

InterMune, Inc.
OCSI-008

PATIENT INFORMED CONSENT

Protocol: OCSI-008 “A Phase I, Randomized, Open-Label, Pharmacokinetic, Drug Interaction Study to Assess the Effect of Oritavancin on the Pharmacokinetics of Desipramine and on the QTc Interval of Healthy Adults”

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Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your doctor if you wish. If there is anything you do not understand, please ask.

It is also very important for you to be honest and complete with all the health information that you provide. If you provide false or incomplete information, including past and present medication use, or fail to report side effects, there could be serious health consequences.

Thank you for reading this.

INTRODUCTION AND PURPOSE OF THE STUDY

You are invited to take part in a research study for an investigational antibiotic known as oritavancin. “Investigational” means that the drug is still being tested and has not yet been approved by the United States Food and Drug Administration (FDA). Antibiotics are used to treat infections caused by bacteria. Oritavancin interferes with the way bacteria build and maintain the cell membranes that surround and protect them. If the bacteria cannot maintain these membranes, they usually die and the infection goes away. Some bacteria are no longer affected by the antibiotics currently available, so new antibiotics are needed. The sponsor of the study, InterMune, is doing studies on oritavancin to get information that the FDA requires for drug approval. Several studies have been completed which show that oritavancin can treat infections caused by these resistant bacteria.

All of the people participating in the study will receive oritavancin. Half of the participants will receive desipramine and the other half will receive placebo. Desipramine

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has been approved by the FDA for the treatment of depression. It is processed (metabolized) in the liver using a specific enzyme pathway. "Placebo" is an inert (inactive) substance and is primarily used in clinical studies to compare the effects of different medications under investigation.

The purposes of the study are: (1) to determine if oritavancin will have any interaction with the enzyme system that breaks down the desipramine, (2) to determine if oritavancin will have any effect on the heart rhythm and (3) to assess the drug concentration and safety of oritavancin over the duration of the study.

STUDY OVERVIEW

Up to 70 healthy volunteers will be enrolled in this study. This study is only being conducted at the PAREXEL Phase 1 Unit in Baltimore, MD. The screening period will last for up to 28 days. During this time, the study staff will determine if you are eligible for the study. If you qualify for the study, you will be housed at the clinic for 24 days. During this time, you will either receive desipramine or placebo by mouth for 21 days. All volunteers will also receive oritavancin (800 mg) from Days 8 to 21 as an intravenous (IV) infusion over 90 minutes. This means that the drug solution is given through a needle in your hand or arm by an IV pump. The IV pump is a machine that controls how fast you receive the drug. A special device, called a PICC line (peripherally inserted central catheter) will be inserted into a large vein in your arm. All of the blood draws will be obtained from this line if possible.

On Day 22, you will be discharged from the clinic and asked to return 7 times for check-ups and tests during the next 28 days. The actual procedures that will be used in this study are described later in this document.

STUDY PROCEDURES

Once you have read this document and had the chance to ask questions, you will have to decide if you wish to participate in the study. If you decide to participate, you will be asked to sign this document. If you decide to participate in this study, you will have screening procedures to determine if you qualify for entry into the study.

The following tests will be performed during the Screening Visit to determine if you are eligible to participate in the study:

1. A complete medical history will be obtained, including a description of any medications you are taking (including vitamins, herbals and medications available over the counter) and any medication allergies that you are aware of.
2. A complete physical examination, including your height, weight, frame size determination and vital signs (pulse, heart rate, blood pressure, and temperature). Females will not receive a breast or pelvic exam. Neither males nor females will receive a rectal exam.

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3. Approximately 30 mL of blood (about 2 tablespoons) will be taken from a vein in your arm to assess your complete blood count, the function of your kidneys and liver, your electrolytes (such as sodium and potassium), total cholesterol and how quickly your body processes (metabolizes) certain drugs. The tests will also determine if you have any evidence of hepatitis A, hepatitis B or hepatitis C or HIV infection. Your blood will also be checked for evidence of alcohol use. Finally, you will be asked to provide a urine sample for routine testing and drug screening. (All results of drug testing will remain private.) If you are a female of childbearing potential you will have an additional blood test, approximately 7mL of blood (about 1 heaping teaspoon), to determine if they are pregnant.
4. You will also have an electrocardiogram (ECG). During the ECG, 10 adhesive electrode pads will be placed on your chest, arms, and legs. These connect to the ECG machine. In order to get a good picture of your heart's electrical activity small areas of hair may have to be shaved from the chest, arms and legs.

The doctor will then review the results of the examination and the tests to determine if you are eligible for the study. If he decides that you qualify, you will be randomly assigned (like flipping a coin) to receive either placebo or desipramine along with oritavancin. This means that you will be assigned to either drug by chance. This study is open label, which means that you and your doctor will know which drug you will receive. If you qualify for the study, the doctor or nurse will arrange the time for you to be admitted to the research unit.

IN-PATIENT STUDY PROCEDURES—DAYS –1 TO 22

Study Day –2—You will be admitted to the research facility three days before the first dosing begins –on Day 1.

Study Day –1—Approximately, 15 mL of blood (about 1 tablespoon) will be taken from a vein in your arm to assess your complete blood count, the function of your kidneys and liver, electrolytes and cholesterol. Your blood will be checked again for evidence of alcohol use. If you are a female of child-bearing potential you will also have blood drawn for a pregnancy test. You will be asked to provide a urine sample for routine testing and drug screening. You will also have one ECG.

Also on Day -1, a special device, called a PICC line (peripherally inserted central catheter) will be inserted into a large vein in your arm. The catheter is a tube like structure that has its tip placed into a large central vein. All of the blood draws will be obtained from this line. The oritavancin may also be given through this line. Before putting in the PICC line, a small ultrasound probe will be placed in the area of potential line placement to look for and examine your veins. The ultrasound uses sound waves (which are not harmful) to look at the veins and see where they are located. Ultrasound can also determine if the veins are good enough to handle a catheter. This is done to reduce unnecessary discomfort as well as the potential problems from trying to place a

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catheter in an inadequate vein. After a good vein is found, the skin on your arm will be cleaned well to prevent infection. A local anesthetic will be used to numb the skin. It is given through a small needle and usually stings before it numbs. It is very similar to novocaine, used by the dentist. Ultrasound will be used again to find the vein and direct the introducer needle into it. The introducer will enable the PICC line itself to be inserted into the vein in your arm. A small guidewire will be placed through the introducer needle into the vein. The guidewire will be slowly pushed forward and will be stopped in a large vein just before it enters the heart. A sheath and dilator will be inserted over the guidewire to open up the vein for the catheter. The guidewire and dilator will be removed, leaving the sheath in place. The PICC line will be inserted through the sheath, which will then be removed. The catheter will be secured to the skin with a Velcro device. The area over the line will then be dressed with sterile dressing and taped in place. You will then have a chest x-ray to make sure that the line is in the correct place. The nurses in the clinic will look after your PICC line and will replace the dressings on a strict schedule to prevent any infection. The line will also be flushed on a regular schedule. This means that a small amount of fluid will be placed into the line to make sure that it is functioning properly. It is important that you keep the area clean and dry. The PICC line will be removed on Day 22.

Study Day 0—This is the day before drug dosing starts. You will have vital signs taken and be asked how you feel. You will have 14 ECGs at various intervals over the next 24 hours. We will call these “Serial ECGs”.

Study Days 1 to 7—Study drug dosing starts on Day 1. Half of the volunteers will receive desipramine 50 mgs and the other half will receive placebo by mouth each day. Each day, you will be asked how you feel and vital signs will be obtained. On Day 7, all females of childbearing capacity will have blood drawn for a pregnancy test.

On Days 1 and 7, all of the volunteers will have 14 Serial ECGs over a 24-hour period. The volunteers who receive desipramine will have blood drawn from the PICC line 12 times at various intervals over 24 hours to check desipramine drug levels. On Days 4, 5 and 6, the volunteers taking desipramine will also have a single blood draw just before the desipramine dose.

Subjects who receive placebo will not have any blood drawn to check drug blood levels from Days 1 to 7.

Study Days 8 to 21—Starting on Day 8, oritavancin (800 mg) will be given IV through a catheter (a small tube placed in your arm to keep the vein open for delivering medication or taking blood). The placebo and desipramine dosing will continue as well. All of the oritavancin infusions will be given over 90 minutes using an IV pump. Vital signs will be obtained each day and you will also be asked to report any illness or problems that occurred since the last the last time you were asked. On Days 8, 14, and 21, all volunteers will have blood drawn to determine drug levels 12 times over a 24-hour period. Also on Days 8, 14, and 21, everyone will have 14 Serial ECGs over the same 24-hour period.

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On Days 8, and 14, approximately 15 mL of blood (about 1 tablespoon) will be drawn from the PICC line to assess your complete blood count, the function of your kidneys and liver, electrolytes and cholesterol. You will also be asked to give a urine sample for routine testing.

Study Day 22—The Serial ECGs and blood draws that started on Day 21 will be finishing on Day 22. Approximately 15 mL of blood (about 1 tablespoon) will be drawn from the PICC line to assess your complete blood count, the function of your kidneys and liver, electrolytes and cholesterol. You will also be asked to give a urine sample for routine testing. When all of the blood draws are complete, a trained member of the research team will remove the PICC line. In most people, the skin where the PICC line was inserted usually heals quickly. You will also have a physical exam, vital signs and an exit interview to ask how you are feeling.

When all study related procedures scheduled for Day 22 are complete, you will be checked out of the research unit.

OUTPATIENT ASSESSMENTS—DAYS 23 TO 49

You will be asked to return to the research unit 7 times for a brief visit. This will happen on Study Days 23, 24, 26, 28, 35, 42 and 49. At each visit, you will be asked to report any illnesses or problems that have occurred since the last visit and your vital signs will be obtained. Blood will be drawn at each visit for blood levels of either desipramine or oritavancin or both. You will also have a single ECG at each outpatient visit.

On Days 28, 35, and 49, approximately 15 mL of blood (about 1 tablespoon) will be drawn from a vein in your arm to assess your complete blood count, the function of your kidneys and liver, electrolytes and cholesterol. You will also be asked to give a urine sample for routine testing. On Day 49, females of childbearing capacity will also have a urine pregnancy test.

A physical exam will be obtained on Days 35 and 49.

EARLY TERMINATION

If you must stop the study for any reason and you received any dose of study medication, you will have the same testing and procedures that are outlined for Day 49. Specifically, you would have blood drawn to check your complete blood count, liver and kidney function, electrolytes and cholesterol. You will be asked to give a urine sample for routine testing and females of childbearing capacity will have a urine pregnancy test. You will have an ECG, a physical exam along with vital signs and you will be asked to report any illness or problems that occurred since the last visit. No drug level testing will be done however.

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HIV AND HEPATITIS TESTING

As required by the study, and if study staff is exposed to your blood, you agree to have your blood tested for the hepatitis viruses. You also agree to have your blood tested for HIV (Human Immunodeficiency Virus), the virus that causes AIDS (Acquired Immunodeficiency Syndrome). Any volunteer with a positive hepatitis virus or HIV test may not be able to stay in the study. You will give your consent to have HIV testing in a separate consent form.

RISKS, INCONVENIENCES AND DISCOMFORT

All drugs have side effects, and there are risks associated with participation in this study. There may also be risks involved, which are currently not known. You will be told of any important new information developed during the course of the study that may affect your decision to participate or continue your participation in the study.

Risks from Oritavancin

As of May 1, 2002 approximately 1150 subjects have taken oritavancin. Adverse events (side-effects) from completed and ongoing studies for which information is available are included in the discussion below.

The most common side effects possibly related to oritavancin include rash, diarrhea and pain and irritation at the site of the study drug infusion (phlebitis). Allergic reactions, such as rash/redness, flushing, nausea, vomiting, diarrhea, shortness of breath and low blood pressure have been reported in some studies with oritavancin. To reduce the chance of these side effects, oritavancin will be given over a period of 90 minutes.

Phlebitis was observed in a previous study when both oritavancin and desipramine were given to healthy adult volunteers. In some of the volunteers, the phlebitis was considered painful and it did not resolve (go away) for several weeks. In some of the volunteers it took longer. The exact cause of the phlebitis in the previous study is still under active investigation by InterMune. If you do develop phlebitis, the oritavancin infusion may be infused through the PICC line to prevent further problems. You will be carefully monitored for the development of phlebitis throughout the study.

Other side effects associated with oritavancin include a decrease in the number of red blood cells (anemia), fast breathing rate, temporary (reversible) changes in liver enzyme tests that are not accompanied by symptoms, abnormal kidney function, abdominal pain, water retention (edema), shaking chills (rigors), chest tightness, fever, itching, difficulty sleeping and mouth infection (thrush).

Oritavancin may interfere with some blood clotting tests, but no bleeding problems have been noted. Based on in vitro data (data obtained from studies done in a test tube), oritavancin could cause changes in the heart rhythm (arrhythmia). Electrocardiograms (which measure the electrical activity of the heart) have been done on subjects and animals that have been exposed to oritavancin. At this time, there is no evidence that oritavancin causes abnormalities of the heart rhythm and no evidence that it causes any

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changes in the electrocardiogram over and above those of a similar antibiotic that has been on the market for many years—vancomycin (Vancocin[®]).

Because oritavancin is similar to the antibiotics vancomycin or teicoplanin (Targocid[®]), people who are known to be allergic to either of these two antibiotics should not receive oritavancin. Antibiotics can cause diarrhea with or without blood in some people, so this could also occur with oritavancin. Oritavancin may stay in the body for a longer period of time than most drugs. Therefore, side effects may take longer to go away.

Rare or unknown side effects could possibly occur, including life-threatening reactions.

Risks from Desipramine

The most common side effects of desipramine include: blood pressure changes, changes in heart rhythm, confusion, anxiety, allergic reactions (rash/redness, flushing, nausea, vomiting, diarrhea, shortness of breath, and low blood pressure), restlessness, trouble sleeping, nightmares, numbness/tingling, dry mouth, increased sensitivity to sunlight, loss of appetite, nausea, vomiting, bad taste in the mouth, weight changes, increased sweating, weakness, fatigue, and an increased need to urinate.

Risks from Placebo

Placebo is an inert substance that is formed into either a pill or tablet. It has no medical effect or side effects. It is used primarily in research studies in order to compare the effects of the medications under study.

Risks from PICC Lines

Specially trained medical professionals will place the PICC lines in your arm. PICC lines are usually safe and well tolerated and complications are rare. Complications can include pain and inflammation of the vein (phlebitis) and infection. If the line is not positioned properly, it may not be possible to draw blood or give medications through the line. If this is the case, the positioning can be changed. The line may come out accidentally or blood may leak from around the line. Rarely, a clot can develop in the line itself. If this happens, the staff may use a small amount of an anti-clotting agent (Cathflo Activase (Alteplase[®])) to clear the line.

Other Possible Side Effects and Risks

The long time you spend in the research unit may make you uncomfortable.

You will be undergoing tests and procedures as part of this study, some of which may be associated with potential side effects or risks. For example, blood being taken from a vein for tests may cause some discomfort and may occasionally cause some bleeding or bruising, infection, fainting, pain at the needle site, dizziness or the development of a collection of blood under the skin (hematoma).

If you have an injury, bad effect or any other unusual health experience during this study, make sure that you tell the nurses, study coordinator or the physician immediately.

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There may be unknown risks of possible harmful interaction with other medication you take. Therefore, it is very important that you tell the study staff if you take any medications (including over-the-counter medications and vitamins) other than the study drug during course of the study.

For Women of Childbearing Potential/Pregnancy Information

Females of childbearing potential have additional risks to consider. Use of either oritavancin or vancomycin may involve risks to the embryo or fetus, which are unforeseeable, if you become pregnant.

Animal studies that might predict if vancomycin or oritavancin has potential risks for your embryo, fetus or unborn child have not been done. **If you are a female of childbearing potential, you will be admitted to the study only if you are not pregnant as determined by a pregnancy test, and you agree to use at least a barrier method of contraception from the time you sign the consent, while you are taking the study medication and until the last study visit at Day 49.** If you are pregnant, there may be unknown risks to your embryo, fetus or unborn child as a result of participating in this study.

If you are pregnant, become pregnant or are currently breast-feeding, you may not participate in this study. If you are pregnant or currently breast feeding, you understand that the embryo, fetus or child may be exposed to unknown risks. If you do become pregnant while on this study, you must inform your doctor immediately, so that you can be counseled, withdrawn from the study and referred for appropriate care. The study Sponsor, InterMune, Inc., and the study doctor will follow the progress of your pregnancy until the termination of the pregnancy or for 6 months following the birth of your child.

POTENTIAL BENEFITS

You may receive information about your health from any physical examinations or laboratory tests to be done in this study.

Since you do not have any of the conditions for which oritavancin is being developed, you will not benefit medically from being a part of this study.

If you decide to participate in this study, knowledge will be gained about the study drug. This information will benefit the Sponsor of the study, InterMune, and may benefit people in the future.

ALTERNATIVE THERAPIES

At this time, you are not sick and do not require an antibiotic for treatment. Because you do not need an antibiotic, there are no alternatives that apply in this instance.

REPORTING HEALTH EXPERIENCES

If you have an injury, bad effect, or any other unusual health experience during this study, make sure that you immediately tell the nurses or Dr. Stock at phone number [REDACTED]

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██████ You may call at any time, day or night to discuss your health concerns or experiences.

PATIENT'S RIGHTS

If you do not want to participate in this experimental study, you can still have your medical questions answered to the best of your physician's ability. Your ongoing medical care will not be affected by your decision to participate in this study or not to participate. Refusal to participate will not involve any penalty or loss of benefits to which you are otherwise entitled.

You may withdraw from the study at any time without jeopardizing your future medical care or possible involvement in subsequent clinical studies. Your participation in this study is entirely voluntary, and you may elect to withdraw from this study at any time.

You may also be withdrawn from the study, and the study medication may be stopped without your consent, for some of the following reasons: 1.) changes in your health that might make continued participation harmful to you, 2.) your failure to keep appointments, 3.) if you decide that you do not want to take the study drug, 4.) if the investigator considers that it would not be in your best interest to continue, 5.) if the investigator or the Sponsor decide to suspend or stop the study. If the study medication is stopped or you withdraw from the study and you have taken any dose of study medication, the procedures outlined in the Early Termination section will be completed.

You will also be informed of any new findings that develop that may relate to your willingness to continue participation in the study. The FDA or InterMune may make changes to the study procedures at any time. If changes occur prior to the start of the study, reasonable attempts will be made to notify you prior to the study check in. Changes made after the study has started will be communicated to you as soon as they have been approved. You can use this information to help you decide if you want to continue in the study.

COMPENSATION

You will not be charged for your participation in this study, for the study medication or for any study-related procedures or tests. As one of the conditions for entry into this study, you must be healthy. All costs for routine treatment of any pre-existing medical condition that you may have, including Emergency Room visits, hospitalizations and tests that are not outlined in the study protocol, will be borne by you or your health insurer.

In the event that you are physically injured as a direct result of the study drug or procedures: (1.) PAREXEL will arrange for appropriate medical treatment for you and (2.) InterMune shall pay for such medical treatments that are not covered by your medical insurance and are considered related to your injury. No other compensation of any type shall be provided by InterMune. If you have an underlying pre-existing medical problem,

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InterMune shall not pay for the treatment of medical complications that are part of the natural course of your illness.

If you have questions about compensation, you may contact PAREXEL study staff. If you have questions about compensation if you have a research related injury or for medical treatments available to you in the event of a research-related injury, you may contact Dr. Tom Stock at [REDACTED]

You will receive up to \$4,725 as reimbursement of expenses for participation in this study if you complete all parts of this study, including the scheduled visits up to and including Day 49. If you do not complete this study for any reason you will be compensated for the visits completed at a prorated rate as indicated below:

\$150 for each overnight stay

\$100 for each follow-up visit

\$425 study completion bonus

All payments will be made to you following your final visit.

In addition, you will receive \$10 for screening.

CONFIDENTIALITY

You understand that all information specific to you and that can be identified as yours, will be held confidential and will not be released without your written permission to the extent permitted by law.

Your records and results will not be identified in any publication resulting from these studies as pertaining to you specifically. Information obtained from this study that does not identify you individually will be given to InterMune, and/or its representatives and may be published or given to regulatory authorities in the United States or other countries in which regulatory approval of oritavancin may be sought.

You will be issued a code number, known only to you and the study personnel. All information about you will be identified only by this code number and your initials, and not by your name. Information about the code will be kept in a locked, secure location and access limited only to study personnel, InterMune, and/or its designee(s), the FDA or the Institutional Review Board. Any information about you, including your test status will not be shared with anyone else (including your spouse or family or health providers), without your written permission.

However, in certain circumstances, InterMune and/or its designee(s), the FDA or Institutional Review Board may request to review your records. If this happens, their request will be honored. If you decide to participate in the study, you understand that you will also be giving consent for the medical investigators and their study staff to review your medical records for the purpose of this study.

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Also, your original medical records may be reviewed by InterMune and/or its representatives, the Institutional Review Board for this study, and regulatory authorities (FDA) for the purpose of verifying clinical trial procedures and/or data. Your medical information may be held and processed on a computer.

Finally, it is possible that collected information relating to the study will be analyzed by InterMune in the future to evaluate oritavancin for other possible uses or for other medical or scientific purposes other than those currently proposed.

By signing this consent form, you authorize the record review, information storage, and data transfer described above.

QUESTIONS

If you have any questions about this study, please contact Dr. Tom Stock at [REDACTED]
[REDACTED]

If you have any questions about your rights as a participant in a research study, please feel free to contact the Western Institutional Review Board at:
3535 Seventh Ave SW
Olympia, WA 98508
Phone: 1-800-562-4789

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VOLUNTEER'S STATEMENT

You, the undersigned, hereby voluntarily consent to participate in a research study entitled "A Phase 1, Randomized, Open-Label, Pharmacokinetic, Drug Interaction Study to Assess the Effect of Oritavancin on the Pharmacokinetics of Desipramine and on the QTc Interval of Healthy Adults".

You understand that Dr. Stock is the Principal Investigator of this study. You further understand that this Investigator is in charge of the study and will be responsible for safeguarding your welfare while you participate in the study. You understand that the Institutional Review Board has approved this study. If you believe that there is any infringement on your rights or if you have questions about your rights as a research subject, you may contact _____ at _____.

You are satisfied that the study personnel have explained the nature of the study, the procedures, the benefits and the risks adequately to you. You understand that you may contact them if you have further questions. You understand the statements in all of the preceding sections of this Informed Consent document.

This version of the Informed Consent replaces all versions previously signed.

You will receive a copy of this consent statement for your own information.

_____ Printed Name of Study Participant	_____ Signature of Study Participant	_____ Date
_____ Printed Name of Person Obtaining Consent	_____ Signature of Person Obtaining Consent	_____ Date
_____ Printed Name of Investigator or Sub- Investigator	_____ Signature of Investigator or Sub- Investigator	_____ Date