

**Safety and Efficacy of Dalbavancin vs. Vancomycin in Skin and Soft Tissue
Infections with Suspected or Confirmed MSRA**

Informed Consent Form For:

**A PHASE 3, RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY
TO EVALUATE THE SAFETY AND EFFICACY OF DALBAVANCIN
VERSUS VANCOMYCIN IN THE TREATMENT OF SKIN AND SOFT
TISSUE INFECTIONS WITH SUSPECTED OR CONFIRMED
METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)**

Protocol: VER001-16

Sponsor: Vicuron Pharmaceuticals Inc.
455 South Gulph Road
Suite 310
King of Prussia, PA 19406

Investigator:
Name
Affiliation
Street Address
City, State
Telephone Number (24 hours)
Pager Beeper number

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Invitation to Participate: You are being asked to participate in a clinical research study being conducted by Dr. _____ and his/her designated study staff to test the safety and effectiveness of the experimental antibiotic dalbavancin on skin and soft tissue infections with suspected or confirmed methicillin resistant *Staphylococcus aureus*. This research is funded by Vicuron Pharmaceuticals Inc. (the sponsor company). In order for you to decide whether or not you agree to be part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent.

This informed consent form gives you detailed information about the research study, which the investigator or a member of his/her study staff will discuss with you. This discussion should go over all parts of this research study: its purposes, the procedures that will be performed, any risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study and all of your questions have been answered, if you still wish to participate, you, along with the investigator or a member of his/her study staff, and a witness will be asked to sign this informed consent and you will receive a copy of it to keep as a record.

You understand that although the study will be under the direct supervision of this investigator, other professionals (doctors, nurses, etc.) who work with the investigator may be designated to assist or act for him/her.

Purpose: The number of bacterial infections that are resistant to currently available antibiotics is increasing. Methicillin is an antibiotic that some bacteria have become resistant to. When bacteria become resistant to an antibiotic, it means that there is a good chance that the antibiotic will not help your body get rid of the infection that the bacteria is causing. These types of infections can be especially dangerous to people who have weakened immune systems (the system in your body that helps you fight off infection) and/or individuals who are hospitalized. Vicuron is developing a new antibiotic, known as dalbavancin, which may be effective against a variety of bacterial infections that are resistant to other antibiotics. The purpose of this study is to evaluate the potential effectiveness and safety of dalbavancin compared to vancomycin, an antibiotic which is used in the treatment of adults with skin and soft tissue infections suspected to be caused by bacteria resistant to other drugs.

Duration: Your participation in this study will last for a maximum of 42 days.

Selection of Participants: This research study will be conducted at approximately 40 - 50 sites, within North America and will involve approximately one hundred and fifty (150) participants, who are at least 18 years old.

You are being asked to participate in this research study because you have been diagnosed

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with a skin and soft tissue infection that is either suspected or known to be caused by bacteria resistant to other antibiotics.

Before entering this study or undergoing any tests for the study, you will be asked to sign this informed consent form, indicating your willingness to participate in this study. In order to be eligible to participate in this study, you must meet certain criteria that will be evaluated and determined by the investigator and/or study staff. You must agree to attend all scheduled visits and follow instructions given to you by the study staff.

The investigator and/or study staff will evaluate your medical condition and history to determine whether you are eligible to participate in this study. In addition, you may **NOT** participate in this study if any of the following apply to you:

- You participated in an investigational drug or device study within the previous 30 days;
- You previously participated in this study or another dalbavancin study;
- The investigator believes you would not be able to fully participate in the study;
- If you are a female: you are pregnant or nursing, or unwilling to practice an effective method of birth control during the study and for at least 30 days ~~6-weeks~~ after your last dose of study drug;
- You have no means of contacting or visiting the investigator and/or study staff as required by the study or in the event of an emergency.

Procedures: If you qualify to be in the study and agree to participate, you will be assigned by chance (like picking a name from a hat) to receive one of the following treatments:

- standard intravenous (IV, in your vein) treatment, 1000 mg of vancomycin infused over 60 minutes, given two times a day for up to 14 days.

OR

- a single IV 1000 mg dose of dalbavancin infused over 30 minutes on study Day 1, followed by a single IV 500 mg dose of dalbavancin infused over 30 minutes if necessary on study Day 8.

You have a 2 in 3 (66%) chance of receiving the investigational study drug, dalbavancin and a 1 in 3 chance of receiving vancomycin. You and the study doctor will know what study drug you are receiving.

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If you are receiving vancomycin, once you have received at least 24 hours of IV treatment, and you have had a decrease in your fever (if you had a fever at the start of the study) or your infection shows signs of improvement (healing), the investigator may decide to switch you to oral (a pill taken by mouth) antibiotic treatment. That antibiotic will be chosen based upon what antibiotics the bacteria is susceptible to. When a bacteria is susceptible to a medicine it means the medicine has activity against the bacteria and a chance of healing the infection caused by the bacteria.

Also, if at any time after you have started receiving vancomycin, the investigator is able to determine that the bacteria causing your infection is susceptible to methicillin you will be switched to a different IV antibiotic called cefazolin, an FDA approved antibiotic. In that case you will receive cefazolin, 500 - 1000 mg every 8 hours.

Regardless of the study arm you are assigned to, if the investigator knows or thinks that you have a mixed infection (an infection caused by more than one type of bacteria), you may also receive one of the following additional IV antibiotics:

- aztreonam
- metronidazole

If you agree to participate in this study, the following events will occur:

Baseline/Screening: Before receiving study drug,

- The study will be discussed with you. You will be asked to sign this consent form.
- You will be asked about your medical/surgical history in the last 2 months and any medications you have taken in the past 3 weeks and/or are currently taking.
- You will also be given a physical examination.
- Your vital signs will be taken (heart rate, temperature, and blood pressure).
- Urine will be collected and blood (about 1 - 2 tablespoons) will be drawn for laboratory tests. The blood and urine will be used to monitor your safety and the status of your infection. Some of the blood may be sent to the laboratory for culture (to see if bacteria grow). A rectal swab will also be obtained to monitor for normal body bacteria that may be resistant to vancomycin.
- If you are a female of childbearing potential, a portion of the blood and urine sample will be used for pregnancy testing. The results of this test must be negative in order for you to participate in the study
- Your skin and soft tissue infection site (wound site) will be examined by the investigator.
- Samples from your wound will be taken and sent to the laboratory for culture. This will be done by rubbing a swab over the infected area or using a needle or sharp instrument to remove some of the infected fluid (also called pus) or tissue. The test results from the culture will allow the investigator to see which type of bacteria are causing your infection and to make sure the antibiotics that you are receiving are

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appropriate.

If the procedures and test results indicate that you are eligible for this study, you will be assigned to one of the two study treatments, as described above.

On treatment:

During the study visits

- You will be monitored closely for possible side effects.
- You will be asked about any symptoms or illnesses that you may have experienced.
- You will be asked about any medications or therapies you are taking.
- On Day 1, you will have your vital signs taken (heart rate, temperature, and blood pressure) before and after your first dose of study drug.
- From Day 2 on (while you are in the hospital), you will have your temperature assessed daily.
- Blood (about 1 tablespoon) may be drawn and sent to the laboratory for culture during the study if the investigator suspects that you have an infection in your blood.

After you have received at least 24 hours of IV treatment, if you are in the vancomycin arm, the investigator may decide to switch you to an oral (taken by mouth) antibiotic as described above. If you are switched to oral antibiotic, your vital signs will be taken and your wound will be examined on the day the switch is made.

If the investigator feels that you are well enough at any time during the study, it is possible that you could be discharged from the hospital while on study drug. If you are still receiving IV treatment, arrangements will be made to provide your infusions at an infusion facility, hospital, office, or at your home with the help of a home health care agency.

If you are discharged from the hospital on oral antibiotic, you will be sent home with your pills. It is important that you store the medication in a safe location, and that you take the medication as instructed. The study drug must be taken only by the person taking part in this study. It must be kept out of reach of children and others who might not be able to read or understand.

If at any time you feel that you have experienced a side effect from the study drug, or that your wound is getting worse, you should contact the study doctor and/or study staff immediately.

Days 4 and 8

All participants will be assessed on Days 4 and 8. If you are sent home prior to Day 4, you will need to return for these assessments.

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On Days 4 and 8

- Your vital signs will be taken (heart rate, temperature, and blood pressure).
- Your wound site will be examined.
- If the investigator feels that your current antibiotic is not working and you need to be switched to a different antibiotic, samples may be taken of your wound and sent to the laboratory for culture. If your wound has begun to heal (the skin is beginning to close) and there is no material to sample, this test may not be done.
- You will have blood (about 1 – 2 tablespoons) drawn for laboratory tests. If you are taking vancomycin, the amount of drug in your blood will be measured. Based on this information, the investigator may determine that the dose of vancomycin needs to be increased or decreased.
- If the results of your previous urine test were abnormal, urine will also be collected. The blood and urine will be used to monitor your safety as well as the status of your infection.
- You will be asked about any symptoms or illnesses that you may have experienced.
- You will be asked about any medications or therapies you are taking.

On Day 8 only

- You will also be asked to complete a questionnaire that asks about any whether or not the treatment made your daily activities more difficult.

The investigator will decide one of the following:

- Your infection has healed and you have completed treatment;
- Your infection is improving but requires an additional week of treatment;
- Your infection is not improving or is getting worse. In that case you will discontinue from the study and the investigator will switch you to a different treatment at his/her discretion.

If you continue you will receive the same treatment you have been receiving for the previous 8 days. If you are taking vancomycin, IV or oral, you will continue on that treatment for an additional 7 days. If you are taking dalbavancin you will receive a single 500 mg infusion.

End of Treatment:

After you have completed your study drug you will have an end of treatment assessment. If you have been taking vancomycin, that means the assessment will be within 2 days after your last dose was administered. If you have been taking dalbavancin, the assessment will be within 9 days after your last dose was administered. If you have been discharged from the hospital, you will need to return to the hospital, clinic or investigator's office for this assessment. If you have any unused study drug, it is important that you bring this with you.

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During this assessment

- You will have a physical exam.
- Your vital signs will be taken (heart rate, temperature, and blood pressure)
- Blood (about 1 – 2 tablespoons) will be drawn for laboratory tests.
- If the results of your previous urine test were abnormal, urine will also be collected. The blood and urine will be used to monitor your safety, as well as the status of your infection.
- Your wound will be examined and samples will be taken if possible, for culture. If the skin around your wound has healed, no samples will be taken.
- You will be asked about any symptoms or illnesses that you may have experienced.
- You will be asked about any medications or therapies you are taking.
- You will be asked to complete a questionnaire that asks about whether or not the treatment made your daily activities more difficult.
- You will be asked to complete a questionnaire that asks about any changes in your attendance at work or changes in the ability to do your job.

Follow-up

You will have a follow up assessment about 12 to 16 days after you took your study drug. If you have been discharged from the hospital, you will need to return to the hospital, clinic or investigator's office for this assessment. During this assessment:

- You will have a complete physical exam,
- Your vital signs taken (heart rate, temperature, and blood pressure)
- Blood (about 1 – 2 tablespoons) will be drawn for laboratory tests.
- If the results of your previous urine test were abnormal, urine will also be collected. The blood and urine will be used to monitor your safety, as well as the status of your infection. A rectal swab will also be obtained to monitor for normal body bacteria that may be resistant to vancomycin.
- Your wound will be examined and samples will be taken if possible, for culture. If the skin around your wound has healed, no samples will be taken.
- You will be asked about any symptoms or illnesses that you may have experienced.
- You will be asked about any medications or therapies you are taking.
- You will be asked to complete a questionnaire that asks questions about any changes in your attendance at work or changes in the ability to do your job.

Late Follow-up

If the investigator felt that your wound was healed during your last study visit (the follow-up visit), you will be contacted by telephone 36 – 42 days after you started medication for a late follow-up assessment. During this phone call, the investigator and/or study staff will question you regarding any medications or therapies you are taking. You will also be asked about your wound and how you have been feeling since your last visit.

You have the right to either refuse to participate and/or stop your participation in this study at any time and for any reason without penalty or loss of benefits to which you would otherwise be entitled.

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Benefits: No direct benefit can be guaranteed to you by participating in this clinical study. If the drug works, you may receive some benefit. If it does not work, you personally will not receive any clinical benefit from your participation in this study. While you may not receive direct benefits, your participation in this study may benefit future patients with skin and soft tissue infections.

Risks:

Dalbavancin

Dalbavancin has been given to 56 healthy patients in single doses of up to 1120 mg (a dosage higher than the one planned for this study) and multiple doses of up to 1600 mg over 7 days. In addition, 42 patients with skin and soft tissue infections received single and multiple doses of dalbavancin. So far dalbavancin has been well tolerated. The side effects that have been reported have been mild to moderate in severity and are similar to those associated with FDA approved antibiotics that are in the same category of drugs as dalbavancin. These include:

- redness at the IV site
- fatigue
- fever
- headache
- dizziness
- abdominal pain
- diarrhea
- sour/upset stomach
- nausea
- nasal congestion
- urinary tract infection
- itching/rash

There have also been some abnormal laboratory findings, including:

- increased number of eosinophils (a type of white blood cell) in the blood
- increased levels of glucose in the blood
- protein in the urine
- blood in the urine

In exceptional cases, hearing impairment has been observed with other drugs in this class. Tests have been done to see if dalbavancin causes hearing impairment. To date there has been no evidence of hearing impairment due to dalbavancin.

Vancomycin

The following are some of the side effects reported when taking vancomycin:

- diarrhea
- headache
- upset stomach

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- vomiting
- difficulty falling asleep or staying asleep
- constipation
- rash
- dizziness
- fever
- redness at the IV site

You will be given a copy of the package insert for vancomycin. This document will tell you more about the risks of vancomycin.

Cefazolin, Aztreonam, and Metronidazole

The following are some of the side effects reported when taking cefazolin, aztreonam, or metronidazole:

- diarrhea
- headache
- upset stomach
- vomiting
- sore mouth or tongue
- itching/rash
- fever

You will be given a copy of the package insert for these drugs. These documents will tell you more about the risks of cefazolin, aztreonam, and metronidazole.

Blood Samples

Risks associated with drawing blood from your arm include pain, bruising, swelling, lightheadedness, and on rare occasion, infection and nerve damage (some numbness and tingling).

Pregnancy

Risks to pregnant women, the embryo, the fetus and nursing children are unknown. Therefore, if you are a female who is capable of becoming pregnant (have not had a hysterectomy and/or are not at least one year post menopause) you must use a reliable method of preventing pregnancy from the time of the first dose of study medication through 6-weeks 30 days after the last dose of study medication. Adequate birth control methods include:

- intrauterine device (IUD),
- hormonal contraceptives plus barrier contraceptive,
- hormone delivery system plus barrier contraceptive
- condom in combination with contraceptive cream, jelly or foam.

Hormonal contraceptives alone are not sufficient. If you become pregnant during the course of the study, you should notify the investigator as soon as possible.

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There also may be risks and discomforts that are not yet known.

New Findings: You will be told in a timely manner of any significant new information regarding the safety and/or effectiveness of dalbavancin that may affect your willingness to stay in this study.

Costs: You will not incur any charges for study drug or study related procedures.

Compensation: You will not receive any payment for participation in this study. The investigator and his/her study staff do receive compensation from the sponsor (Vicuron) for your participation in the study as well as for the time and materials they use to track your progress in the study.

Alternatives: Standard antibiotic therapy is available if you choose not to participate in this study. Your medical doctor would determine alternative therapy. Consult your medical doctor for more information regarding alternative treatments.

Confidentiality: You should understand that all information collected in this study will be kept strictly confidential, except as required by law. All personal health information collected in this research study (the "study information"), including, but not limited to medical/surgical history, past and current medications, vital signs, physical examination and laboratory results, other assessments and photographs and samples of your wound may be disclosed by the investigator or other research study staff to regulatory agencies {including the U.S. Food and Drug Administration ("FDA")} and the study sponsor, Vicuron and its employees, agents and/or contractors. Vicuron, in turn, will collate and interpret the study information and report it to the FDA and/or other appropriate regulatory agencies, who will use this information for the purposes of determining whether or not to grant regulatory approval for the drug dalbavancin. The investigator or other research study staff may also disclose study information to the Institutional Review Board ("IRB")/Ethics Committee (EC) that oversees the conduct of the research study for the purpose of protecting the rights and welfare of subjects enrolled in the research study. Your medical records and information will be kept confidential within the limits of the law. If any publication results from this research your identity will not be revealed.

Your signature on this informed consent form also serves as the authorization for the disclosure of the study information as outlined above. This authorization will expire at the end of the research study. You have the right to revoke this authorization at any time, provided that the revocation is in writing. However, if you exercise your right to revoke this authorization, you will be discontinued from participation in the research study. Any study information disclosed before the authorization is revoked cannot be retracted or retrieved and any actions taken in reliance on this information will not be affected. Absolute confidentiality of the study information cannot be guaranteed. Disclosed study information may be subject to further disclosure by the recipients of the

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study information and therefore, may no longer be protected under federal privacy regulations.

Withdrawal: Your participation in this study is completely voluntary and you may either refuse to participate or withdraw at any time without penalty, without affecting your present or future care by the hospital, or without loss of benefits to which you would otherwise be entitled. Also understand that should the investigator and/or study staff, the sponsor (Vicuron), the Institutional Review Board (IRB)/Ethics Committee (EC), the US Food and Drug Administration (FDA) or Health Canada find it necessary and/or in your best interests, they may withdraw you from this study or stop the entire study without your consent.

In the event that you stop participating in the study for any reason, you will be asked to return to the research center to undergo the final evaluations. It is important for your health and safety to have these final procedures completed.

Injury: If you participate in this study you will be exposed to certain risks of physical injury, in addition to those connected with standard forms of therapy (see "Risks" section). In addition, it is possible that in the course of this study, new side effects of dalbavancin that result in physical injury may be discovered. Medical therapy will be arranged by _____ (institution name) if you have been injured as a direct result of participation in this research study.

Vicuron (sponsor) will pay for medical care to treat any physical injury incurred as a direct result of the study drug or study procedures. You agree to cooperate in obtaining any proceeds from insurance or other third party coverage that may be available to you for such medical care. No financial payments or other forms of compensation (such as lost wages or discomfort) or medical treatment beyond that which is offered above will be available; however, your legal rights are not waived by signing this form.

Subject Rights and Research-Related Injury: If you need further information regarding your rights as a research subject, you may contact _____ at (xxx) xxx-xxxx. This individual is an impartial person who is not involved in the conduct of the study. If you believe you have been injured due to study procedures or if you have any questions about the research, or your rights as a research subject, contact Dr. _____ by calling (xxx) xxx-xxxx. You should take this opportunity to ask questions and have them answered to your satisfaction.

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SIGNATURE OF SUBJECT or LEGALLY ACCEPTABLE REPRESENTATIVE

You, ([] subject, [] legal guardian, [] surrogate or [] caregiver) understand this informed consent form after having read it and having it explained to you in your primary language (or interpreted accordingly), and have been given enough time to ask questions and to decide whether to participate. You freely agree to participate (or agree to the subject's participation, if you are a legally acceptable representative) in this research study. Upon signing below, you will receive a copy of the consent form.

Printed Name of Subject

Date & Time

Signature of Subject

Printed Name of Legally Acceptable Representative, *if applicable*

Date & Time, *if applicable*

Signature of Legally Acceptable Representative, *if applicable*

Relationship to Subject, *if applicable*

***SIGNATURE OF READER/TRANSLATOR IF
THE SUBJECT / LEGALLY ACCEPTABLE REPRESENTATIVE
DOES NOT READ ENGLISH WELL***

The person, who has signed above, _____, does not read English well. You, the reader / translator, read English well and are fluent in (name of the language) _____, a language the subject or legally acceptable representative understands well. You have translated for the subject or legally acceptable representative the entire content of this informed consent form. To the best of your knowledge, the subject or legally acceptable representative understands the contents of this informed consent form and has had an opportunity to ask questions regarding the informed consent form and the study, and that these questions have been answered to the complete satisfaction of the subject or legally acceptable representative.

Printed Name of Reader / Translator, *if applicable*

Date & Time, *if applicable*

Signature of Reader / Translator, *if applicable*

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SIGNATURE OF WITNESS

You, the witness, confirms, to the best of your knowledge, that the subject or legally acceptable representative understands the contents of this informed consent form and has had an opportunity to ask questions regarding the informed consent form and the study, and that these questions have been answered to the complete satisfaction of the subject or legally acceptable representative.

Printed Name of Witness

Date & Time

Signature of Witness

***SIGNATURE OF PERSON CONDUCTING THE INFORMED CONSENT
(Investigator or Designated Study Staff Representative)***

To the best of my knowledge the subject, (or legally acceptable representative) _____, has assimilated the entire content of the above consent form, and understands the study and its risks well. The subject's questions and/or those of his/her legally acceptable representative have been accurately answered to his/her/their complete satisfaction.

Printed Name of Person Conducting Informed Consent

Date & Time

Signature of Person Conducting Informed Consent