

Patient Information and Consent Form

Consent for Participation in a Clinical Research Study

Title: A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant *Staphylococcus aureus*

Protocol No.: 0015

Sponsor:



Investigator:

Location:

The sponsor of this study, Theravance, Inc, is paying **[Institution/health care provider] {and Dr. [PI] if relevant}** to perform this research.

INTRODUCTION

You may be eligible to participate in a research study to help determine if an investigational antibiotic, telavancin, is safe and effective in the treatment of hospital-acquired pneumonia (HAP) that is caused by a Gram-positive bacteria known as *Staphylococcus aureus*. Your study doctor has determined that you may have acquired pneumonia in a health care facility, which may be suitable for investigational treatment with telavancin. At present, telavancin is an investigational drug, which means it has not been approved for use by any Health Authority such as the US Food and Drug Administration (FDA).

You must be at least 18 years of age to participate in this study. Before you can take part in this study, you must first read and sign this Patient Information and Consent Form.

This research study is being conducted in about 150 centers in several countries. Up to 750 patients with the diagnosis of HAP will participate in this study. You will be in this study for up to 5 weeks including the treatment period and follow-up.

PURPOSE OF THE STUDY

The purpose of the study is to evaluate the safety and effectiveness (how well it works) of telavancin compared to another antibiotic called vancomycin.

Vancomycin is already approved by Health Authorities including the US Food and Drug Administration for use in HAP. Data collected during this study also may be used for other research purposes that have not yet been specified.

BACKGROUND

Infections caused by “Gram-positive” bacteria are important because these types of infections may cause serious and life-threatening diseases in both healthy patients and patients who are already sick. Vancomycin is a drug that may be given to patients with these types of infections, but sometimes these bacteria do not respond completely to vancomycin. The development of a new drug that can treat infections caused by these bacteria is important and would give doctors another drug to use.

STUDY PROCEDURES

If you qualify for participation, you will receive study drug for at least 7 days but not more than 21 days. The study staff will perform procedures required by the study plan. The study staff will see you at least twice a day while you are receiving treatment. You may be hospitalized for the entire duration of the study, or you may be released from the hospital and asked to return to the hospital or clinic for treatments or study tests. The procedures are explained in this information and consent form.

First the study doctor will determine if you meet the requirements to enter this study.

Once you have agreed to take part in this study and have signed this information and consent form, the following screening procedures will be done.

- Record your past medical history, past and current medications and treatments
- Review signs and symptoms of infection, including body temperature, heart rate and breathing rate
- Take blood and urine samples for laboratory tests, including tests to check for infection in your blood or urine and to identify which bacteria might be causing the infection.
- A pregnancy test from your blood if you are female and able to have a child
- A chest x-ray or computed tomography (CT) scan of your lungs, which is a picture taken to confirm your pneumonia
- The amount of oxygen in your blood will be checked.
- A sample from your lung fluid will be taken to confirm your infection and to identify the bacteria causing the infection. Your study doctor will decide the best way to obtain this sample. You may be asked to take a deep breath and cough out sputum for a specimen. If you require a ventilator, the specimen will be obtained through the tube connecting you to the ventilator.

- Three (3) 12-lead ECGs will be performed that will check your heartbeat. This determines your heart's condition and also your eligibility to participate in the study. The ECG will be done 3 times, with a 5 to 10 minute period between each ECG. These 3 ECGs will also be sent to an outside laboratory for a standardized review.
- Patients at some study centers will be asked to give an additional blood sample for tests to check blood clotting. The study doctor will ask you if you want to give these blood samples.

Your study doctor or nurse will review all of the medications you are taking. Some of these may need to be stopped prior to your participation in this study. These medications may include nonstudy antibiotics and other investigational agents. The study doctor will discuss this with you. The purpose of stopping other medications is to allow your study doctor to tell if the study drug is helping to treat your infection and how safe it is.

If you meet all of the entry requirements for this study and agree to take part, you can continue in the study and will receive the first dose of study drug. It is important that you receive all doses of study antibiotic, as directed by your study doctor. If you are released from the hospital before you receive all required doses of study drug, your study doctor will make arrangements for you to receive all remaining doses of the study drug at home or at the study center.

You will be randomized to either telavancin or vancomycin at a 1:1 ratio; that is, you have a 50% (one out of two) chance of receiving telavancin and a 50% (one out of two) chance of receiving vancomycin during the treatment period. Neither you nor your study doctor will know what treatment you are receiving.

If you take part in this study, you will have the following tests and procedures.

The study drugs will be given for 7 to 21 days. The telavancin and vancomycin will be given as 60-minute intravenous infusions. In other words, you will receive this medication through your IV. The medication will be in an IV bag that the nurse will attach to your existing IV tubing and the medicine will drip in over a one-hour period. If you are randomized to receive vancomycin, each day you will receive two 60-minute infusions of vancomycin separated by 12 hours. If you are randomized to receive telavancin, each day you will receive one 60-minute infusion of telavancin and one 60-minute infusion of placebo separated by 12 hours. This placebo is a bag of dextrose (sugar) water given through your IV. Regardless of which treatment you are assigned, you will always be receiving medicine to treat your infection.

While you are receiving study drug, you will be checked daily to see how you are reacting to the study drug and how the study drug is working. You will be asked questions about how you feel and you will have tests such as vital sign measurements, electrocardiograms (ECGs) and laboratory tests.

The following tests will be done daily:

- Review signs and symptoms of infection, including body temperature
- Review of medications and adverse events (possible side effects)

On Days 4 and 7 of study drug treatment, the following procedures will be done in addition to the daily checks.

- You will be asked to provide a blood sample and a urine sample for laboratory tests. The blood sample will also be used for a pregnancy test for women of childbearing potential.
- Three (3) 12-lead ECGs [extraneous wording]
- Chest x-ray or CT scan
- The amount of oxygen in your blood will be checked.
- The study doctor may need to take a sample from your lungs to check for infection. The study doctor will tell you if this test is required for you.
- On or around Day 4, patients at some study centers will be asked to give additional blood samples for tests to check blood clotting and the amount of study drug in your blood. The study doctor will ask you if you want to give these blood samples. If you do, five (5) additional blood samples will be drawn for testing of blood clotting and study drug levels.

Depending on how long your study doctor wants you to receive study drug treatment, you may have more tests. On Days 10, 14, 17 and 21 of study drug treatment, the following procedures will be done in addition to the daily checks.

- You will be asked to provide a blood sample and a urine sample for laboratory tests. The blood sample will also be used for a pregnancy test for women of childbearing potential.
- Three (3) 12-lead ECGs

The End-of-Therapy visit will occur on the day of your last dose of study drug or within 3 days after the last dose of study drug. If you have been released from the hospital by this time, you will need to return to the study doctor's office for this visit. The following evaluations will be done at this visit.

- You will be asked to provide a blood sample and a urine sample for laboratory tests. The blood sample will also be used for a pregnancy test for women of childbearing potential.
- Three (3) 12-lead ECGs
- Review of medications and adverse events (possible side effects)
- Chest x-ray or CT scan
- The amount of oxygen in your blood will be checked.
- Review of signs and symptoms of your infection, including body temperature
- The study doctor may need to take a sample from your lungs to check for infection. The study doctor will tell you at the visit if this test is required for you.

The Follow-up visit will occur within 7 to 14 days after your last dose of study drug. If you have been released from the hospital by this time, you will need to return to the study doctor's office for this visit. The following procedures will be done.

- You will be asked to provide a blood sample and a urine sample for laboratory tests.
- Review of medications and adverse events (possible side effects)
- Review of signs and symptoms of your infection, including body temperature
- In certain cases the study doctor may need to take a sample from your lungs to check for infection. The study doctor will tell you at the visit if this test is required for you.

If you complete all study visits and have all required blood samples drawn, the total amount of blood drawn during the study will not exceed 300 milliliters (20 tablespoons).

There is a possibility that any of the tests conducted at any visit may need to be repeated if your study doctor determines it is in your best interest. Your study doctor will inform you if this is necessary.

ADDITIONAL MEDICATIONS

Your study doctor may also choose to give you a drug called aztreonam and/or a drug called metronidazole in addition to the study drugs. Aztreonam is an approved antibiotic for the treatment of certain bacterial infections caused by a type of bacteria known as Gram-negative bacteria. Your study doctor may choose to give these drugs to you if your infection is one that is caused by a combination of bacteria including Gram-negative bacteria. Metronidazole is an approved antibiotic for the treatment of certain bacterial infections caused by a type of bacteria known as anaerobic bacteria. [I think that wording will only confuse patients.] Your study doctor may choose to give this drug to you if your infection is one that is caused by a combination of bacteria including anaerobic bacteria.

It is important that you receive all doses of the study drugs, as directed by your study doctor.

It is also important to tell the study doctor what prescription drugs, vitamins, herbal preparations, or over the counter drugs you are taking at any time before or during the study. The purpose of stopping the other drugs you are taking is to allow the study doctor to be able to tell how safe the study drug is and if the study drug is helping to cure your infection.

RISKS AND SIDE EFFECTS

When taking any medication, undesirable side effects may sometimes happen. Telavancin is an investigational drug, and there may be risks and side effects that are not known yet.

The safety and how well **telavancin** works has not been fully studied in humans. The possible side effects that have been seen in patients who have received **telavancin** include:

- nausea
- vomiting
- flushing (feeling warm and turning red - especially around the face and neck)
- change in taste (metallic or soapy taste)
- tingling in the hands and feet
- redness, pain and/or itching at the injection site
- changes in the electrical conduction of the heart, resulting in abnormal ECG
- decreases in kidney function that return to normal when telavancin is stopped
- decreases in platelet counts (cells that help blood clot) that return to normal when telavancin is stopped
- headache
- rash
- itching
- anxiety
- ringing in the ears

In animals given telavancin over a long period, increases in tests that measure liver function were found. These elevated values decreased when telavancin was stopped.

The risks and side effects seen in patients treated with **vancomycin** include:

- flushing (feeling warm and turning red - especially around the face and neck)
- itching
- rash
- fever
- chills
- feeling of general discomfort
- muscle or joint pain
- damage to the nerves
- hearing loss
- neurological disorder such as convulsions
- redness, pain and/or itching at the injection site
- anaphylaxis (drop in blood pressure and/or swelling of airway passage with difficulty breathing, possibly resulting in death)
- nausea
- vomiting
- diarrhea
- stomach pain
- damage to the liver
- sores in the mouth
- decreased number of blood cells
- bleeding

The risks and side effects seen in patients treated with recommended doses of **aztreonam** include:

- redness and itching at the injection site
- diarrhea
- bleeding of the stomach or intestine
- shortness of breath
- low blood pressure
- dizziness
- confusion
- seizure
- vertigo
- weakness
- chest pain
- difficulty sleeping
- altered vision
- feeling of general discomfort
- redness and itching and/or infection of the vagina
- elevated lab test results that suggest liver or kidney damage and problems with blood clotting
- anaphylaxis (drop in blood pressure and/or swelling of airway passage with difficulty breathing, possibly resulting in death)
- rash
- stomach cramps
- fever
- headache
- muscle aches
- ringing in the ear
- altered taste
- sores in the mouth
- tongue numbness
- bad breath
- sneezing and nasal congestion
- abnormal sensation
- breast tenderness
- sweating

The risks and side effects seen in patients treated with recommended doses of **metronidazole** include:

- seizures
- nausea
- stomach pain
- altered taste
- headache
- fainting
- lack of muscle coordination
- redness and itching at the injection site
- nerve damage
- vomiting
- diarrhea
- decreased blood cells
- dizziness
- confusion
- fever
- darkened urine

If you have any of the symptoms or any side effects listed above, you should inform the study doctor or study nurse immediately. If you have any symptoms or side effects different from the above listed risks and side effects, you should notify your study doctor as well. During the study, the study staff will ask you about any drugs you have taken since the start of the study, as well as any changes in the types or amounts of drugs that you take. The combination of the study drugs and other drugs you might be taking during the study could be harmful to you. All drugs have a potential risk of an allergic reaction, which if not treated properly, could be severe, life-threatening or result in death.

The insertion of the needle for the study drug IV and the insertion of the needle for drawing of blood samples for the required laboratory tests may cause discomfort or pain at the site of the insertions. Bruising may occur in some patients at the needle site. There is also the possibility of fainting and/or an infection at the needle site.

Chest x-rays or CT scans will expose you to low levels of radiation. Your study doctor will inform you of the risks associated with these tests, which are done as part of the usual care for patients with pneumonia.

There also may be other risks or side effects that are unknown.

Women of Childbearing Potential (if applicable)

Being a part of this study while pregnant may expose the unborn child to significant risks. In pregnant animals, limb abnormalities were found after being given high doses of telavancin. It is unknown if this was an effect of the drug. Therefore, pregnant women and women who are nursing their babies will be excluded from the study. If you are a woman of childbearing potential, a serum pregnancy test will be done. This test must be negative before you can enter this study. If you are sexually active, you must agree to use appropriate contraceptive measures for at least one month after the last study infusion. Medically acceptable contraceptives include: (1) surgical sterilization, (2) approved hormonal contraceptives (such as birth control pills, Depo-Provera, or Lupron Depot), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). If you do become pregnant during this study, you must inform your study physician immediately.

Contraceptives for Men (if applicable)

In animal studies, telavancin decreased sperm motility (the ability of sperm to move) that was related to an increase in the number of abnormal sperm. A decrease in the total number of sperm was also found. It is unknown what effects telavancin has on human sperm.

The treatment used in this study could affect your sperm and could potentially harm a child that you may father while on this study. If you are sexually active, you must agree to use a medically acceptable form of birth control during the study and for 3 months after your participation has ended. Medically acceptable contraceptives include: (1) surgical sterilization, or (2) a condom used with a spermicide. If your female partner becomes pregnant during this study, you must inform your study physician immediately.

BENEFITS

You may or may not receive any medical benefit from your participation in this study. In the future, other people with a similar condition may benefit from the knowledge obtained from this study.

ALTERNATIVE TREATMENTS

If you choose not to participate in this study, your doctor will discuss alternative treatments with you that may include the comparator antibiotic (vancomycin) used in this study.

RIGHT TO WITHDRAW

Your participation in this study is voluntary. You may choose not to be in the study. If you agree to be in the study, you may withdraw at any time. If you withdraw from the study, you will be asked to complete the End-of-Therapy visit which is to be done within 3 days of your last dose of study medication and the Follow-up visit which is done 7-14 days from your last dose of study medication. These visits are explained in detail in this consent form under the "Study Procedures" section and are needed to check the safety of the study drugs. No additional data, other than what has been outlined in this section will be collected for study purposes unless the data concern an adverse event [This has been explained/defined previously.] related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor. All study related information captured during the study prior to your withdrawal couldn't be removed or withdrawn.

Your decision not to take part or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at **[Institution/health care provider]**. If you decide to withdraw, we ask that you contact Dr. **[PI]** in writing and let **[him/her]** know that you are withdrawing from the study. **[His/her]** mailing address is **[address]**.

You or your legally authorized representative will be told in a timely manner if new information becomes available that may affect your willingness to continue in this study.

INVOLUNTARY WITHDRAWAL

Your participation in this study may be discontinued by your study doctor or by the sponsoring company without your consent if you do not follow your study doctor's instructions or if, in the study doctor's opinion, your safety or well being is in question. This includes the following reasons: an adverse event, clinical failure, a major violation of the protocol (for example, a diagnosis other than HAP), pregnancy, a QTc > 500 msec (a particular type of heart problem) on two consecutive ECG measurements, the need for prohibited medication, or the termination of the study by the sponsor.

The Food and Drug Administration (FDA) or other health authority may also stop the study.

COSTS

You will not be charged for the study drug/comparator antibiotics, or for tests required by the study. You will be receiving medical care as a part of this research study. Costs for other necessary therapies and tests not conducted under this study will be charged to you or your insurance.

[Optional: You will be compensated XXXX for each completed study visit after you leave the hospital for your travel, time and related expenses. You will be considered to have a “completed study visit” if you follow the study-related procedures for that visit specified in this information and consent form. This includes returning for the study visits, completing all study drug treatments, and laboratory procedures (as well as any additional tests that are deemed to be necessary to determine the cause or significance of any abnormal test results), and completing and returning all study documents, as requested.

It is also possible that the cost of travel to and from the doctor’s office to attend study visits may be greater than the amount of the compensation that will be provided to you for completed study visits, as described above. It is also possible that you may lose wages during the time that you are hospitalized and or attend study visits. No additional compensation is available in these cases.]

CONFIDENTIALITY

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. You will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of [Institution/health care provider]. For records disclosed outside of [Institution/health care provider], you will be assigned a unique study code number. The key to the code will be kept in a locked file in Dr. [PI]’s office.

As part of the study, Dr. [PI] and [his/her] study team will report the results of your study-related laboratory tests and ECGs to those named below. These test results will be reported to the study sponsor, Theravance, Inc., and to [REDACTED]

[REDACTED]
representatives of the sponsor.

Your records also may be reviewed in order to meet federal, state or foreign regulations. Reviewers may include, for example, representatives from the Food and Drug Administration; representatives of Theravance, Inc. [REDACTED]
[REDACTED]

the health authorities in the participating countries [or list countries]; and the [Institution/health care provider’s] Institutional Review Board or Ethics Committee. If your research record is reviewed by any of these groups, they may also need to review your entire medical record.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. Your permission for this review of confidential information is granted by signing this document.

This information may be further disclosed by the sponsor of this study, Theravance, Inc. If disclosed by the sponsor, the information is no longer covered by the federal privacy regulations.

Information that could identify you by name will not be used if the results of this study are published.

RECORD RETENTION

Your study results will be retained in your research record for two years after the investigational product is approved; or if the product is not approved, until two years after shipment and delivery of the investigational product is discontinued, whichever is longer. At that time either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at **[Institution/health care provider]**. Any research information in your medical record will be kept indefinitely.

INJURY

In case of injury, please contact:

Dr. _____ at telephone number _____ (24 hour number).

Immediate necessary care is available if you are injured as a result of taking part in this study.

If you follow the directions given to you by the study doctor and staff as well follow all study procedures and during the course of this study, you suffer a physical injury or illness as a result of procedures or treatment plan for this study; Theravance, Inc. will pay for medical expenses not covered by a government agency, insurer, or another third party. To be eligible for payment under this paragraph, you must immediately notify your study doctor of the physical injury or illness.

Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not available.

QUESTIONS

If you have any questions about this study you may contact the study doctor,

Dr. _____ at telephone number _____.

If you have questions regarding your rights as a participant in this study, you may contact:

_____ at telephone number _____ at the
[Institutional Review Board/Ethics Committee or Office of Risk
Management].

STATEMENT OF CONSENT

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask the questions I have, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree to participate in this study, with the understanding that I may withdraw at any time without affecting my current or future medical care. I authorize the review of my confidential information as outlined above. I have been told that I will be given a signed copy of this signed consent form."

Name of Subject

Date

Signature of Subject

Name of Legally Authorized Representative
(if applicable)

Date

Signature of Legally Authorized Representative
(if applicable)

Name of Person Obtaining Consent

Date

Signature of Person Obtaining Consent

Name of Witness (if applicable)

Date

Signature of Witness (if applicable)

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