be obtained at the time of screening for serum β -HCG test, and negative serum pregnancy test results will be confirmed as soon as possible and within 72 hours of study entry.
- A urine specimen will be tested for routine values and various types of bacteria. Some patients will have two specimens collected to test for bacteria depending on their symptoms. Your study doctor will inform you if this is the case.
- A blood sample (about three tablespoons) will be taken and tested for routine measurements. In addition, a sample will be tested for the presence of bacteria if you have one or more of the following: current need for a catheter (tube that drains urine from your body), signs of pyelonephritis (kidney infection) or bacteremia (bacteria in the blood).

If you qualify to participate in this study you will be given your first dose of the IV (Intravenous) study drug on Study Day 1. Note that this Study Day 1 may be the same day as your screening visit. You will be assigned by chance (like the flip of a coin) to one of two treatment groups. All patients in this study will receive antibiotic treatment--half the patients will receive doripenem (500mg) and placebo, and the other half will receive placebo and levofloxacin (250mg). A placebo is a dummy treatment that contains no active ingredients. The addition of the placebo is to ensure neither you nor your study doctor knows which treatment group you are in. Your chance of receiving either of the two active drugs (doripenem or levofloxacin) is one in two. Even though neither you nor your doctor will know which treatment you receive, this information is available to the doctor if needed in an emergency.

The nursing staff will administer the study drugs every 8 hours via IV infusions that will last approximately 60 minutes each. While you are on infusion therapy, there will be a total of 4 infusions every 24 hours. Each day, the first dose is two consecutive 60-minute infusions and the second and third doses are one 60-minute infusion each for a total of four daily infusions.

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The length of time you are on study drug IV therapy is dependent upon how well you respond to treatment and will be determined by your study doctor. After an appropriate course of IV study drug therapy you may be switched to FDA-approved standard oral if medically appropriate.

The total number of days of combined double-blind IV study drug therapy and oral levofloxacin therapy will be 10 days.

There are certain circumstances where you may require more than 10 days of study drug therapy. For example, if you are diagnosed with bacteria in your blood or if you exhibit impaired kidney function, the amount of drug you receive and the length of treatment may change. In either case, your study doctor will inform you of the change.

The following procedures will occur when you start intravenous study drug:

On Study Day 1:

- You will be given IV (Intravenous) study drug infusions every 8 hours.
- Your temperature will be taken before each IV study drug infusion.
- An ECG (electrocardiogram) will be performed before your first IV study drug infusion. The ECG is a painless procedure that uses leads or wires taped on your body to record your heartbeats on paper.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- Urine will be collected for bacterial analysis.
- For all women of child-bearing potential, the results of the serum pregnancy test performed at screening will be verified. If the serum test is positive you will be withdrawn from study drug administration.

On Study Day 2:

- You will be given IV study drug infusions every 8 hours.
- Your temperature will be taken before each IV study drug infusion.
- Urine will be collected for bacterial analysis.
- If your previous blood sample was positive for bacteria, this test will be repeated
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- For all women of child-bearing potential, the results of the serum pregnancy test performed at screening will be verified. If the serum test is positive you will be withdrawn from study drug administration.

After at least 2 days (6 doses) of IV study drug therapy while in the hospital, your study doctor may decide to discharge you from the hospital, but will continue IV study drug and other study procedures and assessments under the care of trained medical personnel.

On Study Day 3:

- You will be given IV drug infusions every 8 hours.
- Your temperature will be taken before each IV drug infusion.
- Urine will be collected for routine and bacterial analysis.
- Blood (about three tablespoons) will be taken and analyzed for routine values.
- If your previous blood sample was positive for bacteria, this test will be repeated.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

- For all women of child-bearing potential, the results of the serum pregnancy test performed at screening will be verified. If the serum test is positive you will be withdrawn from study drug administration.

On Study Days 4 through 10:

After you receive at least three 24-hour periods of IV study drug therapy (approximately 9 doses), your study doctor may determine that you are responding positively. If this is the case he/she may permanently discontinue the intravenously administered study drug and switch you to standard (non-experimental, FDA approved) care consisting of oral levofloxacin (250mg once daily). In other words, based on your therapeutic response to the IV study drug, your doctor will determine if or when you may switch to standard oral antibiotics. Each day:

- You will be given IV study drug infusions every 8 hours or oral levofloxacin (once daily).
- Your temperature will be taken before each IV drug infusion until you are switched to oral levofloxacin. Note that if you have a fever that has not resolved in 4 days (96 hrs), the study doctor may order additional testing such as an ultrasound or IV pyelography (a series of x-rays taken of the kidneys, their collecting or drainage system [the ureters], and the bladder following the injection of dye via a catheter.)
- A urine sample will be collected for bacterial analysis each day until two days in a row show no signs of bacteria.
- If your previous blood sample was positive for bacteria, this test will be repeated daily until there are no signs of bacteria two days in a row.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed daily until you are switched to oral levofloxacin.

End of IV Therapy visit:

This visit occurs at the end of treatment with IV study drug therapy. This may occur either, on the day that your study doctor determines that you can be switched to oral antibiotics or on the day you prematurely discontinue from the study. If you have been discharged from the hospital, you will need to return for this visit on an outpatient basis. At this visit the following procedures will be performed:

- A urine sample will be collected for bacteria and routine analysis.
- Blood (about three tablespoons) will be collected for routine analysis.
- You will be given a complete physical examination.
- Your vital signs (temperature, blood pressure, pulse rate, height, weight) will be taken.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- If you withdraw completely from this study a serum pregnancy test will be performed in all women of child-bearing potential.

Test of Cure Visit:

This will occur between 6 and 9 days after your last dose of study drug. If you have been discharged from the hospital, you will need to return for this visit on an outpatient basis. Procedures at this visit include:

- A urine sample will be collected for bacteria and routine analysis.
- Blood (about three tablespoons) will be collected for routine analysis.
- If you are a woman of childbearing potential a serum pregnancy test will be performed.
- You will be given a complete physical examination.
- Your vital signs (temperature, blood pressure, pulse rate, height, weight) will be taken.

- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

Final (Late) Follow-up visit:

This will occur between 28 and 35 days after your last dose of study drug. If you are no longer in the hospital you will need to return for this visit on an outpatient basis. At this visit:

- Your temperature will be taken.
- A urine specimen will be collected for bacterial analysis, and routine analysis if necessary.
- Blood (about three tablespoons) will be collected for routine analysis if necessary.
- If you are a woman of childbearing potential, a serum pregnancy test will be performed if one was not performed at the TOC visit.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

Throughout the study the study doctor will record your medications, signs and symptoms of the disease under study or any new illness. It is very important that you inform your doctor of any sickness or changes in medication during the study.

RISKS AND DISCOMFORTS

Certain side effects and discomforts associated with the study drugs may occur. The most frequent side effects and discomforts reported for doripenem are rash, headache, tiredness, dizziness, postural dizziness (dizziness that occurs with a change of body position), constipation, abdominal pain/discomfort, diarrhea/loose stools, nausea, phlebitis (inflammation in the veins), blurred vision, and loss of or decreased appetite.

In previous studies of doripenem, one case of significant allergic reaction was reported (including a sensation of a swollen throat and difficulty breathing due to fluid buildup around the lungs).

The most frequent side effects and discomforts reported for levofloxacin, are nausea, diarrhea, itching, abdominal pain, dizziness, flatulence (passing of gas), rash and vaginitis (infection of the vagina) in women.

There have been reports of elevated liver enzymes, which can indicate liver damage. Seizures may also be caused, especially in people with a history of seizures, or taking medication to control seizures. Doripenem may decrease the blood levels of sodium valproate, which is a drug to control seizures. If you are taking sodium valproate you must inform your study doctor so he/she can adjust your medication.

There may also be side effects and discomforts that are not listed here or are not yet known for either study drug. In addition, you might experience some discomfort, pain or bruising at the site where the IV is used or where the blood will be drawn.

Moreover, you or your legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to your willingness to continue participation in this study. You should inform your study doctor or staff immediately if you have a history of allergies to antibiotics. Tell the study doctor or study staff right away if you have any problems. Your study doctor may temporarily or permanently stop your study drug at any time.

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The risks associated with pyelography (x-ray of your kidneys and urinary tract using an injected dye) include hot flashes, nausea and vomiting, urinary tract infections and pain. Rarely, more severe side effects such as difficulty breathing, low blood pressure, swelling of the mouth or throat or cardiac arrest can occur.

You may experience discomfort as an ultrasound device is pressed against your abdomen and the gel used to make the device move more easily across your skin may feel cold.

There may be a possibility that the study treatment may damage an unborn child, and for this reason, if you are pregnant or plan to become pregnant, you may not participate in this study. Females of childbearing potential must use an acceptable method of birth control throughout the entire study and for at least one month after study treatment. You must have approval for your birth control method from the study doctor prior to participating in the study and get approval of any changes prior to initiating them.

BENEFITS

If the study drug is effective, you may benefit by a cure of your kidney or urinary tract infection. However, you may not benefit from participating in this study and your infection may worsen. By taking part in this study you may contribute new information that may benefit patients in the future.

ALTERNATIVES

You do not need to take part in this research study to get treatment for a complicated urinary tract infection or pyelonephritis (kidney infection). If you decide not to participate in this study, you may receive the standard treatment(s). Standard treatments include a number of FDA approved antibiotics such as ciprofloxacin, amoxicillin, ertapenem and ceftriaxone. Ask the study doctor for more information about these alternative treatments including risks and side effects.

COSTS

You will not have to pay for any of the drugs, medical examinations, procedures, hospitalization, or laboratory tests that are required by this study. You will not receive payment for participation in this study.

COMPENSATION

If you are injured because of your participation in this study, treatment for the injury will be made available through [name of physician] and this institution. The sponsor will pay the costs of this treatment not paid by your medical insurance. No other financial compensation will be provided from the sponsor. You retain all legal rights while participating in this study. You have the right to seek legal advice and/or other treatments if you are injured during the study.

WHOM TO CONTACT

You can ask questions about this form or the study at any time and your doctor or delegate will answer any questions you may have. If you have additional questions during the course of the study about the trial or your rights as a research subject, you may address them to [name] at [contact details].

In the event of a research-related injury or if any other problems arise, please contact [investigator name] at [address and telephone number].

VOLUNTARY PARTICIPATION/ TERMINATION/ TERMINATION PROCEDURES

Your participation in this study is voluntary. You may refuse to participate or may discontinue participation at any time during the study without penalty or loss of benefits to which you are otherwise entitled. If you terminate your participation, you may receive a standard treatment and no prejudice will be shown towards you for medical care or participation in future research studies. In addition, your participation may be terminated by the investigator or the sponsor without regard to your consent if you need additional medication, violate the study plan, experience a study-related injury, or for administrative reasons. If your participation is terminated, you are encouraged to complete the termination procedures (medical examination and laboratory tests) for your own safety. Patients who are terminated early for the reasons described above will be asked to complete the procedures for the End of IV Therapy Visit (see procedures section). You will then be asked to return to complete the Final (Late) follow up visit as scheduled (see procedures section).

You may be withdrawn from the study due to the results of the urine and blood bacterial testing. The study doctor will explain why this has occurred. In this event, you will be asked to immediately complete the End of IV Therapy Procedures and then return in 28-35 days to complete a Final (Late) Follow up visit (see procedures section) and a pregnancy test if you are a female of child bearing potential.

You will be given a copy of this signed and dated information sheet.

SPONSORSHIP/FUNDING

The investigator receives funding from Peninsula Pharmaceuticals, Inc. who is the sponsor of this study.

CONFIDENTIALITY AND AUTHORIZATION TO ACCESS AND USE MEDICAL INFORMATION

The information collected during this study will be kept confidential to the extent provided by federal, state and local law. Only a number and initials will be used to identify you. You will not be personally identified in any reports or publications that may result from this research study. Because of the research goals of this study, however, your study records cannot be kept completely confidential. Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by authorized representatives of the following:

- The study personnel
- Peninsula Pharmaceuticals, Inc. (sponsor) and its agents and [REDACTED]
- In addition, in order to review the study findings, FDA (the US drug agency) and other regulatory agencies may review your medical records.
- US Department of Health and Human Services (DHHS) agencies.
- The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) that oversees the research study at your site.

The following sections provide a specific description of how your information will be used and disclosed if you participate in this research study. If you decide to participate in the study, you will be asked to authorize those uses and disclosures by signing this form. If you choose not to authorize these uses and disclosures of your information, you will not be able to participate in the study.

The medical information that will be collected from you if you participate in the study includes:

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- Information obtained from procedures to determine your eligibility to participate in the trial, including a routine medical history, physical exam, x-rays, electrocardiogram (ECG), blood and urine tests, vital signs, and pregnancy test
- Information that is created or collected from you during your participation in the study, including all procedures performed during the study.
- Information contained in your underlying medical records related to your medical history and treatment.

The above information may identify you by name, address, telephone number, social security number, health plan number, study number, date of birth, dates relating to various medical procedures, or other identifying information.

If you sign this form and participate in the study, the study personnel will be authorized to use the information described above to carry out the purposes of the research study. The study personnel will also be authorized to disclose the information described above to the following parties involved in the research study:

- Peninsula Pharmaceuticals, Inc., [REDACTED] or other agents designated by Peninsula Pharmaceuticals, Inc., to collect or review study data.
- The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) that oversees the research study at your site.
- Government regulatory agencies including FDA (the US drug Agency) and other governmental agencies in other countries.

Once your information is disclosed to the study sponsors, the IRB/IEC or government agencies as described above, there is a potential that your medical information will be re-disclosed and will no longer be protected by US federal privacy regulations. The laws of your state may provide further protection.

While the study is in progress, your access to your study records will be temporarily suspended. You will be able to access your information when the research study is completed. You have the right to see and copy the medical information collected from you in the course of the study for as long as that information is maintained by the study personnel and other entities subject to federal privacy regulation.

This authorization has no expiration date. In signing this form, you authorize the use and disclosure of your information for purposes of the study at any time in the future.

You may revoke your authorization at any time by sending a written request to [insert name of responsible study personnel] at [insert address]. If you revoke your authorization, your participation in the study will end and the study personnel will stop collecting medical information from you. In addition, study personnel will stop using your information and will stop disclosing your information to the parties described above, except to the extent study personnel have relied on information that has already been collected from you. For example, the study

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personnel may need to use or disclose information obtained before you revoked your authorization in order to preserve the scientific integrity of the study.

- **SUBJECT'S STATEMENT OF CONSENT AND AUTHORIZATION**

I have read and understand the statements in this informed consent. I have had the opportunity to ask questions and I am satisfied with the explanations provided by the consent process. I voluntarily consent to participate in the study and I authorize the use and disclosure of my information in connection with the study. I understand that I (or my legally acceptable representative) will receive a signed copy of this consent and authorization form.

SIGNATURES_____
Signature of Subject_____
Signature of Investigator/Delegate_____
Date (personally by Subject)_____
Date (personally by Investigator/Delegate)_____
Printed name of Subject_____
Printed name of Investigator/Delegate