

Patient Information – Template A

(DAP-SST9901): A PHASE III, INVESTIGATOR-BLINDED MULTICENTER, RANDOMIZED STUDY TO COMPARE THE SAFETY AND EFFICACY OF DAPTOMYCIN WITH THAT OF VANCOMYCIN OR SELECTED SEMI-SYNTHETIC PENICILLIN IN THE TREATMENT OF ADULT HOSPITALIZED SUBJECTS WITH COMPLICATED BACTERIAL SKIN AND SOFT TISSUE INFECTIONS DUE, AT LEAST IN PART, TO GRAM-POSITIVE BACTERIA

Introduction

Your doctor has diagnosed you as having a skin infection and is asking you to participate in a research study, in which daptomycin is one of the study drugs. Daptomycin is an investigational new drug that belongs to a class of antibiotics known as “lipopeptides” (a very small protein with a fatty tail). An investigational drug is a drug that has not yet been approved by the Health Authorities to be sold as a medication. Research studies in animals and in humans have shown that daptomycin may be a safe and effective medication in the treatment of infections caused by gram-positive bacteria. Daptomycin has been given to more than 300 humans.

Purpose of the Study

The purpose of this study is to compare the safety and efficacy of daptomycin in comparison to vancomycin or a semi-synthetic penicillin which are already approved for use in the treatment of complicated skin and soft tissue infections caused by gram-positive bacteria. This study will help to validate the results from previous studies and to determine if daptomycin effectively treats infections of the skin and soft tissue. The study has been reviewed and approved by an independent ethics committee. The research study at this medical center is part of a large, international study being conducted in approximately 65 centers in nine (9) countries, and will involve approximately 400 adult patients.

Procedures to be Followed During The Study

If you choose to volunteer for the study, you will be randomly (like tossing a coin) assigned to one of two treatment groups. The medicines which will be given to patients in the two groups are:

1. Investigational Drug: Daptomycin
2. Comparator Drug: A. Vancomycin OR
B. Semi-synthetic penicillin (flucloxacillin, oxacillin or cloxacillin)

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You will have an equal chance of receiving either a comparator drug or the investigational drug. Neither you or your doctor will know which drug you will receive. This information, however, is available to your doctor in case of an emergency.

Your doctor may need to adjust your treatment according to the type of bacteria responsible for your skin infection by adding aztreonam and/or metronidazole. If you are placed in the comparator group, another study doctor (who knows which medication you are receiving) may change the comparator drug you receive. Semi-synthetic penicillins may be substituted if vancomycin was your initial therapy. Similarly, vancomycin may be substituted if semi-synthetic penicillin was your initial therapy.

You will receive one of the above drugs intravenously for 7-14 days. This may be extended up to a total of 28 days if your doctor feels that it is necessary to treat your infection for a longer period of time. If your doctor feels it is in your best interest, or if you decide to withdraw from the research study, you will stop receiving the assigned medication and you will receive appropriate alternative treatment. Your total involvement with the study, including follow-up visits, is planned to be a maximum of 44 days. However, your doctor will determine the actual length of time.

The procedures described below are usually part of standard medical care for the type of illness you have, and would normally be recommended by your doctor whether or not you participate in the research study. If you choose to participate in the study, however, you will be asked to donate more blood samples than would usually be collected: the total amount of blood collected will be approximately 240 mL. The actual amount will vary depending on the length of time that you are participating in the study. In addition, a member of the study staff may seek your consent to collect six additional blood samples (approximately 50mL in total). If you choose to refuse these additional samples, this will not jeopardize your participation in the study or the medical care that you receive.

If you consent to participate in this study, you will enter the study after having completed the usual tests for entry to the hospital and those that your doctor thinks necessary. These include taking blood samples for laboratory testing, collecting a sample from the infected site for examination, a physical examination (including vital signs) and medical history. An X-ray of the infected site may be necessary in some cases. If you are a woman of child-bearing potential (i.e. if you are not post-menopausal nor surgically sterilized), you will be tested for pregnancy. The result of this urine and/or blood test must be negative prior to taking part in the study.

During the study you will be seen by your doctor or a member of his/her staff. Your temperature will be taken, and you will be examined in order to evaluate the effectiveness of the drugs, and to look for any possible side effects of the drug(s). Blood and urine samples for laboratory tests will be collected during the period when you are receiving the study drug(s), at the end of treatment and possibly during the post-therapy visits (if medically necessary). Samples from the infected site will be obtained, if possible, periodically during the study, at the end of treatment and during the follow-up visits to test for the presence of bacteria. A physical examination (including vital signs) will be performed during and after you complete the treatment.

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If you are discharged from hospital before the end of the study period, you will have to return to see your doctor and have these procedures performed and undergo any additional tests that your doctor thinks that are in your best interest. This also applies if your doctor withdraws you from participating in the study prematurely, or if you decide to withdraw yourself.

If you become well enough, your doctor may discharge you from the hospital and switch you to an oral medication to take at home. After stopping the study medication you will be required to return to the hospital between day 7 - 12 for a post-therapy evaluation and between day 21 - 28 for a post study evaluation. You have to call your doctor or the study staff and talk to them before taking any other medications or applying any topical medicated ointments/lotions to the infected skin area. If your symptoms recur before any of the scheduled visits, you will contact the study staff.

Potential Risks and Discomforts

General

Daptomycin is the study drug under current clinical investigation. All other study drugs used in the study are approved by health authorities for the type of infection that you have. Some side effects are common to virtually all antibiotics. You 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 you may experience pain, tenderness, and bruising. Therefore your doctor has asked you about any drug allergies that you know about or think you may have. People with known allergies to any of the above listed drugs or related drugs should not participate in this research study. 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. As with any medication, there is also the possibility of side effects not presently known.

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 improved when daptomycin administration was stopped. While not expected to occur in this study due to the once per day dosing, it is possible. Therefore you will be tested for signs of muscle damage by means of blood tests. If the level continues to rise above a certain amount, your doctor will stop your 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

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experimental, there is a risk that it may not effectively treat your infection. You will be informed of any significant new findings about daptomycin that may affect your decision to continue in the study.

Although very rare, some patients taking vancomycin 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 can be irritating to skin, muscle and blood vessels.

Some patients experience allergic reactions including rash, itching, fever, malaise, muscular pain, joint pain, mouth inflammation, and black or hairy tongue when taking oxacillin. Very rarely, severe allergic reactions have resulted in death. Infrequently, some patients have suffered from kidney or liver problems after treatment with oxacillin.

The main side effects associated with the use of flucloxacillin are rash, suffusion (body fluid spreading to surrounding tissues) and nettle (itchy) rash (hives). At high doses, neutropenia and leucopenia (abnormally low number of white blood cells), and neurotoxicity may occur. It is seen rarely that patients develop hepatitis (liver inflammation), jaundice (yellowing of the skin and pseudomembranous enterocolitis (inflammation of the colon).

The main side effects concerning the use of Cloxacillin are: allergic reactions (rash, itching, fever, fainting), changes of the blood pattern, rise in liver enzymes, jaundice and inflammation of the intestines.

The main side effects associated with the use of intravenous aztreonam are allergic reactions such as skin rash, blood disorders and diarrhea. In addition, side effects may include tenderness and/or swelling at the infusion site, increased liver enzyme values, nausea, vomiting, lowered blood pressure, fever and malaise (weakness).

The main side effects associated with the use of intravenous metronidazole are 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 changes in heart rhythm, headache, dizziness, or become faint.

As other antibiotics are available to treat your infection, your doctor has considered the advantages and risks of each of the alternative treatments (standard antibiotics) as they relate to your infection. Your doctor feels that your medical care is the first priority, and if your infection is not improving the way it should, your treatment will be modified, even if it means that you must stop participating in the research study.

Pregnancy Warning

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Patients who are pregnant or breast-feeding must not take daptomycin. The effect of daptomycin on infants or unborn children has not yet been determined and therefore there is the potential for very serious harmful effects. If you are a female of childbearing potential, you must avoid becoming pregnant while taking part in this study. By your agreement to participate in the clinical trial, you have to take oral contraceptives (birth control pills), implants (Norplant), or injections (Depo Provera) to avoid pregnancy throughout the duration of the study and also use a barrier method (i.e., condoms, diaphragm) with spermicidal foam or gel. Contraception must continue during the study and for at least 30 days after treatment discontinuation. If it is determined that you are pregnant during the study, you will be immediately withdrawn from the study and provided alternative treatment for your infection. You must keep in touch with your doctor during your pregnancy and provide information as to the outcome. The effect of daptomycin on sperm has also not been determined. If you are a male, you must take appropriate precautions described above to avoid getting your partner pregnant.

Benefits

The potential benefits of the research study to participants are limited: daptomycin has not been proven to be better than the available alternative treatments for skin infections. The information gained by your experience as part of the study will contribute to a better understanding of daptomycin, and to the possibility that daptomycin will be made available for the treatment of infections with problematic bacteria, which may not respond to other antibiotics. All study drugs will be provided free of charge.

Compensation for Injury

Medical treatment will be paid (in excess of insurance payments) by Cubist Pharmaceuticals for any injury or illness that is determined to be a direct result of receiving daptomycin treatment in accordance with the protocol, (first appearing while you are receiving daptomycin in the study).

You are obliged to inform your physician in charge of the trial of any worsening of your health status and any unusual events occurring during the study and also thereafter. You are obliged to follow exactly the instructions of the doctors in charge of this study, to take the drugs as prescribed and adhere to the study procedures. Except in case of emergency you may start another medical treatment during the clinical trial, only with the agreement of the physician in charge of the trial. If you do not adhere to the requirements mentioned above, it might affect your insurance coverage. No other compensation by Cubist Pharmaceuticals or (the institution name) is offered.

Confidentiality

All information collected during the study will be maintained in a confidential manner. Your name will not appear in any publication or presentation of the data. For purposes of verifying the study related data, your medical records will be reviewed by employees from Cubist Pharmaceuticals or designee and may also be disclosed to representatives from the Health Authorities. Your physician will ensure that the inspection of

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your medical records will be limited to the extent necessary for that trial and that the personal data will be handled with secrecy and transmitted only in confidential form.

Voluntary Participation

Your participation is voluntary, and you may refuse to participate or withdraw from the study without giving a reason, at any time, without penalty or loss of benefits to which you are otherwise entitled. Any significant new findings developed during the course of this research that might affect your willingness to participate, will be provided to you and your doctor.

Your participation may also be terminated without your consent if your doctor, Cubist Pharmaceuticals Inc., or the Health Authorities feel that it is in your best interest or if you do not follow the study requirements as instructed. In this case you will be informed about the reasons. If your participation is terminated by the doctor, or if you decide not to continue, you should have all of the final clinical evaluations and laboratory tests performed.

Contact Information

If you experience any side effects or injury during your participation in this research study, or if you have any questions about the research or your rights as a study subject, you should contact your study doctor:

Investigator Name: _____

Telephone: _____

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Informed Consent

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Name of Patient: (block letters) _____

I have read and understood the complete patient information (pages 1-6) and have discussed it with my doctor, or his/her representative. The objectives and procedures of the study and the potential risks and benefits of participating in the study were clearly explained to me. Alternative treatment was discussed as well. All of my questions have been answered.

I understand that my participation in this study is voluntary. I understand that I may refuse to participate in, or withdraw from this study at any point and that this will not affect my future medical care. In addition, my doctor may terminate my participation in this study at any time if he/she believes it to be in my best interest. I have had enough time to decide regarding my participation in this trial.

I understand that in the event I become ill or am injured as a result of participating in this research study, medical care will be provided to me. I understand that no funds to provide financial compensation for research related injury or illness are available. I further understand that I retain the right to seek compensation in the event that Cubist or my doctor is negligent.

I agree that my doctor may disclose my medical and research records referring to this trial to the Sponsor (Cubist Pharmaceuticals) and their representatives and partners (Kendle), the local and central Regulatory Authorities, the American Food and Drug Administration (FDA) and other Health Authorities, for the purpose of verifying the trial-related data. My physician will ensure that the inspection of my medical records will be limited to the extent necessary for that trial and that my identity and personal data will be kept confidential. If the results from this study are used for publication, my identity will be kept confidential as well.

After signing, I will receive a copy of this consent form.

My signature below indicates that I voluntarily agree to participate as a study subject in this trial.

Signature of patient

Date (completed by the patient)

Statement of the Investigator

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I have informed the patient of the nature, objectives, course, benefit and risk as well as alternatives concerning this clinical trial. I have answered all questions and did so in a detailed manner. I believe that the patient understood my explanations and that his/her agreement is voluntary. I gave the patient a copy of the Patient Information sheet and of this signed Informed Consent Form.

Name

Signature

Date

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