

**INFORMED CONSENT FOR PARTICIPATION IN CLINICAL RESEARCH**  
**HARTFORD HOSPITAL**

**STUDY TITLE:**

**A Single-Center, Open-Label, Phase I Trial Evaluating the Pharmacokinetics and Tissue Penetration of Oritavancin in Normal Healthy Male Volunteers – Group A**

**PRINCIPAL INVESTIGATOR:** David Nicolau, Pharm.D., FCCP  
**DEPARTMENT:** Center for Anti-Infective Research and Development  
**PHONE:** [REDACTED]  
**EXPECTED DURATION:** 3 months  
**SPONSOR:** InterMune, Inc.

- I. You have been asked to participate as a subject in the research study, “A Single-Center, Open-Label, Phase I Trial Evaluating the Pharmacokinetics and Tissue Penetration of Oritavancin in Normal Healthy Male Volunteers – Group A”. The purpose, procedures, and length of your involvement are stated below:

**A. Purpose of research:**

For you to be able to decide to be part of this study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. This consent form describes the purpose, procedures, possible benefits and risks of the study. Once you understand the study, you will be asked to sign this form if you wish to participate. If you are in any other study, you cannot take part in this study.

Your healthcare provider may be an investigator for this research project, and as an investigator, is interested both in your clinical welfare and in the conduct of this study. The investigator is being paid by InterMune, Inc., the study sponsor, to conduct this study. Before entering this study or at any time during the study, you may ask for a second opinion about your care from another doctor who is in no way associated with this study. You are not under any obligation to participate in this or any other research project.

The lead investigator for this site, Dr. Nicolau, has a potential conflict of interest with this study because he has done one or more of the following: spoken for a fee, been paid as a consultant, or bought stock in the company sponsoring the study. Before agreeing to participate, you may obtain more information about the potential conflict of interest if you wish, by calling the research staff or by calling [REDACTED] at [REDACTED]

The drug that is being evaluated in this study is an antibiotic called oritavancin, which is made by the study sponsor, InterMune, Inc. Oritavancin is currently not approved by the Food and Drug Administration (FDA) for general use. At the present time, the drug is being tested in patients in a large study for the treatment of skin infections. The study you are volunteering for involves healthy subjects and will give scientific information to support a FDA indication for the treatment of skin infections. This study will measure how much of a specific dose of oritavancin reaches the skin, when given intravenously (through the vein) as 200 mg once per day for three consecutive days. Blisters will be used to mimic (imitate) a skin infection on your arm, and the

fluid from these blisters will be collected with a needle to measure how much oritavancin is in your skin. Approximately 20 teaspoonfuls of blood will be collected and a total of 7 blisters will be made throughout the study. The information from this study will help the investigator and the sponsor to better understand the effects of oritavancin in killing bacteria that cause skin infections. Eight subjects in total may be asked to participate in this research study.

**B. Procedures:** Your participation in this study will involve the following procedures:

1. To participate in the study, you will need to be screened (interviewed) by one of the investigators to make sure you meet the following general criteria: **a)** be able to give written informed consent and understand and comply with the requirements of the study; **b)** be a healthy male between 18 and 65 years of age; **c)** be willing to abstain from alcohol use during the entire course of the study; **d)** be healthy as determined by a medical history, physical examination (or check-up), vital signs (blood pressure, heart and breathing rate, and temperature), height and weight measurement, ECG (measures how the heart beats by placing suction cups attached to a machine on specific parts of your body), and routine laboratory tests (blood tests); and **e)** not have any other characteristics as discussed by the investigator that would prevent you from participating.
2. If you are appropriate for the study and sign this consent form, you will undergo two evaluations before the start of the study. The first evaluation will be done at the screening visit, within 21 days before receiving oritavancin, as described above. A second evaluation will be performed 1 day before the first dose of study drug to make sure you are still eligible. These evaluations will both include a physical exam and a medical history.
3. If still eligible, you will receive intravenous oritavancin 200 mg every morning for three consecutive days.
  - A. You will be required to report to the Clinical Research Center (CRC) the evening before the first dose and stay there until the afternoon of the next day following dosing.
  - B. On study day 1, the following will take place:
    - A single blood sample (approximately 1 teaspoonful) for drug analysis will be taken before giving you the first oritavancin dose.
    - You will be given the first intravenous dose of oritavancin that will last for approximately 1 hour.
    - You will be allowed to leave the CRC 2 to 4 hours after receiving the dose for that day.
    - Any reaction to the drug will be closely monitored and a concomitant medication review will be conducted throughout the study.
  - C. On study day 2, you must report to the CRC at approximately 7am in the morning to receive the 2<sup>nd</sup> dose of oritavancin. On this day, the following will take place:
    - You will be given the 2<sup>nd</sup> intravenous dose of oritavancin.
    - You will be allowed to leave the CRC 2 to 4 hours after receiving the dose for the day.
    - You will be required to come back to the study center at approximately 6pm that same day to begin the next part of the study, which will last approximately 48 hours.
    - You will be provided dinner that night, but will not be allowed to eat anything from 11pm until 2 hours after you receive the 3<sup>rd</sup> dose of oritavancin on study day 3.

- Upon your return that night, a series of 4 drops of a blister producing ointment (cantharidin) will be placed on your forearms and covered first with a band-aid, then with a protectant spray. Four fluid-filled blisters will begin to form in a few hours from which a series of samples will be taken using a thin needle on study day 3.
- Any reaction to the drug will be closely monitored and a concomitant medication review will be conducted throughout the study.

D. On study days 3 and 4, the following will take place:

- Blood samples (approximately 2 teaspoonfuls) and a urine sample will be taken before giving you the final oritavancin dose to test routine laboratory results.
- You will receive the 3<sup>rd</sup> and final dose of oritavancin at approximately 7am on study day 3.
- Vital signs will be monitored before, , and after the oritavancin dose.
- From the 4 blisters that grew on your forearm overnight, a series of 7 blister fluid samples will be taken with a thin needle at specific time intervals starting just prior to starting the final oritavancin dose.
- Seven blood samples (1 just before the oritavancin dose and 6 after) of 5 ml each (approximately 2 ½ tablespoonfuls total) will also be taken at specific time intervals for drug analysis.
- On the evening of study day 3, a single drop of blister producing ointment (cantharidin) will be again placed on your forearm and then covered with a band-aid and a protective spray.
- The last blood and blister samples will be taken in the morning of study day 4.
- After this, the blisters will be drained and covered with sterile dressing to allow healing.
- You will be free to leave later that afternoon to return 2 days later (study day 6).
- Any reaction to the drug will be closely monitored and a concomitant medication review will be conducted throughout the study.

E. On study days 6 and 7, the following will take place:

- You will return to the CRC at approximately 6pm on study day 6 and will be required to stay for approximately 18 hours.
- On the evening of day 6, one drop of blister producing ointment (cantharidin) will be placed on your forearm and will be covered with a band-aid and a protective spray. A single fluid-filled blister will begin to form in a few hours from which a blister sample will be taken using a thin needle the following day.
- On study day 7, a blister fluid and a blood sample (approximately 2 teaspoonfuls of blood) will be taken at a specified time.
- The blister will be drained and covered with sterile dressing to allow healing.
- You will be allowed to leave the CRC later that afternoon to return 2 days later (study day 8).
- Any reaction to the drug will be closely monitored and a concomitant medication review will be conducted throughout the study.

F. On study days 8 and 9, the following will take place:

- You will return to the CRC at approximately 6pm on study day 8 and will be required to stay for approximately 18 hours.
- On the evening of day 8, one drop of blister producing ointment (cantharidin) will be placed on your forearm and will be covered with a band-aid and a protective spray. A

single fluid-filled blister will begin to form in a few hours from which a blister sample will be taken using a thin needle the following day.

- On study day 9, a blister fluid and a blood sample (approximately 2 teaspoonfuls of blood) will be taken at a specified time.
- The blister will be drained and covered with sterile dressing to allow healing.
- You will be allowed to leave the CRC later that afternoon to return 3 days later (study day 12).
- Any reaction to the drug will be closely monitored and a concomitant medication review will be conducted throughout the study.

G. On study day 12, the following will take place:

- This is the last day of the study. You will return to the CRC the morning of study day 12 to get the last blood sample. A single blood sample (approximately 2 teaspoonfuls) and a urine sample will be taken at a specified time.
- Any reaction to the drug will be closely monitored and a concomitant medication review will be conducted throughout the study.
- Before you leave the study center you must undergo a final brief physical exam including inspection of the healing blisters, vital signs and samples of blood (approximately 4 teaspoonfuls) and urine for laboratory tests. You will also be reminded to notify study personnel if you have any unusual signs or symptoms during the next month.

Of the item(s) listed above, the following is/are **experimental**:

1. Oritavancin is an experimental intravenous antibiotic that has not yet been approved by the FDA.
2. The application of cantharidin ointment to cause a blister is an experimental process.
3. The collection of skin blister fluid and blood to determine how much drug is contained in each will be conducted for experimental purposes.

C. **Duration of Participation:** This study will take place at Hartford Hospital in the CRC located on the 6<sup>th</sup> floor of the Education and Resource Center. Your participation will last for up to 5 weeks, depending upon when you are initially screened to participate. The study itself will last 13 days.

II. The possible **risks**, discomforts and side effects of the procedures are described below, including safeguards to be used for your protection:

1. Side effects that might occur due to oritavancin administration are minimal. You may develop an allergic reaction to oritavancin. An allergic reaction is possible with any drug and can be life-threatening. An allergy to oritavancin may result if you have had an allergic reaction to vancomycin, teicoplanin or any other glycopeptide antibiotic in the past. Oritavancin is generally safe and well tolerated. Side effects experienced in human trials include sleep disturbance, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea), histamine-related infusion reactions (itching, red skin, allergic reactions), asymptomatic reversible elevations in liver enzyme tests (clinically insignificant increases in the enzymes produced by your liver), and phlebitis (vein irritation).

2. If you are allergic to glycopeptides such as vancomycin, teicoplanin or oritavancin, you must not participate in this study. You will also inform your study doctor about any medication you have recently taken to enable him/her to decide if you can be included in this study.
3. Cantharidin administration: although cantharidin is not an FDA approved drug, it has been in use for many years for the treatment of warts and a certain virus infection of the skin. Cantharidin has been shown to be well tolerated but risks include skin infection (cellulitis) and inflammation (swelling) of the lymphatic channels. The use of cantharidin to produce skin blisters was well tolerated in numerous investigations similar to this present study. You may feel minor discomfort within the first few hours after administration of cantharidin such as burning, tingling or itching, and may also note some redness of the skin. The raised blister will disappear within 4 to 7 days after drainage. Skin discolorations (redness) due to blisters may last 3 weeks up to 16 weeks and varies among individuals. Although not usual, the use of cantharidin may potentially lead to scarring, specifically if scratched. If burning or swelling of the arms continues after 7 days of drainage, you should notify Drs. [REDACTED] or Nicolau immediately for follow-up.

It is important to note that cantharidin is for external use only. It is very toxic if swallowed and causes vomiting, diarrhea, abdominal pain and a fall in blood pressure. Deaths from swallowing cantharidin-containing materials have been reported. It is also very irritating to the eyes.

4. Risks associated with the drawing of blood samples include bruising and pain at the site of the blood draw and a possibility of feeling faint from having your blood drawn. An infection at the site where blood is drawn is also possible but rare.
5. You may be inconvenienced by the timing of the procedures and by the overnight hospitalization.
6. You will be told immediately of any information that becomes available that may affect your willingness to participate in this study.
7. The study drugs used in this study may involve other risks – including possible life threatening reactions – that are not known at present.

III. There are possible **benefits** to you or others to be expected from your participation in this research as described below:

1. You will not receive direct benefits from participating in this study. However, your participation will provide information about the study treatment that may benefit others.

IV. There may be **other treatments** for your condition. You should consider these as well as the treatments in the study just described. Other treatments are:

1. Since this is not a treatment study, no other treatment alternatives exist.

V. The investigator is willing to answer any **questions** you may have concerning the procedures herein described. You do not have to sign this consent until all the questions you have at this time

have been answered. Future questions about this study may be directed to Dr. David Nicolau [REDACTED] or [REDACTED]. If you have questions regarding your rights as a research subject, you may contact an IRB Representative at (860) 545-4410. You have the right to ask questions about this study at any time and are encouraged to do so.

If you have questions about the research in general, you can call [REDACTED] at [REDACTED].

If you have questions about the treatments during the research project, you are free to call **Doctors . Nicolau** [REDACTED] or [REDACTED]. If you experience an injury you believe is related to this study, you will contact Drs. Nicolau or [REDACTED] at the above numbers.

If you have any confidential issues to discuss, such as problems or complaints, you may call Patients Relations at (860) 545-1400 and talk to someone who is not connected with the research.

- VI. Your participation is voluntary** and you may refuse to participate and/or withdraw your consent and discontinue participation in the project at any time without penalty or loss of benefits to which you are otherwise entitled. Your decision whether or not to participate will not affect your future medical care at Hartford Hospital. You may also be withdrawn from the study, and the study medication may be stopped without your consent, for any 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 sponsor decide to suspend or stop the study.

If the study medication is stopped or if you withdraw from the study after you have taken any dose of study medication, the procedures outlined in the end of study visit will be completed.

- VII. You will receive financial compensation** as discussed below:

After the completion of the study (processing of the payment check will take 2 to 4 weeks), you will receive \$1,750.00 in compensation. If you do not complete the study, you will receive compensation consistent with the percentage of study completed. Such amount is taxable income to the recipient and will be reported by Hartford Hospital to the Internal Revenue Service.

- VIII. Your confidentiality** will be guarded to the extent possible. Hartford Hospital will protect all the information about you and your part in this study just as is done for all patients at Hartford Hospital. However, because this is a research study, study personnel, the study sponsor (Intermune Inc.) and/or its designees, the Federal Food and Drug Administration and the institutional review board may have access to these data. Your records will be maintained in accordance with applicable state and federal laws. However, private identifiable information about you may be used or disclosed for purposes of this research project. You may request that your records be released to your personal physician.

The information that may be used or disclosed includes the following:

1. The data and results from this study may also be presented at meetings or in publications, but in those presentations study participants will not be identified by name.
2. This information may be used or disclosed by the Hartford Hospital Center for Anti-infective Research and Development.
3. The information may be disclosed to national and/or international meetings and in publications.

The use or disclosure of the information is permitted until March 2010.

By signing this consent you are agreeing to the use or disclosure of your protected health information as described above. If you do not agree to the use or disclosure of the information as described and therefore do not sign this consent, you may not be in the study.

If, after signing the consent, you change your mind, you have the right to revoke your consent, in writing. However, you may be withdrawn from the study.

Once private information is disclosed, it is subject to redisclosure by the recipient, and no longer can be considered protected.

You may obtain a copy of the Hartford Hospital Privacy Notice for a complete description of the Hospital's privacy practices for protected health information.\* You have the right to review the Notice before signing this consent.

\*The Privacy Notice is expected to be available on or before April 14, 2003, when the Privacy regulations take effect. If you agree to enroll in a study prior to that date, and before the Notice is available, you may request that the Notice be provided to you when it is available.

- IX. Hartford Hospital does not provide insurance coverage to compensate you if you have an **injury** as a result of participating in this research. However, you may still be eligible for compensation. If you are injured, you can file a claim against the state of Connecticut seeking compensation. For a description of this process, or available compensation options, you may contact a representative of the Hartford Hospital Institutional Review Board (IRB) at (860) 545-4410. In case of any injuries as a direct result of taking part in this research project, you will receive help in the following way:

If you have medical insurance, the hospital will collect fees for medical treatment from your insurance company. If you are not fully covered or uninsured, the commercial sponsor of the study or Hartford Hospital will cover these expenses. The hospital will not pay medical expenses at other hospitals or pay for pain and suffering, travel, lost wages, or other indirect costs of taking part in this project.

If you experience any side effect or injury, you should notify your study doctor immediately so that you can receive appropriate medical treatment. If you suffer any adverse reaction or other physical injury resulting directly from the research study drug, InterMune, Inc. will provide reimbursement for the reasonable costs of medical treatment if:

- You took the study drug as instructed by your study doctor
- Your injury was not deliberately caused
- The study doctor was immediately notified about your injury
- You followed the medical advice of the study doctor

You will not be reimbursed for lost wages or other damages or losses or for medical expenses that have been covered by your medical or hospital insurance or by third party or governmental programs providing such coverage. No other form of compensation is available from InterMune, Inc. except remedies available under the law. Compensation for medical expenses is not an admission of fault or liability by InterMune, Inc. or anyone else.

#### **X. Signatures**

I have been given a copy of this informed consent form to keep. I have read it, and I hereby voluntarily agree to participate in the research study, "A Single-Center, Open-Label, Phase I Trial Evaluating the Pharmacokinetics and Tissue Penetration of Oritavancin in Normal Healthy Male Volunteers – Group A", and consent to the performance of the above procedures upon me.

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Participant's Signature // Date

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Relationship if not Self (describe authorization to act on behalf of participant)

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Investigator's Signature or Person Obtaining Consent // Date

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Witness (person observing the explanation of the above information to the participant) - optional unless consent is presented orally.