

**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 Imipenem in Ventilator-Associated Pneumonia**

Protocol Number: **Protocol DORI-10**

Principal Investigator:

Address:

Telephone Number:

It is possible that you are reading this informed consent form because you are the authorized representative for an individual that is on a ventilator (a machine that helps you breathe) that has been diagnosed with pneumonia and is unable to make their own healthcare decisions. The following describes a research study into which this individual is invited to participate. Throughout this document the word "you" will refer to the individual that is on the ventilator, for whom, as the authorized representative, you are being asked to give consent. The study doctor will answer any questions 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 ventilator-associated pneumonia. Pneumonia is a common type of infection. When a person gets pneumonia while on a ventilator (a machine that helps you to breathe) in the hospital, doctors may refer to this as ventilator-associated pneumonia.

Pneumonia is a condition in which your lungs become infected by bacteria, viruses, or other pathogenic organisms (bacteria that cause disease). These types 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 ventilator-associated 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 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 imipenem. This is a medication that has already been approved by the FDA for the treatment of ventilator-associated pneumonia.

Doripenem has been tested previously in several studies with animals and humans. It is expected that approximately 400 subjects in 60 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 on mechanical ventilation in need of treatment of ventilator-associated pneumonia.

DURATION

If you decide to participate in this study, your overall participation will last approximately 5 to 7 weeks.

STUDY PROCEDURES

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 or have an authorized representative that is able to make health care decisions on your behalf.
- Your medical history, current medications, and current symptoms will be reviewed.
- You will be given a complete physical examination which includes a thorough chest examination.
- Your vital signs (temperature, blood pressure, pulse rate, respiratory 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 collected 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 in the blood (bacteremia). Blood will be drawn from each arm at separate locations to test for bacteremia.
- You will be given a 12-lead ECG (electrocardiogram which is an evaluation of the electrical activity of the heart).
- A chest x-ray will be performed.
- The level of oxygen in your blood (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).

Study Design

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 by IV infusion every 8 hours over 4 hours and half will receive imipenem 500mg – 1000 mg by IV infusion every 6 to 8 hours over 30 to 60 minutes. Your chance of receiving either of

the two active drugs (doripenem or imipenem) is one in two. These dosages may be modified, based on your underlying medical condition.

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. The minimum total number of days you will be on IV study medication is 7 days and the maximum is 14 while participating in this study.

Amikacin is an FDA-approved IV antibiotic that may 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 study doctor after culture and susceptibility results are available. Vancomycin is an FDA-approved antibiotic that may be given IV if your study doctor suspects you have certain other types of bacterial infection. Your study doctor may discontinue vancomycin if the suspected bacteria is not confirmed by culture results. The doses of amikacin and vancomycin will be calculated for each individual patient, based on body weight and laboratory results.

The following will occur when you start study medication (many of these procedures would be done, even if you were not participating in a research study):

On Study Day 1 (unless already completed due to combination of Screening visit and Day 1 visit):

- You will be given IV drug infusions either every 8 hours or every 6 hours depending on which drug you are randomized to.
- Your vital signs will be taken.
- You will be given a thorough chest exam.
- A blood sample 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 vital signs 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, a blood sample and urine sample will be collected for routine analysis.
- On day 3 only, a chest x-ray will be performed.
- On day 3 only, a sputum specimen will 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 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 vital signs 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 on days 7, 10 and 14.
- On day 5 and every three days thereafter, (days 8, 11, 14) a blood sample and urine sample will be collected 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 chest x-ray may be performed if needed due to infection status.
- After day 7, your pneumonia infection will be rated daily to determine if you should continue to receive IV medicine or if the medicine is no longer needed.

End of Therapy visit:

This visit occurs at the end of treatment with IV antibiotic therapy. The end of treatment visit will take place either between days 7 and 14, if the study doctor determines that the treatment has been effective, 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. At this visit the following tests will be performed:

- Your vital signs will be taken.
- If your previous blood sample was positive for bacteria, another sample will be taken.
- A blood sample will be taken for routine analysis.
- A sputum specimen will be obtained.
- 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 collected 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 complete physical examination
- A sputum specimen will be obtained (if available).
- Your vital signs will be taken.
- If your previous blood sample was positive for bacteria, another sample will be taken.
- A blood sample 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 collected for routine analysis and to check for various types of bacteria.
- 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 complete physical examination.
- A sputum specimen will be obtained (if available).
- Your vital signs will be taken.
- If your previous blood sample was positive for bacteria, another sample will be taken.
- A blood sample will be taken for 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 collected for routine analysis and to check for various types of bacteria (if necessary).
- 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.

RISKS AND DISCOMFORTS**Doripenem**

Certain side effects and discomforts associated with the study drug (Doripenem) may occur. The most frequent side effects and discomforts reported for doripenem are rash, headache, tiredness, constipation, allergic reaction, irritation at the IV infusion site, 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. There have been reports of elevated liver enzymes, which can indicate liver damage.

Imipenem

The most common adverse reactions to imipenem include thrombocytosis (an increase in the number of platelets in the blood, making one more prone to produce blood clots), diarrhea, rash, phlebitis (inflammation of the vein), oliguria (decreased urine production), tachycardia (rapid heart beat), discolored urine, gastrointestinal problems, vomiting, elevated liver function tests (a possible indication of liver damage), elevated creatinine and BUN (an indication of possible kidney damage), central nervous system toxicity characterized by seizures and allergic reactions (e.g., hives, itching, rash, and difficulty breathing).

Vancomycin

The most common side effects include: chills, fever, nausea, ringing in the ears, hives, rash, and inflammation of the vein. A flushing feeling in the head and neck may occur if the vancomycin is infused too quickly (red-man syndrome). Serious reactions that may occur include decreases in some blood counts making you more prone to bleeding or infection. In addition, vancomycin may be nephrotoxic (damage to the kidney leading to possible kidney failure) and / or ototoxic (damage to the nerves of the ear that may lead to deafness).

Amikacin

The most common side effects include: rash, fever, headache, tingling, tremor, nausea, vomiting, eosinophilia (an elevation of a type of white blood cell), joint aches, anemia, low blood pressure. Serious reactions that may occur include neuromuscular blockade (resulting in paralysis and breathing difficulty resulting in death), nephrotoxicity (damage to the kidney leading to possible kidney failure) and ototoxicity (damage to the nerves of the ear that may lead to deafness).

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

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.

Arterial Blood Gas

This involves using a needle to obtain a blood sample in an artery, usually at the wrist. This procedure can be painful. There is the risk of damage to the artery that can cause bleeding, or blockage of the artery if a blood clot develops at the puncture site. This could allow low blood flow (ischemia) or complete loss of blood flow to the hand, resulting in a gangrene/amputation.

Pregnancy

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 and may be hazardous. 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 you must get approval of any changes prior to initiating them. Hormonal contraceptives are not to be used as the sole method of birth control.

Unknown and Unforeseeable Risks

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this medication, including allergic reaction or interaction with another medication. You will be informed verbally and in writing of any new information, findings or changes to the way the research will be performed that might influence your willingness to continue your participation in this study.

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 exclusively required by this study.

COMPENSATION

You will not receive payment for participation in this study.

IN CASE OF INJURY

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

If you have any questions or problems during this study, or if you think that you may have experienced a research-related injury, you should contact [investigator name] at [address and telephone number].

If you have any questions regarding your rights as a research volunteer, please contact [REDACTED]

[REDACTED] during regular working hours. The Independent Investigational Review Board is a committee established for the purpose of protecting the rights of volunteers in a research study.

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 study doctor 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.

SPONSORSHIP/FUNDING

The study doctor 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 Independent Investigational Review Board, Inc. (IIRB)
- The hospital you are being treated at

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 (but is not limited to):

- 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 The Independent Investigational Review Board, Inc. (IIRB)
- 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. Because of the need to disclose information to these parties, absolute confidentiality cannot be guaranteed.

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