

**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Title: A Phase 1 Open Label Study to Evaluate the Safety and Pharmacokinetics of Intravenous Dalbavancin in Subjects with Severe Renal Impairment or End-Stage Renal Disease and Healthy Subjects with Normal Renal Function

Site of Investigation: Orlando Clinical Research Center
4401 South Orange Avenue, Suite 108
Orlando, FL 32806
24-Hour Telephone Number: (407) 240-7878

Principal Investigator: THOMAS C. MARBURY, MD

Sponsor: Vicuron Pharmaceuticals, Inc.

INTRODUCTION

You are being invited to participate in a clinical research study because you are either a healthy individual or have renal disease. The following information describes the study and your role as a participant. This document is intended to inform you about the nature and risks of the clinical study in which you have been invited to participate. The study doctor or his designee will answer any questions you may have about this consent form and about the study. Please read this consent form carefully and do not hesitate to ask any questions you may have about the information provided below or about any words that you may not understand. Your participation in this study is entirely voluntary. If you choose to participate, you have the right to withdraw from the study at any time.

DESCRIPTION AND PURPOSE OF THE STUDY

The study doctor and Vicuron Pharmaceuticals, Inc., the sponsoring drug company, are conducting this research study of an investigational drug called dalbavancin, an antibiotic being developed which may be effective against bacterial infections that are difficult to treat. An investigational drug is one that has not been approved by the FDA (Food and Drug Administration) for general use in the United States, but may be tested in research studies such as this one. The purpose of the study is to determine if dalbavancin is safe and well tolerated and to calculate how volunteers with severe kidney impairment and volunteers on hemodialysis (end-stage renal disease) and healthy subjects with normal kidney function eliminate dalbavancin. Additional objectives may include adjusting dosage in subjects with kidney disease. Information about any side effects that may occur will also be collected. This study is designed for research purposes only and is not intended for the treatment of any medical condition.

If you agree to participate in this study, you will be one of about 24 people in this study which is being conducted at multiple research centers. The duration of your participation in this study is approximately 81 days, which includes a screening visit within 21 days of entering the study, a 4 day/3 night clinic confinement and 5 outpatient visits.

STUDY PROCEDURES

If you agree to participate in this research study, you must sign this consent form before having any study-related tests or procedures performed.

Volunteers for this study must meet certain requirements. You must be 18 to 80 years of age. You will be assigned to one of three groups based on your kidney function as follows:

- **Group A** – Severe Kidney Impairment
- **Group B** – End-Stage Kidney Impairment (Hemodialysis Subjects)
- **Group C** – Normal Kidney Function

Since this is a study of an investigational drug, it is important to answer all questions honestly and to tell the study staff your complete health history.

SCREENING

You will complete a screening process to determine if you are eligible and willing to participate. You will be required to fast (no food or drink, except water) for at least 10 hours prior to this visit. The following tests will be performed:

- Complete medical history including your medication history and if you have been taking any medications (over the counter or prescription), herbal supplements or vitamins in the past three months.
- General physical examination including vital signs (blood pressure, pulse, temperature), height and weight.
- Electrocardiogram (EKG) - a test to monitor the heart.
- Blood samples for clinical laboratory testing
- Collection of a urine sample for laboratory testing
- Drug screen (for drugs of abuse).
- Female volunteers will have a pregnancy test (must be negative in order to participate in the study).
- Nasal swab for bacterial cultures
- Evaluation of kidney function which may require the collection of urine over a 24 hour period

Screening does not guarantee entry into the study. Entry into the study will depend upon the results of your laboratory tests, study specific guidelines, and the discretion of the study doctor.

DOSING AND PROCEDURES

If you qualify for participation in this study you will be admitted to the clinical research center the evening before dosing (study day -1) and you will remain at the research center through study day 3.

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Study Day -1: You will be admitted to the clinical research center in the afternoon/evening prior to dosing and the following procedures will be performed.

- Nasal swabs for bacterial culture will be collected.
- Your medication history will be reviewed.
- Vital signs will be taken.
- Healthy volunteers (Group C) will be required to provide a stool sample within two days prior to receiving study medication. This sample must be brought to the research center within four hours of collection.
- Women who are able to become pregnant will also have a blood sample collected for a pregnancy test.

Study Day 1-3: On Study Day 1 a catheter (small plastic flexible tube) will be inserted into your vein in your arm. The catheter will allow the study personnel to administer the study drug. An additional catheter may be inserted for blood draws. Before study medication is given, you will be asked to empty your bladder, blood samples will be drawn and vital signs will be taken. You will receive a single dose of 500 mg (milligrams) of dalbavancin over 30 minutes through one of the catheters in your arm.

If you have dialysis treatments (Group B), you may receive your study drug before or after your treatment. Dialysis will be done at the research center. The study personnel will assign when you receive your study drug. Dialysate samples will be taken before dialysis and every hour throughout the dialysis treatment.

Blood samples will be taken to measure the levels of the study drug in the blood at the end of infusion, and at 4 and 12 hours after the start of infusion. Additional blood samples will be taken to measure blood levels of the study drug on Days 2 and 3 at approximately the same time that the study drug was started on Day 1. Subjects in Group A and Group C will have all of their urine collected from Day 1 through 3 (72-hours) beginning immediately after the start of the study drug infusion. The urine collected will be used to measure levels of the study drug over the course of the study. Subjects in Group C only will have all of their feces collected from Day 1 through 3 (72-hours) beginning immediately after the start of the study drug infusion. The feces will be collected to look for study drug. Your blood pressure, pulse, respiration, and temperature will be taken at the end of the infusion and 4 and 12 hours after the start of the infusion. An EKG will be taken shortly after the completion of the study drug infusion. Blood will be drawn on Day 3 for laboratory testing. You will also be given a physical examination including vital signs (heart rate, temperature, and blood pressure) on Day 3. It may be necessary to have your nose swabbed on Day 3. You will go home on Day 3 following the completion of all study procedures. Throughout the study you will be monitored for side effects.

Outpatient Visits: You will return to the clinical research center on days 7, 14, 28, 42, and 60. At each visit, blood samples will be taken at approximately the same time that the study drug was started on Day 1. You may have urine samples collected to measure levels of the study drug over the course of the study or you may be asked to collect a 24-hour

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urine sample on one day within a week of each of the study visit days. Group C participants will be asked to collect a fecal sample within a week of each of the study visit days and return the sample to the clinic within 4 hours. If you have dialysis treatments (Group B), you will have one of your dialysis treatments at the research center between study days 14 to 28 to collect dialysate samples. You will also be given a physical examination including vital signs (heart rate, temperature, and blood pressure) on days 14, 28, and 60. Blood will be drawn on days 14, 28, and 60 for laboratory testing. You may have your nose swabbed on study Days 28 and 60.

During the study, you will be monitored closely for possible side effects. At each visit, you will be asked about any symptoms or illnesses that you may have experienced. In addition, you will be asked to inform the investigator and/or study staff of any medications or therapies you are taking while you are participating in this study.

BLOOD SAMPLING

Blood samples may be drawn from an indwelling catheter. An indwelling catheter is a special needle device designed to be placed in a vein and then remain in the vein over a period of time and is used to obtain multiple blood samples, thus lessening the number of needle punctures. The catheter will be inspected, maintained and may be changed, if necessary. If the use of the catheter is not possible, the blood samples will be taken by individual needle-sticks from one of your arm veins.

Approximately 168 ml (a little more than 2/3 cup) of blood will be collected over the course of the study. For comparison, a standard blood donation at a blood collection center, once in any 56-day period, is about 2 cups of blood. Additional blood samples may be drawn during the study if the study doctor considers it necessary for monitoring your health.

RESTRICTIONS

During your stay in the research center, you must follow the study rules about tobacco, alcohol, or any unauthorized drugs.

Food and beverages will be provided during your stay in the research center. You will be served standard meals and snacks according to a uniform daily diet. You may not bring your own food or beverages.

RISKS AND DISCOMFORTS

Possible risks associated with either the study procedures or study medications are listed below. There may be risks that are not known. Other possible side effects may occur in addition to those listed below. It is important that you tell the study staff about any side effects that you may have had even if you do not think it is related to the study drug.

Dalbavancin: has been well tolerated in healthy subjects administered up to 1120 mg dalbavancin as a single IV dose. Possible side effects are similar to those associated with taking currently available antibiotics that work in a similar manner as dalbavancin. Possible side effects may include diarrhea, abdominal pain, heartburn, liver damage, low grade

fever and kidney damage. Side effects associated with the administration of the drug include pain, redness or discomfort at the infusion site. In exceptional cases, hearing impairment was observed with other drugs in this class that work in a similar manner.

The drug may stay in the blood stream longer in a person whose kidneys are not working normally. In addition, the drug may act on the body longer, and it might also have more side effects. It is also possible that you may experience worsening of your kidney disease.

Unforeseen Risks/New 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 should notify the study doctor immediately if you experience allergy symptoms such as rash, hives, or itching. Untreated allergic symptoms can lead to a medical emergency. 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.

Blood drawing: Local pain, bruising, bleeding, blood clot formation, and in rare instances an infection might occur at the site of the needle stick where blood is drawn and at the site where the catheter is placed. There is also the possibility of dizziness or fainting while your blood is being drawn.

Additional risks: The electrocardiogram (EKG) procedure may cause minimal discomforts during the attachment and removal of the EKG leads to and from the skin.

Pregnancy/Fetal Risks: The effects of the study drug on the unborn child are unknown. Nursing mothers or women who think they may be pregnant are not eligible to participate in this study. **It is very important that you do not become pregnant during this study.** Birth defects, including physical deformities, mental retardation, and other problems, as well as premature birth are known risks of some drugs.

If you are a woman who is able to become pregnant, you must have a negative pregnancy test at the screening visit and at the check-in visit. Women will only be allowed to enter this study if they are surgically sterile (have undergone a bilateral tubal ligation, removal of both ovaries, or total hysterectomy), postmenopausal (at least 1 year without periods), or using a medically acceptable method of birth control for at least 1 month prior to study entry, while participating in the study, and for at least one month after study discharge. Medically acceptable birth control methods for this study include:

- condom with spermicide
- diaphragm with spermicide
- hormonal contraception (i.e. birth control pills) with barrier
- IUD

If you suspect you are pregnant at any time during the study, you must notify the study doctor immediately. If you do become pregnant during your participation in this study, you will be discontinued from the study and all costs for care related to your pregnancy, childbirth, and post-partum/newborn care will be your responsibility. The sponsor may request access to your records as well as your infant's hospital/clinic records from the time your pregnancy is diagnosed and for up to 8 weeks after delivery. If additional follow-up is necessary, your study doctor will inform you of the requested procedures.

BENEFITS

This study is not designed to benefit you directly. You may receive information about your health from the laboratory tests that are performed as a part of this study. Future patients may benefit from the overall conclusions drawn from the results of the study. Information obtained from this study will benefit the sponsor of the study.

COSTS

There is no charge for participating in this research study. The study sponsor pays all the study costs. Orlando Clinical Research Center and the Investigator will receive payment from the sponsor for the time spent on this study.

PAYMENT INFORMATION

You will be paid for taking part in this study as outlined below. This is to compensate you for your time and travel. Each portion of the study has a monetary value assigned to it, which accumulates as you participate in the study. You will be paid within 7 days of the completion of your participation in this study. No additional financial compensation has been arranged.

Schedule of Payments

Visit	Amount
Screening	No Compensation
Day -1 (check-in/admittance)	\$ 50.00
Day 1 & Day 2	\$ 150.00 each day
Day 3 (discharge from clinical research center)	\$ 50.00
Outpatient Visits - Days 7, 14, 28, 21	\$ 50.00 each visit
Day 60 - Final Visit	\$ 100.00

Group B subjects only will receive an additional \$75.00 for the dialysis treatment visit between study days 14-28. Group C only will receive an additional \$50.00 for each outpatient fecal sample collection visit and for each outpatient 24-hour urine collection.

If, at the completion of the study, you have been on time and participated in all clinic visits, study unit confinements and procedures, you will receive an additional \$100.00. Thus, the total compensation for complete participation in this study will be as follows:

- Group A - \$800.00
- Group B - \$875.00
- Group C - \$800.00 plus any additional outpatient visits made for 24-urine collections and fecal sample collections as outlined above.

If you choose to withdraw from the study, you will receive a prorated amount based on the days and/or visits that you have **completed** as outlined above.

In agreeing to participate in this study, you will be acting as an independent contractor, not as an employee of Orlando Clinical Research Center. Because payments made to you for participating in this study may be reported to the IRS as income, you are required to provide your social security number. No deductions for any state or federal withholding or any other similar taxes will be made. It is the responsibility of the participant to report this compensation on state and federal tax returns and for the payment of any taxes that are due on this compensation.

TREATMENT ALTERNATIVE

Since this study is not intended to provide any therapeutic or other health-related benefit, your alternative is to not participate in this study.

RESEARCH-RELATED INJURIES

If you have any adverse reaction (side effect) to the study drug or changes in your physical or mental condition during the course of the study, you should immediately notify Dr. Marbury or study personnel at (407) 240-7878.

If you are injured during this study and your injury is a direct result of the study drug or the administration of the study drug according to the study directions, medical treatment will be available to you. The costs of treatment will be paid by the Sponsor to the extent it is not covered by your health insurance. No further compensation for research-related injury is available.

Further information regarding medical treatment for research-related injuries can be obtained from the study doctor or other authorized personnel. You must notify the study doctor immediately of any research-related injury.

By signing this form you have not waived any of your legal rights.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

You understand that you are free to withdraw from this study at any time, and you agree to inform the physician immediately if you intend to withdraw. It is understood that your decision to participate in this study or to withdraw from this study will not influence the



availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled.

You agree that the physician in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

His/her judgment that any condition or circumstance may jeopardize your welfare or the integrity of the study.

Failure to follow the instructions of the investigator(s).

If the study is stopped by the sponsor and/or doctors participating in the study prior to completion.

If you withdraw or are withdrawn from the study after having taken the study medication, you will be asked to come back to the clinic for a follow-up visit. At this visit you will have discharge procedures performed and blood tests to ensure that there are no changes to your current health status. You will be asked about any changes in your health or in the medications you are taking.

USE AND DISCLOSURE OF MEDICAL INFORMATION

By signing this informed consent form, you authorize Orlando Clinical Research Center (Institution), Thomas C. Marbury, MD (Investigator) and their research staff to use and disclose your personal health information that is created or collected in the course of this research study to domestic and foreign regulatory agencies, including the FDA (Food and Drug Administration), affiliated Institutional Review Boards and privacy boards, the research Sponsor, its affiliates, agents, and employees, other research sites involved in the study, health care providers who provide services to you in connection with this study, and laboratories and other individuals and organizations that analyze your health information in connection with this study.

Your personal health information may be used or disclosed in order to conduct this research study, as necessary for your research-related treatment or payment for such treatment, to allow the Institution to conduct its normal business operations, and to ensure that information related to the study is available to the parties that need it for research purposes. This personal health information may include, but is not limited to, your name, address, telephone number, date of birth, government-issued identification number, and medical records and charts, including the results of all tests and procedures performed during the study.

Please be aware that after disclosure by the Institution, Investigator, or research staff, there is the possibility that your personal health information may be shared with other entities and may no longer be protected by applicable privacy laws and regulations. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. If reports or articles are written about the study, you will not be identified by name in them.

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You have the right to request access to your personal health information from the above-named Investigator. To ensure proper evaluation of test results, your access to these study results may not be allowed until after the study has been completed.

This authorization does not expire. However, you may revoke this authorization for use and disclosure of your personal health information by providing written notice to the Investigator. If you revoke this authorization, neither the Institution, the Investigator, the research staff, nor the research Sponsor will be able to use or disclose your personal health information from this study except to the extent that they have already relied on this information to conduct the study.

You may refuse to sign this authorization. However, under federal law your study records cannot be used or disclosed by Orlando Clinical Research Center for research purposes unless you sign this authorization. *You may not participate in the study unless you sign this authorization.*

PERSONS TO CONTACT

You have the right to ask any questions concerning the potential and/or unknown hazards of this study at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study medication, contact Dr. Marbury or his research staff at (407) 240-7878, 24-hours a day.

If you have any questions regarding your rights as a research volunteer, please contact [REDACTED] Chairman of the Independent Investigational Review Board, Inc. at toll free [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.

SIGNATURES

You have read in a language that you understand well the above information. The content and meaning of this information has been explained to you. You hereby voluntarily consent and offer to take part in this study and authorize the use and disclosure of your medical information. You understand that you have not given up any of your legal rights by signing this informed consent. You understand that you will receive a copy of the signed informed consent.

You confirm that you have read and understand the study informed consent form for the above study and have had satisfactory answers to any questions you have asked.

<u>Date</u>	<u>Print Subject Name</u>	<u>Subject Signature</u>
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The information contained in this document was fully and carefully explained to the study participant. Furthermore, the study participant has been given the opportunity to ask any questions regarding the nature, risks, and benefits of his/her participation in this research study.

<u>Date</u>	<u>Printed Name of Person Conducting the Informed Consent discussion</u>	<u>Signature of Person conducting the Informed Consent discussion</u>
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Independent Investigational Review Board, Inc.
Approved: 7/29/03