

Daptomycin  
CSR\DAF-98-01\05

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**TEMPLATE INFORMED CONSENT FORM**

**THE INFORMED CONSENT FORM MUST**

**BE PRINTED ON INSTITUTIONAL LETTERHEAD  
OR AT LEAST INCLUDE THE  
NAME, ADDRESS, AND TELEPHONE NUMBER  
OF THE INVESTIGATOR ON THE FIRST PAGE**

A MULTICENTER, INVESTIGATOR-BLINDED, RANDOMIZED STUDY TO COMPARE THE SAFETY AND EFFICACY OF IV DAPTOMYCIN WITH THAT OF VANCOMYCIN OR A SEMI-SYNTHETIC PENICILLIN IN THE TREATMENT OF COMPLICATED BACTERIAL SKIN AND SOFT TISSUE INFECTIONS DUE TO GRAM-POSITIVE BACTERIA (DAP-SST9801-Revision A)

**Introduction**

Daptomycin is an investigational new drug which belongs to a class of antibiotics known as "lipopeptides" (a very small protein with a fatty tail). An investigational drug is one that has not yet been approved by the United States Food and Drug Administration (FDA) to be sold as a medication. Because there is evidence from research studies in animals and in humans that daptomycin may be a safe and effective medication, the FDA has allowed it be used as a treatment under very strict supervision for the purpose of evaluation. Only by collecting information from research studies, such as this one, will the researchers and the FDA be able to make a final determination.

**Purpose of the Study**

I have been asked to participate in a clinical research study to evaluate the safety and efficacy of daptomycin (an investigational antibiotic) in the treatment of complicated skin and soft tissue infections due to one specific group of bacteria (gram-positive). The information collected in this study will help determine if daptomycin effectively treats infections of the skin and soft tissue. The research study at this medical center is part of a large study being conducted in approximately 35-50 centers, and will involve between 400 and 500 adult subjects.

**Procedures to be Followed During The Study**

If I choose to volunteer for the study, I have an equal chance of being assigned to one of the two possible treatment groups. This assignment will be random (like tossing a coin). Before I enroll, neither my doctor, the research staff, nor I will know which of the drug regimens I will be assigned to take. During the treatment, the doctor evaluating my infection will not know which treatment I am receiving. If I am assigned to receive daptomycin, the dose will depend on my weight. Neither the research staff, nor I have the ability to select which initial treatment I will receive. I will be assigned to receive either:

A. Daptomycin 4.0 mg/kg intravenously (through my veins) once every 24 hours (once a day)

or

B. Vancomycin 1.0 gm intravenously, once every 12 hours (twice a day). For some specific types of bacteria I may be given 1.0 gm every 6 hours, or I may be given nafcillin or oxacillin (semi-synthetic penicillins) dosed at 4-12 g/day in equally divided doses (once every 4 to 6 hours).

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No matter which of the above treatments I am assigned, additional antibiotics (aztreonam and/or metronidazole) may be added to my treatment if my doctor feels it is necessary. If my doctor feels that I am improving sufficiently, other specific oral (taken by mouth) antibiotics may be used to continue the treatment after I leave the hospital.

Daptomycin is the only investigational drug that I will be given during this research study. Vancomycin, nafcillin, oxacillin, aztreonam and metronidazole are all antibiotics that have been approved by the FDA.

I will be taking the study drug for 7-14 days, but this may be extended up to a total of 28 days if my doctor feels that it is necessary to treat my infection for a longer period of time. If my study physician feels it is in my best interest or if I decide to withdraw from the research study, the study drug may be stopped at any time. My total involvement with the study is planned to be a maximum of 56 days. However, my study physician will determine the actual length of time.

If I choose to participate, I agree to follow the procedures outlined below:

1. Study Admission - During the study admission period (the 48-hour period prior to the first dose of the study medication), a medical history will be taken and a physical examination including vital signs, height and weight will be performed. An examination of the location of the infection will be done. Blood samples for routine laboratory tests and cultures will be obtained. If I am a woman of childbearing potential (e.g., not surgically sterile and not post-menopausal for one full year), a blood sample will also be taken for a pregnancy test. A urine sample will also be collected for routine analysis. A small portion of blood and a urine specimen will be stored in case additional tests are needed in the future. A specimen will be also taken from the location of my infection for culture and Gram stain. An x-ray of the infected site may be necessary in some cases.

If I still qualify and desire to participate in the research study, I would then begin receiving the study medication. The day I receive my first dose of study drug is called Study Day 1. Just before I receive the first dose of study medication, a blood sample may be taken. My temperature will be taken twice on each day that I receive study drug.

2. Study Day 3 or 4 - Two blood samples may be collected for culture (to determine if there is bacteria in my blood). Additional blood samples may be taken throughout the day to measure the amount of study drug in my blood. After I have been taking the study medication for 3 to 4 days, I will be evaluated by my doctor.
3. Study Day 5 - On the day that I receive my fifth dose of study medication, an additional blood sample will be taken for standard laboratory tests.
4. Study Day 7 - On the day that I receive my seventh dose of study medication and on all subsequent days that I receive study medication, an additional blood sample will be taken for standard laboratory tests.
5. End-of-Therapy Evaluation / Termination - One to three days after I take the last dose of study medication, I will be evaluated by my doctor and a physical examination including vital signs and temperature will be performed. My doctor will evaluate the location of my infection. Blood samples will be taken for routine laboratory tests and if I am a female of childbearing potential and I have withdrawn from the study, a blood sample will be taken for a pregnancy test. Additional blood samples may be taken for culture. A urine sample will also be collected for routine analysis. A small portion of blood and a

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urine specimen may be stored for further testing. A specimen may be taken from the site of my infection as before. I understand that if I have been discharged from the hospital, I will have to return to see my doctor and have these procedures performed, and to undergo any additional tests that my doctor thinks are in my best interest. I understand that it is expected that these procedures will also be done if my doctor withdraws me from participating in the research study ahead of schedule, or if I decide to withdraw myself.

6. The Post Therapy Evaluation – Seven to twelve days after I have taken the last dose of study drug, I will be evaluated by my doctor, and a physical examination including vital signs and temperature will be performed. If my doctor feels that it is necessary, or if it was not obtained at the End-of-Therapy evaluation a urine sample may be taken for routine laboratory tests. A blood sample will be taken for routine tests, and additional blood samples may be taken for culture. If I am a female of childbearing potential, a blood sample will be taken for a pregnancy test. My doctor will evaluate the location of my infection. If my doctor feels it is necessary, a specimen will be taken from the site of my infection and appropriate diagnostic procedures performed. I understand that if I have been discharged from the hospital, I will have to return to see my doctor and have these procedures performed, and to undergo any additional tests that my doctor thinks are in my best interest. A final study visit will be scheduled at this time if my study physician determines that one is necessary.
7. The Post-Study Evaluation (3-4 weeks after my last dose of the study drug) - If my doctor feels it is necessary, I will be reevaluated. A specimen may be taken from the site of my infection. I understand that if I have been discharged from the hospital, I will have to return to see my doctor and have these procedures performed. If my symptoms recur before the scheduled visit I will contact the study staff.

The procedures described above are usually part of standard medical care for the type of illness I have, and would normally be recommended by my doctor whether or not I was participating in the research. This will sometimes depend on how much better my infection was getting, and if I have other illnesses. My doctor has described the above procedures, as they relate to my treatment so that I understand them. My doctor has described to me which of the procedures above he considers to be strictly part of the research study. During the research study, the total amount of blood collected will be approximately 1 cup (240 mL, about one-half the amount collected during a normal blood donation) for the various tests required. This amount may vary depending on the length of time that I am participating in the study.

If I become well enough, my doctor may discharge me from the hospital and switch me to an oral medication to take at home. I agree to call my doctor or the study staff and talk to them before taking any other medications or applying any medicated ointments/lotions.

#### Risks and Discomforts

##### Daptomycin-

Daptomycin is an experimental medication that has been given to more than 300 humans. Daptomycin administration at higher doses (8.0 mg/kg per day, specifically, 4mg/kg twice a day) has been associated with increased levels of CPK (a substance found in the blood which would indicate that muscle has been damaged). This enzyme is also known to increase significantly after injections in the muscle, weight lifting, or other muscle injury. Some subjects treated also reported muscle weakness. Both of these events got better when daptomycin administration was stopped. On Days 3, 5, 7 and daily thereafter, a blood sample will be collected for standard laboratory tests. Included as part of this, I will be tested for signs of muscle damage. While not expected to occur,

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it is possible. If the CPK level exceeds the upper limit of normal by two fold, additional tests will be done on the blood sample to determine what type of muscle is being damaged, and a blood sample will be collected every day so my doctor can monitor the CPK level until it returns to normal. If the level continues to rise above a certain amount, my doctor will stop my participation in the research study. There is some evidence that nerve damage could occur when daptomycin was used in very high doses, but there has been no sign of this in humans. Since daptomycin is experimental, there is a risk that it may not effectively treat my infection.

**Vancocin® (vancomycin)-**

Vancomycin is a currently marketed and commonly used antibiotic. Although very rare, some patients may have allergic reactions which can include one or more of the following: a decrease in blood pressure, wheezing, decreased breathing rate, muscle pain or spasms and redness of the upper body. A few dozen cases of hearing loss, temporary and permanent, have been reported. Some patients have had temporary decreases in the number of white blood cells (for fighting infection) or platelets (for clotting blood). Vancomycin is irritating to skin, muscle and blood vessels.

**Nafcillin -**

Nafcillin is a currently marketed and commonly used antibiotic. It will be used instead of vancomycin to treat infections caused by bacteria that are susceptible to its actions. Some patients experience allergic reactions including rash, itching, fever, malaise, muscular pain, joint pain, abdominal pain, nausea, vomiting, diarrhea, mouth inflammation, and black or hairy tongue. Very rarely, severe allergic reactions have resulted in death. Infrequently, some patients have suffered from kidney or liver problems after treatment with nafcillin.

**Bactocill® (oxacillin) -**

Oxacillin is a currently marketed and commonly used antibiotic. It will be used instead of vancomycin to treat infections caused by bacteria that are susceptible to its actions. Some patients experience allergic reactions including rash, itching, fever, malaise, muscular pain, joint pain, abdominal pain, nausea, vomiting, diarrhea, mouth inflammation, and black or hairy tongue. Very rarely, severe allergic reactions have resulted in death. Infrequently, some patients have suffered from kidney or liver problems after treatment with oxacillin.

**Azactam® (aztreonam) -**

Aztreonam is a currently marketed and commonly used antibiotic. It will be used in this research study only when necessary to treat bacteria that are not effectively treated by the other study drugs. Some patients experience allergic reactions and rash.

**Flagyl® (metronidazole) -**

Metronidazole is a currently marketed and commonly used antibiotic. It will be used in this research study only when necessary to treat bacteria that are not effectively treated by the other study drugs. Some patients experience allergic reactions, rash, seizures, or numbness and/or tingling in the arms or legs when treated. An unpleasant, metallic taste is not unusual. Yeast infections can become more serious. Some patients experience headache, dizziness, or become faint. Changes in heart rhythm have also been experienced.

**General -**

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Some side effects are common to virtually all antibiotics. I may experience nausea, vomiting, diarrhea or abdominal pain. Diarrhea may be mild to, in some cases, life-threatening. Some pain, swelling, rash or redness may occur at the site of injection during or shortly after the dose is given. If the medication leaks out of the needle and into the skin I may experience pain, tenderness, and bruising. I have told my doctor about any drug allergies that I know about or think I may have. People with known allergies to any of the above listed drugs or related drugs should not participate in this research study.

[Centers in California: Please refer to Attachment I.A.]

As with any medication, there is also the possibility of side effects not presently known. I will be informed of any significant new findings about daptomycin that may affect my decision to continue in the study.

The possible risks and discomforts of other medications that my doctor is prescribing for me have been explained or will be explained if they become necessary in the future.

Having a needle inserted in a vein for removing blood or giving a drug is a common and standard procedure in medicine. This procedure may be momentarily painful, and there is a risk of bruising and inflammation at the site of injection, lightheadedness or fainting.

I have been told that there are other antibiotics available to treat my infection. I have discussed with my doctor, and now understand, the advantages and risks of each of the alternative treatments (standard antibiotics) as they relate to my infection. I understand that my doctor feels that my medical care is the first priority, and if my infection is not improving the way it should, my treatment will be modified, even if it means that I must stop participating in the research study.

#### Pregnancy Warning

Daptomycin must not be taken by patients who are pregnant or breast-feeding. The effect of daptomycin on infants or unborn children has not yet been determined, and, as with any new drug, there is the potential for very serious harmful effects. The effect of daptomycin on sperm has also not been determined. If I am a female of childbearing potential, I must avoid becoming pregnant while taking part in this study. It is understood that, by my agreement to participate in the clinical trial, I will use a barrier (i.e., condoms, diaphragm) with spermicidal foam or gel. I will use a barrier as above even if I also take oral contraceptives (birth control pills) to avoid pregnancy throughout the duration of the study. If it is determined that I am pregnant during the study, I will be immediately withdrawn from the study and provided alternative treatment for my infection. I understand that I must keep in touch with my doctor during my pregnancy and provide information as to the outcome. If I am a male, I understand that I must take the same precautions described above to avoid getting my partner pregnant.

I have discussed, and understand the risks and discomforts of the above listed study drugs, and the treatments which my doctor might use if they occur. Close medical supervision will be provided throughout the study.

#### Benefits

The potential benefits of the research study include the possibility of curing this present infection. The information gained by my experience as part of the study will contribute to a better understanding of the antibiotic, daptomycin. All study drugs will be provided free of charge.

#### Compensation for Injury

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I understand that, in the event of any illness or injury resulting directly from my 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 used in diagnosis and treatment.

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

#### Legal Rights

The above "Compensation For Injury" statement does not limit my legal rights.

#### Confidentiality

All information collected during the study will be maintained in a confidential manner. My name will not appear in any publication or presentation of the data. I understand that my medical records will be reviewed by employees from Cubist Pharmaceuticals, Inc., and Advanced Biologics<sup>LLC</sup>, and may also be examined by representatives from the FDA or the Institutional Review Board. My medical records and any related study documents will be available for review for a minimum of two years, and possibly much longer. The confidentiality of the records will be maintained within legal limits. I understand that any samples of my blood, tissue, etc. taken as part of the research becomes the property of Cubist Pharmaceuticals, Inc., and that I have surrendered all rights to them or future products derived from them.

#### Voluntary Participation

I understand that my participation is voluntary, and that I may refuse to participate or withdraw from the study at any time without penalty or loss of benefits to which I am otherwise entitled. My participation may also be terminated without my consent if my doctor, Cubist Pharmaceuticals Inc., Advanced Biologics<sup>LLC</sup>, or the FDA feel that it is in my best interest or if I do not follow the study requirements as instructed. If my participation is terminated by the doctor, or if I decide not to continue, I understand that I should have all of the final clinical evaluations and laboratory tests performed.

#### Contact Information

If I experience any side effects, adverse events or injury during my participation in this research study, I should contact \_\_\_\_\_ at \_\_\_\_-\_\_\_\_-\_\_\_\_. If I have any questions about the research I should contact my study doctor (the investigator) at \_\_\_\_-\_\_\_\_-\_\_\_\_. If I have any questions about my rights as a study subject, I should contact (IRB) at \_\_\_\_-\_\_\_\_-\_\_\_\_. For further information regarding medical treatment and compensation, I may contact \_\_\_\_\_ at \_\_\_\_-\_\_\_\_-\_\_\_\_.

[Centers in California: Please refer to Attachment I.B.]

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I have read and understood this consent form. All of my questions have been answered. I attest that I am at least 18 years of age and voluntarily give my consent to participate in this research study. I have received a copy of this consent form. [Centers in California: Please refer to Attachment 1.C.]

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A. FOR INCAPACITATED ADULT ONLY:

\_\_\_\_\_  
Printed Name and Signature of legal representative Date

Relationship to patient/proof of legal right \_\_\_\_\_

Patient is unable to give consent because \_\_\_\_\_

\_\_\_\_\_  
Printed Name and Signature of Witness Date

\_\_\_\_\_  
Printed Name and Signature of person obtaining consent Date

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B. CONSENT OF ADULT SUBJECTS:

\_\_\_\_\_  
Printed Name and Signature of patient Date

\_\_\_\_\_  
Printed Name and Signature of Witness Date

\_\_\_\_\_  
Printed Name and Signature of person obtaining consent Date

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C. TELEPHONE CONSENT: Section A or B above must be completed within 24 hours.

\_\_\_\_\_  
Printed Name and Signature of Witness Date  
(Must actually hear consent discussion on a second phone)

\_\_\_\_\_  
Printed Name and Signature of person obtaining consent Date

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ATTACHMENT 1  
PROTOCOL DAP-SST9801  
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FOR SITES LOCATED IN CALIFORNIA

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- 1.A. California regulations require a statement regarding the anticipated time to recovery from effects of the drug. Please add to the end of the section on side effects of the study drugs:

**“Given the relatively short time it takes for the drugs to leave my body, it is felt that the time to recover from most of the effects of the drugs should also be short.”**

- 1.B. Regarding questions about the research, California places the responsibility of answering questions on the investigator, rather than that of asking questions on the study subject. California regulations also require the identification of an impartial third party (usually the IRB) to which complaints may be addressed. Please use the following statements, rather than those cited in the sample consent:

**“The investigator will answer any of my questions regarding the research. If I have any questions regarding my rights as a study subject, or if I have any complaints, I may contact (the IRB) (an impartial third party) at \_\_\_\_\_.”**

- 1.C. California regulations require that patients read and, unless the institution is exempt, receive a copy of the Subject’s Bill of Rights. Please include the following statement:

**“I have read and received a copy of the Subject’s Bill of Rights.”**

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