

Peninsula Pharmaceuticals, Inc. / Protocol Number DORI-07

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 with that of Meropenem in Complicated Intra-abdominal Infections."

**Protocol Number:** Protocol DORI-07

**Principal Investigator:**

**Address:**

**Telephone Number:**

You are being asked to consider whether you would like to participate in this clinical 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 complicated intra-abdominal infections. An intra-abdominal infection is a bacterial infection of the abdomen outside of the intestine. It is a common type of infection in patients and requires surgery of the abdomen. This may result from appendicitis (infection of the appendix), perforated ulcer (in the stomach) diverticulitis (inflammation of the intestine's wall), cholecystitis (inflammation of the gallbladder), abscess in the liver or spleen, surgical intervention, or trauma.

The standard treatment for complicated intra-abdominal infection is the administration of antibiotic drugs and surgery. 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 meropenem (for IV injection). This is a medication that has already been approved by the FDA for the treatment of complicated intra-abdominal infection.

Doripenem has been tested previously in several studies with animals and humans. It is expected that approximately 472 subjects in 35 centers in the US, Canada, South America and Europe will be enrolled in this study. Eligible subjects will be those who are currently hospitalized or will be hospitalized for treatment of a complicated intra-abdominal infection.

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**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. In addition, you will be required to call your study staff on a daily basis while taking study medication, to provide a daily update of your health status. 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 done within the 24 hours prior to receiving study medication that will determine whether you are eligible to receive study medication:

- You are to provide written informed consent to participate in this study.
- Your medical history, current medications, and current symptoms will be reviewed.
- You will be given a complete physical examination.
- Your abdomen and surgical wound will be examined thoroughly.
- Your vital signs (temperature, blood pressure, pulse rate, height, and weight) will be taken.
- If you are a woman of child bearing potential you will be administered a pregnancy test.
- A urine specimen will be tested for routine values.
- A blood sample (about three tablespoons) will be taken and tested for routine values, as well as the presence of bacteria if you have signs of bacteremia (bacteria in the blood).
- A sample will be taken from the site of infection and tested for the presence of bacteria.
- Your study doctor may order additional testing such as an ultrasound or a CT scan.
- An ECG (electrocardiogram) will be performed before your first IV drug infusion. The ECG is a painless procedure which uses leads or wires taped on your body to record your heartbeats on paper.

If you qualify to participate in this study you will be given your first dose of the study medication 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 half will receive meropenem (1g) and placebo. 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 meropenem) 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 injection that will last approximately 60 minutes. The length of time you are on drug is dependent upon how well you respond to treatment and will be determined by the study doctor. You may be switched to FDA-approved standard oral antibiotics twice a day (a combination of 875 mg of amoxicillin and 125 mg of clavulanate) as early as the end of Study Day 3 (after you receive 9 doses of intravenous study medication) if medically appropriate. The minimum total number of days you will be on IV and oral study medication is 5 days and the maximum is 14.

The following procedures will occur when you start study medication:

**On Study Day 1:**

- You will be given injections of IV study drug every 8 hours.
- Your temperature will be taken before each injection of IV study drug.
- Your vital signs will be taken.
- Your abdomen and surgical wound will be examined thoroughly.

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

On Study Day 2:

- You will be given injections of IV study drug every 8 hours.
- Your temperature will be taken before each injection of IV study drug.
- Your vital signs will be taken.
- Urine will be collected for routine 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.
- If your study doctor feels it is necessary, a sample may be taken from the site of infection to test for the presence of bacteria.
- Your abdomen and surgical wound will be examined thoroughly.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

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

On Study Day 3:

- You will be given injections of IV study drug every 8 hours.
- Your temperature will be taken before each injection of IV study drug.
- Your vital signs will be taken.
- If your previous blood sample was positive for bacteria, this test will be repeated.
- If your study doctor feels it is necessary, a sample may be taken from the site of infection to test for the presence of bacteria.
- Your abdomen and surgical wound will be examined thoroughly if you are still in the hospital or receiving IV medication.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

After at least 9 doses of IV drug therapy (at the end of Study Day 3 or on Day 4), if your study doctor determines that you are responding to the injections, he/she may permanently discontinue the intravenously administered study drug and switch you to standard (non-experimental, FDA approved) care consisting a combination of oral amoxicillin (875 mg) and clavulanate (125mg).

On Study Days 4 through 14:

Based on your response to the IV therapy, your doctor will determine if/when you may switch to standard oral antibiotics. Each day:

- You will be given injections of IV study drug every 8 hours **or** oral amoxicillin/clavulanate (twice daily).
- Your temperature will be taken before each injection of IV study drug **or** once per day if you are on oral amoxicillin/clavulanate and are still in the hospital.
- Your vital signs will be taken if you are still in the hospital.
- If your previous blood sample was positive for bacteria, this test will be repeated daily until two days in a row show no signs of bacteria.

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- If your study doctor feels it is necessary, a sample may be taken from the site of infection to test for the presence of bacteria.
- Your abdomen and surgical wound will be examined thoroughly if you are still in the hospital or receiving IV medication.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- Starting on Study Day 5, the following will be done once every three days (while you remain on IV treatment)
  - Blood (about three tablespoons) will be collected for routine analysis.
  - Urine will be collected for routine analysis.

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 you prematurely discontinue the study, or if your study doctor determines that you are responding to the injections, on the day that he/she permanently discontinues the intravenously administered study drug and switches you to standard (non-experimental, FDA approved) care consisting a combination of oral amoxicillin (875 mg) and clavulanate (125mg). At this visit the following procedures will be performed:

- A urine sample will be collected for 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, and weight) will be taken.
- Your abdomen and surgical wound will be examined thoroughly.
- If your study doctor feels it is necessary, a sample may be taken from the site of infection to test for the presence of bacteria.
- Your study doctor may order additional testing such as an ultrasound or CT scan.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

Follow-Up visit:

This will occur between 7 and 14 days after your last dose of study medication. 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 routine analysis.
- Blood (about three tablespoons) will be collected for routine analysis.
- If you are a woman of child bearing potential you will be administered a pregnancy test.
- You will be given a complete physical examination.
- Your vital signs (temperature, blood pressure, pulse rate, and weight) will be taken.
- Your abdomen and surgical wound will be examined thoroughly.
- Your study doctor may order additional testing such as an ultrasound or CT scan.
- Whenever possible, a sample may be taken from the site of infection to test for the presence of bacteria.
- 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 42 days after your last dose of study medication. Again, if you are no longer in the hospital you will need to return for this visit on an outpatient basis. At this visit:

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- You will be given a complete physical examination.
- Your vital signs (temperature, blood pressure, pulse rate, and weight) will be taken.
- If indicated, a urine specimen may be collected for routine analysis.
- If indicated, blood (about three tablespoons) may be collected for routine analysis.
- Your abdomen and surgical wound will be examined thoroughly.
- Your study doctor may order additional testing such as an ultrasound or CT scan.
- Whenever possible, a sample may be taken from the site of infection to test for the presence of bacteria.
- 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 drug 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), abdominal pain/discomfort, diarrhea/loose stools, nausea, and loss of or decreased appetite. In addition, there have been reports of elevated liver enzymes, which can indicate liver damage.

The most frequent side effects and discomforts reported for meropenem are nausea, diarrhea, vomiting, rash, itching, and pain at the site of injection, chest discomfort, fever, drowsiness, palpitations, dizziness, and intestinal infection.

The most frequent side effects and discomforts reported for amoxicillin/clavulanate are, anemia (reduction in red blood cells), nausea, diarrhea, vomiting, infection of the intestine, headache fever, vaginitis (infection of the vagina in women), rash and abdominal pain. There may also be side effects and discomforts that are not listed here or are not yet known.

This group of antibiotics may cause severe allergic reactions, especially in people with history of multiple allergies. Seizures may also be caused, especially in people with history of seizures, or taking medications to control seizures. Meropenem and doripenem 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. Inform the study doctor or study staff of any side of these effects or any other effects you experience. 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. If you require a CT scan to evaluate your progress, during the CT scan you may experience a sense of claustrophobia (fear of close spaces); please inform the technician performing the test if you experience this. You may experience discomfort as the ultrasound device is pressed against your abdomen and the gel used to make the device move more easily across your skin may feel cold.

You should inform your study doctor or staff immediately if you have a history of allergies to antibiotics.

Most antibiotics, regardless of classification, can cause the following side effects: inflammation of the vein where the antibiotic is infused (phlebitis), allergic reactions that can cause sudden

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drop in blood pressure, difficulty breathing and even death (anaphylaxis), skin rashes and sloughing (peeling) off of the skin, mouth lesions, pseudo membranous colitis (a disease of the colon characterized by watery, sometimes bloody diarrhea), vaginal and oral yeast infections, constipation.

During the collection of blood samples, you may experience pain and/or bruising at the needle site. Although rare, localized clot formation and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

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. 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.

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. 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.

All positive pregnancy tests must be reported to the [REDACTED] medical monitor within 24 hours of your study doctor's knowledge of the positive results. The positive test results will be recorded on pregnancy forms provided to this site by [REDACTED] following initial report of the pregnancy, and the pregnancy will be followed to the outcome.

If the study doctor finds that you have Hepatitis B or Hepatitis C, your study doctor may be required by state and/or local laws to report these findings. This report may affect your insurance considerations and your social interests.

**BENEFITS**

If the study drug is effective, you may benefit by a cure of your intra-abdominal infection. However, it is possible that you may not personally benefit from participating in this study; although, 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 intra-abdominal 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, levofloxacin, vancomycin 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

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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**

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 should go through the termination procedures (medical examination and laboratory tests) for your own safety. 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. The sponsor of this study is Peninsula Pharmaceuticals, Inc. 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
- The 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.
- 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.

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

- 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

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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 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

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Signature of Subject

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Signature of Investigator/Delegate

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Date (personally by Subject)

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Date (personally by Investigator/Delegate)

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Printed name of Subject

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Printed name of Investigator/Delegate