

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

Sponsor / Study Title: **A Multicenter, Randomized, Open-Label, Phase 3 Study to Compare the Safety and Efficacy of Intravenous Doripenem with that of Intravenous Piperacillin/Tazobactam in Hospital-Acquired Pneumonia**

Protocol Number: **Protocol DORI-09**

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 hospital-acquired pneumonia. Pneumonia is a common type of infection. When a person gets pneumonia while in the hospital, doctors may refer to this as hospital-acquired pneumonia.

Pneumonia is a condition in which your lungs become infected by bacteria, viruses, or other pathogenic organisms (bacteria that cause disease). This type of infection will cause inflammation of the lungs (swelling and fluid in the lungs). Symptoms of Pneumonia include: cough, shortness of breath, fever, shaking chills, chest pain, and exhaustion.

The standard treatment for hospital-acquired pneumonia 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). ***You should inform your study doctor or staff immediately if you have a history of allergies to antibiotics.***

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 antibiotic treatment to be used in this study is piperacillin/tazobactam. This is a medication that has already been approved by the FDA for the treatment of hospital-acquired pneumonia.

Doripenem has been tested previously in several studies with animals and humans. It is expected that approximately 300 subjects in 70 centers in the U.S. and other international study sites will be enrolled in this study. Eligible subjects will be those who are currently hospitalized or who will be hospitalized for treatment of hospital-acquired pneumonia.

PROCEDURES

If you decide to participate in this study, your overall participation will last approximately 5 to 7 weeks. You will be asked to undergo a number of tests during your hospital stay. Your study visits will occur as follows:

Screening visit:

This first visit consists of a series of study tests 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 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 given a pregnancy test.
- A urine specimen will be tested for routine analysis and to check for various types of bacteria.
- A sputum specimen will be obtained.
- A blood sample (about three tablespoons) will be taken for routine analysis as well as checking for the presence of bacteria if you have signs of pyelonephritis (bacterial infection of the kidney) or bacteremia (bacteria in the blood). Blood will be drawn from each arm at separate locations to test for bacteremia.
- You will be given a thorough chest exam.
- You will be given a 12-lead ECG (electrocardiogram which is an evaluation of heart activity).
- A chest x-ray will be performed.
- Oxygenation status will be determined. This will be done either by pulse oximetry (a noninvasive monitoring probe that is clipped to the ear or finger) or by arterial blood gases (a blood sample drawn from the artery instead of a vein which can be painful).

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 half will receive piperacillin/tazobactam (4.5g). Your chance of receiving either of the two active drugs (doripenem or piperacillin/tazobactam) is one in two. The nursing staff will administer either doripenem every 8 hours via IV injection that will last approximately 60 minutes or they will administer piperacillin/tazobactam every 6 hours via IV injection that will last approximately 30 minutes.

The length of time you are on study medication is dependent upon how well you respond to treatment which will be determined by the study doctor. You may be switched to FDA-approved standard oral antibiotics as early as the end of Study Day 3 (after you receive either 9 doses of intravenous doripenem or 12 doses of piperacillin/tazobactam) if medically appropriate. The minimum total number of days you will be on IV and/or oral study medication is 7 days and the maximum is 14.

Amikacin will also be started with the initiation of IV study drug to treat a certain type of bacteria. This may be discontinued at the discretion of the investigator after culture and susceptibility results are available. IV vancomycin may be given if your study doctor suspects you have a certain type of bacterial infection. Your study doctor may discontinue vancomycin if the suspected bacteria is not confirmed by culture results.

The following tests will occur when you start study medication:

On Study Day 1:

- You will be given IV drug infusions either every 8 hours or every 6 hours depending on which drug you are randomized to.
- Your temperature will be taken before each IV drug infusion.
- Your vital signs (temperature, blood pressure, pulse rate) will be taken.
- You will be given a thorough chest exam.
- Blood (about three tablespoons) will be taken for routine analysis.
- A sputum specimen may be collected.
- Oxygenation status will be determined.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

On Study Days 2 and 3:

- You will be given IV drug infusions either every 8 hours or every 6 hours depending on which drug you are randomized to.
- You will be given a thorough chest exam.
- Your temperature will be taken before each IV drug infusion.
- Your vital signs (temperature, blood pressure, pulse rate) will be taken.
- If your previous blood sample was positive for bacteria, this test will be repeated every 24 hours until 2 consecutive samples are negative.
- On day 3 only, blood (about three tablespoons) will be taken and routine tests performed.
- Oxygenation status will be determined.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.

On Study Days 4 through 14:

- You will be given IV drug infusions either every 8 hours or every 6 hours depending on which drug you are randomized to.
- You will be given a thorough chest exam.
- Your temperature will be taken before each IV drug infusion.
- Your vital signs (temperature, blood pressure, pulse rate) will be taken.
- If your previous blood sample was positive for bacteria, this test will be repeated every 24 hours until 2 consecutive samples are negative.
- A sputum specimen will be obtained (if available).
- On day 5 and every three days thereafter, (8, 11, 14) blood (about three tablespoons) will be taken for routine analysis.
- Oxygenation status will be determined.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- A urine specimen will be tested for routine analysis and to check for various types of bacteria.

After at least 72 hours of IV study drug therapy are administered, (9 doses of doripenem or 12 doses of piperacillin/tazobactam) you may be switched to a standard treatment (non-

experimental, FDA approved) consisting of oral levofloxacin (750mg once daily) or another oral antibiotic, if medically indicated.

End of Therapy visit:

This visit occurs at the end of treatment with IV therapy. The end of treatment visit will take place either between days 3 and 14, if the study doctor determines that your infection has been cured, or if you stop the study early. If you have been discharged from the hospital, you will need to return for this visit on an outpatient basis and bring back any remaining oral medicine. At this visit the following tests will be performed:

- You will be given a thorough chest exam.
- Your vital signs (temperature, blood pressure, pulse rate) will be taken.
- If your previous blood sample was positive for bacteria, another sample will be taken.
- Blood (about three tablespoons) will be taken for routine analysis.
- A sputum specimen will be obtained (if available).
- Oxygenation status will be determined.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- A urine specimen will be tested for routine values and various types of bacteria.
- You will be given a complete physical examination.
- A chest x-ray will be performed.

Follow-Up visit:

This will occur between 7 to 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:

- You will be given a thorough clinical examination of the chest.
- A sputum specimen will be obtained (if available).
- Your vital signs (temperature, blood pressure, pulse rate,) will be taken.
- If your previous blood sample was positive for bacteria, another sample will be taken.
- Blood (about three tablespoons) will be taken routine analysis.
- Oxygenation status will be determined.
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- A urine specimen will be tested for routine for routine analysis and to check for various types of bacteria.
- You will be given a complete physical examination.
- A chest x-ray will be performed.

Final (Late) Follow-up visit:

This will occur between 28 and 35 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:

- You will be given a thorough chest exam.
- A sputum specimen will be obtained (if available).
- Your vital signs (temperature, blood pressure, pulse rate) will be taken.
- If your previous blood sample was positive for bacteria, another sample will be taken.

- Blood (about three tablespoons) will be taken routine analysis (if necessary).
- Oxygenation status will be determined (if necessary).
- Any medical symptoms you may have, as well as current and recent medication use, will be reviewed.
- A urine specimen will be tested for routine analysis and to check for various types of bacteria (if necessary).
- You will be given a complete physical examination.
- A chest x-ray will be performed (if necessary).
- If you are a woman of child bearing potential you will be given a pregnancy test.

Throughout the study the study doctor will note any medications you are taking and your symptoms. It is very important that you inform your doctor of any sickness or changes in medication during the study. If any of your blood tests are not normal, the study doctor may draw more blood in order to determine the reason. The study doctor may also test for Hepatitis B or Hepatitis C virus (a virus that infects the liver).

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.

The most frequent side effects and discomforts reported for piperacillin/tazobactam, are nausea, diarrhea, itching, abdominal pain, dizziness, rash, anxiety, and headache.

The most frequent side effects and discomforts reported for vancomycin are lightheadedness or faintness, flushing, back and neck muscle pain, rash, itching, difficulty breathing, upset stomach vomiting, dizziness, vertigo, ringing in the ears and hearing loss.

The most frequent side effects and discomforts reported for Amikacin are upset stomach, vomiting, fatigue and pale skin.

The most frequent side effects and discomforts reported for Levofloxacin are upset stomach, diarrhea, vomiting, stomach pain, headache, restlessness skin rash, itching, hives, difficulty breathing or swallowing, swelling of the face or throat, yellowing of the skin or eyes, dark urine, pale or dark stools, blood in urine, inflammation or rupture of a tendon, seizures, rapid, irregular, or pounding heartbeats.

There may also be side effects and discomforts that are not listed here or are not yet known.

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 line is inserted or where the blood will be drawn. 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. 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. Risk associated with an embryo or fetus is unknown. Females of childbearing potential must use an acceptable method of birth control during this study and for at least 1 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.

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 Pneumonia. 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 your Pneumonia. 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 and amoxicillin. 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.

COMPENSATION

You will not receive payment for participation in this study.

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 his/her 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 [IRB name] at [IRB 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 toward 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 it is determined that 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 consent form.

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 study identification 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]
- The FDA (the U.S. drug agency) and other regulatory agencies may review your medical records in order to review the study findings
- 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:

- 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 the FDA (the U.S. 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 during 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 personnel may need to use or disclose information obtained before you revoked your authorization in order to preserve the scientific integrity of the study.

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• **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

Date (personally by Subject)

Printed name of Subject

Signature of Person conducting the
Informed Consent Discussion

Date (personally by Person conducting the
the Informed Consent Discussion)

Printed name of Person conducting Informed Consent Discussion

I certify that under state law I am the legally authorized representative of the participant named above and that I am authorized to sign this consent to his/her participation in the medical research study described above. I also am authorized to sign this authorization to release medical records and health information as described above.

Signature of Legal Representative

Date

Printed name of Legal Representative