

Research Consent Form

(page 1 of 8)

Principal Investigator:

Protocol No. DAP-IE-01-02

Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus*

Purpose of study.

This is a research study to determine whether daptomycin will treat serious bacterial infections due to *Staphylococcus aureus* ("staph infections"). Daptomycin is a new investigational antibiotic that is being studied in the United States and other countries. Daptomycin has not been approved for sale. You are being asked to take part in this study because your doctor has determined that you have a bloodstream infection with staphylococcus. Over 400 subjects are expected to participate in this study during the next two years at about 80 centers.

Description of the study, procedures to be used, and how long it will last.

If you participate in this study, you will be assigned by chance (similar to "the toss of a coin") to receive either daptomycin or conventional antibiotics. You will have an equal chance ("50-50") of receiving either treatment. The conventional antibiotics are nafcillin or vancomycin, in combination with gentamicin. Those drugs are approved for sale in this country and are typically used for the treatment of your infection. If you are assigned to conventional antibiotics, your doctor will decide which of those antibiotics you will receive based on laboratory tests of the bacteria infecting you and also whether or not you are allergic to penicillins.

If you participate in this study, you will be treated for 2 to 4 weeks or possibly more, based on your doctor's decision. You will also be seen for follow-up visits at 6 and 12 weeks after treatment is completed. Your total duration of participation in the study will be a maximum of 4 ½ months. All of the treatments in this study are administered by intravenous infusion ("by vein"). Daptomycin is administered once each day; nafcillin six times each day; and vancomycin and gentamicin typically one to three times each day.

Use this text if applicable:

It is important to begin treatment for your serious infection as soon as possible. The laboratory may have used a non-FDA approved test in order to properly identify the "bug" that is infecting your blood. The non-approved method is being used in order to rapidly identify the bug and begin treatment. The results of this test will be confirmed using the laboratory's standard approved method.

If you chose to participate, the following tests or procedures will be done as part of this study:

At the beginning of the study, you will have a medication history and a medical history taken, and a physical examination, chest x-ray, and electrocardiogram (heart rhythm recording) performed. You will answer questions about your overall health. Blood and urine samples will be taken for laboratory tests. If you are a woman who can become pregnant, a pregnancy test will also be performed. If you

Subject's Name: _____, _____ Date: _____
Last First

IRB _____

Approved: _____

Expires: _____

Subject's Initials

Research Consent Form

(page 2 of 8)

Principal Investigator:

Protocol No. DAP-IE-01-02

Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus*

are pregnant, you will not be able to participate in this study.

While you are receiving treatment, you will be asked each day about how you are feeling and whether there is anything that feels different or is bothering you. You will answer questions about your overall health once each week. Blood tests will be taken most days while you are receiving treatment to see if the bacteria are gone from your bloodstream and to see if you are having any reactions to the study medications. At the beginning, the tests will require about 1–2 tablespoons of blood; later, the tests will require about 2 teaspoons of blood. The blood for this study will usually be obtained at the same time your doctor is ordering any other tests you need. Over the course of the entire study, the blood tests will require about 16 tablespoons of blood, which is about half the amount collected during a typical blood donation. You will have an electrocardiogram (heart rhythm recording) performed once each week.

On or before the 5th day of treatment, you will also have a study of your heart that is done with sound waves. Because of the kind of infection you have, your doctor would probably have this heart study performed even if you weren't in the study. This study, which is called a transesophageal echocardiogram ("TEE"), is needed to determine whether the bacteria in your blood have infected your heart valves. During this study you will swallow a small pea-sized device ("transducer"). To help you swallow this, the back of your throat will be sprayed with numbing medicine. You will also be given some medicine to help you relax. During this study, you will lie on an examination table. You will also have your heart rhythm recorded and your blood pressure checked. The study takes 1 ½ to 2 hours to complete. A technician or doctor will be with you during the entire test.

On the 5th day of treatment, if you are receiving daptomycin you will have five additional blood samples (1 teaspoon each) at different times taken to measure the level of antibiotic in your body.

Use this text if applicable:

All subjects will receive at least 3 to 7 days of inpatient antibiotic therapy depending on the severity of your infection. However, situations may arise where you will complete the remainder of your antibiotic treatment as an outpatient. In this case a home health nurse will come to your home to administer the antibiotics intravenously (as they were administered in the hospital).

At the end of treatment and at the follow-up visits after treatment, you will again be asked how you are feeling and answer questions about your overall health and you will have a physical examination and blood tests, including a pregnancy test if applicable.

IRB _____

Approved: _____

Expires: _____

Subject's Initials _____

Principal Investigator:**Protocol No. DAP-IE-01-02****Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus***

Termination. Your participation in this study may be stopped at any time without your consent for any of the following reasons:

You develop side effects that are considered dangerous.

Your infection is not getting better.

You do not follow the study requirements.

You become pregnant.

Administrative or regulatory decision, or other reasons.

If your participation is terminated, you will have the final clinical evaluations and laboratory tests performed as described above.

Your Responsibilities in this study. As a participant in an investigational new drug study, you are responsible for notifying your study doctor of any changes in your health while participating in this study. If you become pregnant, you must notify your study doctor immediately. If you choose to stop your participation in the study, you must notify your study doctor immediately so that a plan can be made for your continued medical care. At that time, you must have the end of treatment evaluations performed as described above.

Reasonably foreseeable discomforts or inconveniences of the study.

The echocardiogram requires lying still on an examination table for an hour which may be uncomfortable for some persons. Some of the follow-up visits after treatment may be inconvenient. There may be some discomfort, swelling, or bruising around the vein from which blood is drawn. Some patients may become lightheaded or faint when blood is being drawn.

Because you have a serious infection, your doctor would probably order many of the examinations and procedures described above even if you do not participate in this study.

Reasonably foreseeable risks of study.

Daptomycin has been given to approximately 1200 subjects in phase 2/3 clinical studies. About 65 of those subjects received a dose of 6 mg/kg every 24 hours; over a thousand subjects received a dose of 4 mg/kg every 24 hours. The frequency and severity of side effects among subjects who received daptomycin at either dose was similar to that seen in subjects who received other antibiotics.

Approximately 3 to 6% of subjects reported constipation, nausea, injection site reactions, headache, diarrhea, insomnia, rash, swelling, vomiting, abdominal pain and abnormal liver function tests.

IRB _____

Approved: _____

Expires: _____

Subject's Initials

Research Consent Form

(page 4 of 8)

Principal Investigator:

Protocol No. DAP-IE-01-02

Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus*

Approximately 1 to 3% of subjects reported itching, elevated CPK (muscle enzymes), fungal infections, low blood pressure, urinary tract infection, renal failure, dizziness, anemia, shortness of breath, fever, limb pain, high blood pressure, indigestion, joint pain, skin infection, low blood sugar, cough, back pain, low serum potassium, high blood sugar, decreased appetite, anxiety, chest pain, sore throat, heart failure, and confusion.

Additional effects that occurred in less than 1% of subjects and were considered possibly drug-related included: fatigue, weakness, rigors, discomfort, jitteriness, flushing, allergic reactions, increased white blood cells, decreased platelets, increased eosinophils, prolonged clotting time, irregular heart beat, eczema, abdominal distension, gas, mouth sore, jaundice, increased serum lactate dehydrogenase, low blood magnesium, increased blood bicarbonate, abnormal blood salt levels, muscle aches, muscle cramps, muscle weakness, bone infection, vertigo, mental status change, tingling, taste disturbance, eye irritation.

A few subjects treated with daptomycin have reported muscle weakness. This problem resolved completely without specific treatment when daptomycin was stopped.

One subject who developed a severe allergic reaction following daptomycin administration required urgent care and treatment for the reaction and recovered fully.

One subject who received daptomycin was diagnosed with Bell's Palsy (facial droop).

Inflammation of the large intestine (bowels) has been reported with nearly all antibacterial agents and may range in severity from mild to life threatening.

There may be other risks associated with the use of daptomycin, including interactions with other drugs that are not presently known. You will be informed in a timely manner of any significant new findings about daptomycin that may affect your decision to continue in the study. This information will be available to you even if you withdraw or are withdrawn from the study for any reason.

Pregnancy Warning. The effect of daptomycin on sperm, ova, infants, and unborn children has not yet been determined and may be harmful. You may not participate in this study if you are pregnant or breast-feeding. If you are a woman who can become pregnant, you must avoid becoming pregnant while receiving study treatment and for at least 30 days after treatment is stopped. For that period you must use a barrier method of contraception (birth control) such as condoms or diaphragm together with spermicidal foam or gel. If you are a man, you must use these methods to avoid getting your partner pregnant.

If you become pregnant while receiving study treatment, you will be withdrawn from the study and provided alternative treatment for your infection. Your study doctor will determine what follow-up visits are necessary during your pregnancy. You must see your study doctor as requested and provide information about the outcome of the pregnancy.

IRB _____

Approved: _____

Expires: _____

Subject's Initials _____

Principal Investigator:

Protocol No.

DAP-IE-01-02

Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus*

Vancomycin. Kidney damage (renal failure) has been reported in some patients given vancomycin. Generally, this problem has been reported in patients who received high doses of vancomycin, had prior kidney problems, or were also receiving gentamicin or a similar antibiotic. For most patients, the kidney damage resolved when vancomycin was stopped. To minimize the risk of these problems if you are given vancomycin, your doctor will be checking the levels of vancomycin in your blood and will be adjusting your dose if necessary.

Hearing loss has been reported in a few patients who received vancomycin. Most of these patients had kidney problems or prior hearing loss or were also receiving another drug that causes hearing problems. Dizziness and ringing in the ears have been reported rarely.

Rapid infusion of vancomycin may cause reactions that include low blood pressure, wheezing, shortness of breath, hives, rash, redness and flushing of the upper body, or pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours. In this study if you receive vancomycin it will be given slowly (over 60 minutes) so these reactions should not occur.

The following side effects have been reported infrequently in patients who received vancomycin: allergic reactions, swelling at the injection site, fever, nausea, chills, skin rashes, swelling and inflammation of the mucous membranes, and, rarely, inflammation of the blood vessels. A small number of patients who received vancomycin have been reported to have a decrease in the number of certain types of white blood cells. This abnormality returned to normal when the drug was stopped. A decrease in the number of blood clotting cells has been reported rarely.

Nafcillin. Allergic reactions to nafcillin have been reported. The risk of such reactions may be increased in patients who are allergic to penicillin and related drugs. Immediate allergic reactions typically occur within 20 minutes of receiving nafcillin, but may start up to 48 hours later. The reactions range in severity from a skin rash with itching and swelling ("hives") to swelling of the mucous membranes, swelling of the voice box with coughing and wheezing, fever, and low blood pressure. Very rarely severe immediate allergic reactions can result in death.

Delayed allergic reactions may occur after 48 hours and sometimes as late as 2 to 4 weeks after starting nafcillin. These delayed reactions may include fever, hives, skin rashes, nausea, vomiting, diarrhea, mouth and tongue ulcers, and pain in the muscles, joints and abdomen. Rarely, nafcillin has been reported to damage nerve tissue, damage kidneys, and to decrease certain types of white blood cells.

IRB _____

Approved: _____

Expires: _____

Subject's Initials _____

Principal Investigator:**Protocol No. DAP-IE-01-02****Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus***

Gentamicin. Side effects that have been reported in subjects who received gentamicin include kidney damage (renal failure) and damage to the nerves that are involved in hearing and balance. The nerve damage can be associated with hearing loss, which may be irreversible, and with ringing in the ears and dizziness. Other nerve problems that have been reported with gentamicin include numbness and tingling and muscle weakness. The risk of these problems is greater in patients who have existing kidney problems and in patients who receive high doses or prolonged therapy. To minimize the risk of these problems if you are given gentamicin, your doctor may check the levels of gentamicin in your blood and will adjust your dose if necessary.

Other reported reactions possibly related to gentamicin include: respiratory depression, lethargy, confusion, depression, eye problems, decreased appetite, weight loss, low blood pressure, high blood pressure, rash, itching, hives, generalized burning, voice box edema, allergic reactions, fever, headache, nausea, vomiting, increased salivation, irritation in the mouth, skin lesions, swelling of the brain, scar tissue in the lungs, hair loss, joint pain, pain and irritation at injection site, and enlargement of the liver and spleen.

Abnormal laboratory tests that have been observed in patients receiving gentamicin include: increased serum levels of liver enzymes; decreased serum calcium, magnesium, sodium, potassium; decreased red cell and white cell blood counts and decreased blood clotting cells. These abnormalities may or may not be associated with clinical symptoms.

Blood drawing. Rarely, infections occur at the blood-drawing site.

Expected benefits of study.

There are no known direct benefits to you for participating in this study.

Other treatment available.

There are other antibiotics available to treat your infection. The benefits and risks of these treatments may differ from those of daptomycin or the other antibiotics used in this study. Your doctor can discuss with you the other treatments available and their risk and benefits.

New Findings.

You will be told in a timely manner of any significant new findings that develop during the course of this study and that may relate to your willingness to continue to participate.

IRB _____

Approved: _____

Expires: _____

Subject's Initials

Research Consent Form

(page 7 of 8)

Principal Investigator:

Protocol No. DAP-IE-01-02

Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus*

Confidentiality

All information collected during the study will be maintained in a confidential manner, and in compliance with regulations provided by the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Your name will not appear in any publication or presentation of the data. By signing this form you authorize that all records relating to your participation in this study, including medical information, may be reviewed or disclosed for scientific or regulatory purposes related to this research study, by employees from Cubist Pharmaceuticals, Inc. (Cubist), an agent working on behalf of Cubist (a legally authorized representative of Cubist), representatives from the Food and Drug Administration or other governmental regulatory agencies, and the Institutional Review Board. Your research records remain part of the study even if you withdraw from the study. You may not participate in this research study without signing this Informed Consent/Authorization for Use and Disclosure of Health Information.

Your research and medical records will be available for review for at least two years following completion of the study, and possibly much longer. Your authorization for the use and/or disclosure of your health information will continue indefinitely. You are free to withdraw your consent, including your authorization regarding the use and disclosure of your health information, and to discontinue participation at any time without prejudice to you or effect on your medical care. You may revoke this Authorization at any time, except to the extent that the law allows us to continue using your information. Revocation of this Authorization will likely result in your discontinuation in participating in this study. If you decide to terminate your participation in this study, you should notify the study coordinator. If you are transferred to another facility prior to the end of your participation in this study, your signature on this document authorizes your study doctor, the monitors, auditors, and inspectors mentioned above to access your medical records at that other facility. In the rare event that your information is required to be disclosed by law to another entity, Cubist cannot assure that confidentiality of your information will be maintained.

Use this text if applicable:

By signing this form, you consent to the inspection and copying of your research and medical records by specifically authorized monitors. In addition, outside physicians located at the Duke University Hospital Echo Core lab, who are not involved in your care, will be reviewing the echocardiogram performed on you. DUE TO THE PROCESS BY WHICH ECHOCARDIOGRAMS ARE RECORDED AT (insert Institution name), YOUR NAME MAY NOT BE ABLE TO BE REMOVED FROM THE TAPE PRIOR TO SENDING IT TO DUKE UNIVERSITY HOSPITAL. BY SIGNING THIS FORM, YOU CONSENT TO THE RELEASE OF THE ECHOCARDIOGRAM TAPE TO DUKE UNIVERSITY ECHO CORE LAB WITH YOUR NAME ON IT. You may expect the same confidentiality from these physicians and monitors that you expect from the Principal Investigator and his/her assistants.

IRB _____

Approved: _____

Expires: _____

Subject's Initials _____

Principal Investigator:**Protocol No. DAP-IE-01-02****Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus*****Authorizing access to other medical records.**

If you are transferred to another facility prior to the end of your participation in this study, your signature on this document authorizes your study doctor, the monitors, auditors, and inspectors mentioned above to access your medical records at that other facility.

Access to research records.

You may see your research information as allowed by law. If the treatment you received in this study needs to remain unknown (blinded) until the study data is analyzed, you see this information only after the data has been analyzed.

Costs.

You will not be charged for the study drug or for any examinations, procedures, or laboratory tests that are done solely for the purpose of this study.

Reimbursement for participation. You will be given \$## for your time and effort in participating in this study. [*Omit paragraph if no compensation.*]

Compensation for Injury.

In the event of any illness or injury resulting directly from participation in this research project, Dr. (*the investigator's name*) will provide medical treatment at (*the institution name*). The medical treatment provided might include, if necessary, laboratory tests, x-rays, medications, and other procedures for diagnosis and treatment.

Cubist Pharmaceuticals, Inc. will pay for medical treatment in excess of insurance payments for any injury or illness that is determined by the sponsor and the investigator to be a direct result of receiving daptomycin in accordance with the study plan (first appearing while you are receiving daptomycin in the study). No other compensation is offered by Cubist Pharmaceuticals, Inc. or by (*the institution name*).

Legal Rights.

The above "Compensation For Injury" statement does not limit your legal rights. You do not waive any legal rights by signing this consent form.

IRB _____

Approved: _____

Expires: _____

Subject's Initials

Research Consent Form

(page 9 of 8)

Principal Investigator:

Protocol No. DAP-IE-01-02

Title: A Phase 3, Multicenter, Randomized, Open-Label, Comparative Study To Assess the Safety and Efficacy of Daptomycin Compared To Conventional Therapy in the Treatment of Subjects with Infective Endocarditis or Bacteremia Due To *Staphylococcus aureus*

RESEARCH SUBJECT'S RIGHTS. I have read or have had read to me all of the above.

The study person indicated below has explained the study to me and answered all of my questions. I have been told of the discomforts and risks of the study. I have been told of alternative choices of treatment available to me.

I understand that if I have any **medical questions** about this research study, I can call Dr. (*the investigator's name*) at (###) ###-### during regular working hours.

I understand that if I have any **medical problems** possibly related to this study that during the day I can call Dr. (*the investigator's name*) at (###) ###-### and that after working hours I can call

[Note to Investigator: *this should be a contact point that can always reach a clinician after hours – for example, a hospital operator or an answering service who can reach a physician on call. It should not be the home or work phone number of a single individual or simply “call the Emergency Room”.*]

I understand that, if at any point during this study I have any **questions regarding my rights** as a research subject, I may contact _____ at (###) ###-### during regular working hours.

[Note to Investigator: *this should be someone at the hospital approved by the IRB; it should not be the Investigator or other study personnel.*]

I understand that I do not have to participate in this study and that, if I do participate, I may withdraw from the study at any time. I understand that, if I refuse to participate or if I decide to withdraw, I will not suffer any penalty, loss of rights, or loss of benefits to which I am entitled.

I understand my rights as a research subject and I voluntarily consent to participate in this study. I will receive a signed copy of this consent form.

Subject's Signature	Date	Name (print)
---------------------	------	--------------

Signature of Subject's Representative (if applicable)	Date	Name (print)	(if applicable)
---	------	--------------	-----------------

Signature of Person Obtaining Consent	Date	Name (print)
---------------------------------------	------	--------------

IRB _____

Approved: _____

Expires: _____

Subject's Initials _____