

NDA 21,572

Cubist Pharmaceuticals, Inc.

Daptomycin
Clinical Study Report \DAP-ADT-04-02\31

Report Date: 25 July 2005

16.1.3 List of IEACs or IRBs- Representative Written Information for Subject and Sample Consent Forms

The IRB was:

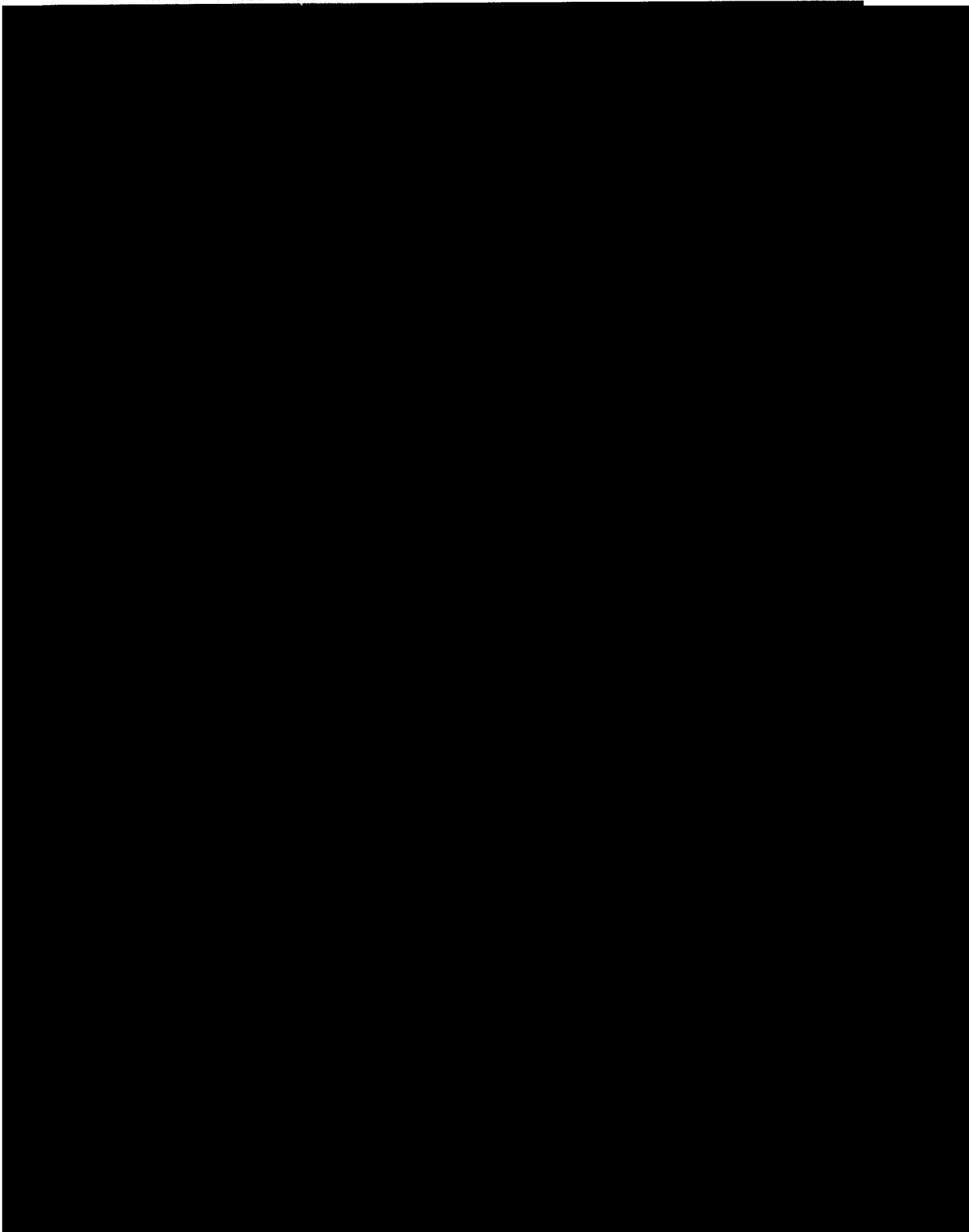




INDEPENDENT
INVESTIGATIONAL
REVIEW BOARD INC.

Cubist Pharmaceuticals, Inc.

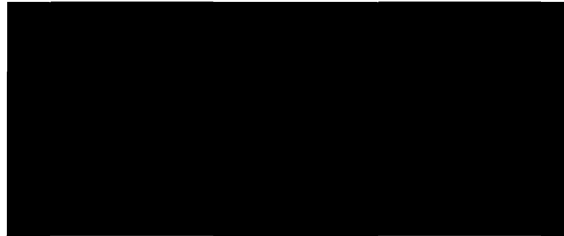
MEMBERSHIP ROSTER



**INFORMED CONSENT AUTHORIZATION TO PARTICIPATE
IN A CLINICAL INVESTIGATION**

Title: (Protocol: DAP-ADT-04-02) A Randomized, Double-Blind, Placebo Controlled, Multiple Dose, Safety and Pharmacokinetic Study of Ascending Doses of Daptomycin in Healthy Volunteers

Site of Investigation:



Principal Investigator:

Sponsor: Cubist Pharmaceuticals, Inc.

Participant's Name: _____

You are invited to participate in a drug research study because you are a healthy individual. However, before you give your consent to be a volunteer, we want you to read the following and ask as many questions as necessary to be sure that you understand what your participation will involve.

NATURE AND PURPOSE OF THE STUDY

The study doctor and Cubist Pharmaceuticals, Inc. (the study sponsor) are studying daptomycin, which is an antibiotic medication that has been approved by the Food and Drug Administration (FDA), for the treatment of skin infections. An antibiotic is a medication that is used to eliminate an infection caused by bacteria or germs. It is anticipated that the treatment of certain infections will require higher doses of daptomycin than what is currently approved by the FDA to treat skin infections. The dosage levels being studied are not currently approved by the FDA and are therefore considered investigational.

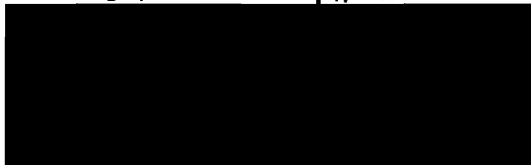
The purpose of this study is to better understand the amount of daptomycin that gets into your blood when multiple doses of daptomycin are administered to healthy volunteers for up to 14 days. In addition, the safety and tolerability of these dosage levels in healthy volunteers will also be assessed. The study medication will be administered intravenously through a vein in your arm once a day for 14 days. This study is for research purposes only and is not designed to treat a medical condition.

SUBJECT SELECTION

You may be offered an opportunity to participate in this research study if you meet the following criteria:

- Are able to spend up to 17 days within the study clinic without going home,
- Healthy, males and females between the ages of 18 and 45, inclusive, (Females of childbearing potential must practice reliable birth control)

Version : 01/18/05
Protocol DAP-ADT-04-02



Initials: _____
Date: _____

measures during study treatment and for at least 30 days after study completion and must not be pregnant prior to the administration of study medication and must not be breastfeeding),

- Have met screening criteria for inclusion in the study and all test results are satisfactory,
- Have not used any antibiotic within 15 days prior to the start of the study,
- Have not received an investigational drug for at least 30 days prior to the study screening,
- Have not donated blood or had excessive blood loss within 30 days prior to the study screening.

It is important that you answer all of the screening questions completely. You must disclose all past and present diseases, allergies and all medications that you are taking, including prescription and non-prescription drugs.

Approximately 36 volunteers will be enrolled in this single center research study.

STUDY DURATION

The duration of your participation in this study is up to approximately 35 days. If you are assigned to one of the first 2 groups (Group 1 or 2), you will have to stay in the clinic for 18 days/17 nights and return for a follow-up visit 12 to 16 days after the last dose of study medication. If you are assigned to group 3, you will have to stay in the clinic for 6 days/5 nights. A study screening visit is required within 14 days prior to the start of the study for all potential participants.

STUDY PROCEDURE

Study Design

This study is considered a randomized, double-blind, placebo-controlled dose escalation study. This means that the first group of volunteers will be assigned to receive the 10 mg/kg intravenous (by vein) dose of Daptomycin or will receive placebo. Placebo is a "dummy" solution that has no active medication.

The results of how well this dose level is tolerated will determine if the next group gets a higher dose or a lower dose. If it is well tolerated then 12 mg/kg or placebo will be administered and if it is poorly tolerated a lower dose, 8mg/kg or placebo will be given.

Of the 12 volunteers enrolled in either group, 9 will receive Daptomycin and 3 will receive placebo. The study medication will be given for 14 days.

After the completion of these two groups, a third dose group will be enrolled that will be a lower dosage (either 6 mg/kg or 8 mg/kg given intravenously) based on the results of the higher dose levels. This group will receive treatment for 4 days only.

You will not have a choice as to which group you are assigned or whether you receive daptomycin or placebo. Neither you nor the study doctor will know if you

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

are receiving daptomycin or placebo. However, this information can be obtained if medically necessary.

Screening

You will report to the clinic for a screening visit. At this time you will be asked for personal information regarding your date of birth, race, sex, weight and height. Your medical and medication history will be reviewed. A physical examination including the measurement of your vital signs (blood pressure, heart rate and temperature), and an electrocardiogram (ECG-recording of the electrical activity of the heart) will be performed. Blood and urine will be collected for clinical laboratory evaluation including a screening for hepatitis, HIV, drugs of abuse and a pregnancy test for women of childbearing potential.

Positive test results for hepatitis and HIV must be reported to a local health agency. This is the legal obligation of medical personnel in this state. A separate consent form is necessary in order to perform the HIV testing.

If you are in group 1 or 2, a simple test of nerve function designed to measure the speed at which electrical impulses travel through nerves will be conducted. A special sensor will be placed on your wrist and a mild electric stimulus will be applied to your wrist causing your thumb to twitch.

You will be permitted to participate in this study at the discretion of the study doctor if the results of the study screening laboratory tests are satisfactory. You will be advised of the study restrictions and when to report to the clinic to begin the study. You will be considered an alternate for this study until such time that you have received study medication.

Dosing and Procedures

If you meet the criteria of the 'screening' section, you will report to the clinic on the day prior to the start of dosing, Day-1. If you are in groups 1 or 2, the test to measure the speed at which electrical impulses travel through the nerves will be repeated. All participants will have a physical examination including the measurement of vital signs. Blood and urine will be collected for clinical laboratory evaluation including a pregnancy test for women of childbearing potential. In addition, you will be asked to report any medications that you have taken.

Frequently throughout the study all participants will have their vital signs monitored and be asked questions about how they are feeling and if they have used any additional medications

Groups 1 & 2

You will have an ECG, blood will be collected twice, and urine collected once prior to dosing on Day 1. An intravenous catheter (small tube) will be inserted into a vein in your arm in order to administer the study medication. The catheter site will be inspected, maintained and may be changed by the study staff as needed. You will receive the study medication as an intravenous infusion that will last about 30 minutes. You will collect all of your urine in special containers over the next 24

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

hours. Blood will be collected an additional 8 times in the 12 hours after dosing. Blood samples will be collected on the mornings of Days 2 and 3 prior to dosing. On the morning of Day 4 you will have a physical examination, an ECG and 2 blood samples will be collected prior to dosing. Blood will be collected an additional 8 times in the 12 hours after dosing. A blood sample will be collected on the morning of Day 5 just prior to dosing. On Day 6 you will receive study medication.

On the morning of Day 7, you will have a physical examination, an ECG, blood will be collected twice and urine will be collected once prior to dosing. You will collect all of your urine in special containers over the next 24 hours. A second ECG will be done after dosing. Blood will be collected an additional 8 times in the 12 hours after dosing. A blood sample will be collected prior to dosing on Day 8.

You will continue to receive study medication on Days 9 through 13. Blood will be collected prior to dosing on Day 9 and twice on Day 11. An ECG will be performed prior to and after dosing on Day 10.

On Day 14 you will have a physical examination, an ECG, blood will be collected twice and urine collected once prior to dosing. You will collect all of your urine in special containers over the next 24 hours and will receive your last dose of study medication. The test to measure the speed at which electrical impulses travel through your nerves will be conducted one hour after dosing. Blood will be collected an additional 8 times in the 12 hours after dosing.

On the 15th day of the confinement you will have blood collected two times and once on the 16th confinement day.

On the 17th confinement day you will have a physical examination, ECG and blood and urine will be collected including a pregnancy test for women of childbearing potential. You will be asked how you are feeling and if you have taken any other medications. You will then be permitted to leave the clinic with instructions when to return for a follow-up visit.

Follow-up Visit (Groups 1 and 2)

You will report to the clinic for a follow-up visit between 9 to 13 days after your clinic discharge. At this time the test to measure the speed at which electrical impulses travel through your nerves will be conducted. You will be asked how you have been feeling. You will also receive a telephone call 30 days after your last dose of study medication to ask how you have been feeling.

Group 3

Blood will be collected twice and urine once prior to dosing on Day 1. An intravenous catheter (small tube) will be inserted into a vein in your arm in order to administer the study medication. The catheter site will be inspected, maintained and changed as necessary by the clinic staff. You will receive the study medication as an intravenous infusion that will last about 30 minutes on Days 1 through 4. You will collect all of your urine in special containers for 24 hours after dosing on Day 1.

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

Blood will be collected an additional 8 times in the 12 hours after dosing on Day 1. Blood will be collected prior to dosing on Days 2 and 3.

On Day 4 you will have a physical examination, an ECG and blood will be collected twice prior to dosing. You will receive your last dose of study medication. Blood will be collected an additional 8 times in the 12 hours after dosing.

Post-Study Assessment

On the 5th and final confinement day blood and urine will be collected including a pregnancy test for women of childbearing potential. You will be asked how you are feeling and if you have taken any medications. You will be discharged from the study.

You may require longer observation in the clinic or additional laboratory testing based on the effects of the study medication or the results of laboratory tests.

Withdrawal Procedures

If you withdraw early from the study, for any reason, you will be asked to complete the lab testing and discharge procedures outlined in the final Post-Study Assessment for your group.

Blood Sampling

Groups 1 and 2

Blood samples will be taken approximately 53 times throughout the course of the study including study screening, clinic confinement, and post-study assessment. Approximately 375 ml of blood (slightly more than 1½ cups) will be withdrawn throughout the study.

Group 3

Blood will be collected approximately 26 times throughout the course of the study including study screening and clinic confinement. Approximately 210 ml of blood (slightly less than 1 cup) will be withdrawn throughout the study.

A standard blood donation is 500 ml (approximately 2 cups) of blood in a 56 day period.

Additional blood samples may be required if any of your lab tests results are abnormal.

Meals

Standardized meals and snacks will be provided at regular times throughout your clinic confinement.

Restrictions

To participate in this trial, you must not perform any strenuous physical exercise within 7 days prior to your first dose of study medication and while you are confined to the study clinic. Any medication administered by intramuscular

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

injection must be discontinued 7 days prior to Study Day 1 and may be resumed following discharge from the clinic.

Drugs for high cholesterol such as Zocor®, Mevacor®, Lipitor®, etc. must be discontinued 7 days prior to Study Day 1 and may be resumed following discharge from the clinic. If you are taking any medication, you must inform the study doctor and get approval to continue this medication during the study.

Antibiotic therapy (oral, intravenous, topical) must be discontinued 15 days prior to Study Day 1. Antibiotic therapy following discharge from the clinic is acceptable.

You must not consume alcoholic beverages from 3 days prior to Study Day 1 until discharge from the study clinic.

PHYSICIAN AVAILABILITY

A study physician will be present in the clinic during study drug administration (in the clinic) and on-call at all other times during this study, in the event of any type of medical emergency.

RISKS AND DISCOMFORTS

Daptomycin

Daptomycin has been given to approximately 1400 subjects in clinical studies sponsored by Cubist Pharmaceuticals, Inc. (Cubist). About 85 of those subjects received a dose of 6 mg/kg every 24 hours; over 1300 subjects received a dose of 4 mg/kg every 24 hours. Of the 1400 subjects treated with daptomycin in clinical studies sponsored by Cubist, the most commonly reported adverse events (occurring in approximately 2-6% of the subjects) were disorders relating to the stomach and Intestine (diarrhea, constipation, nausea and vomiting), injection site reactions (redness, itching, swelling, infection), swelling, headache, problems sleeping, urinary tract infection, anxiety, kidney failure, dizziness, and rash. Some of the less reported adverse events included laboratory abnormalities and changes in blood pressure. These laboratory changes typically go unnoticed by subjects, however, could be serious in nature requiring discontinuation from the study or other medical intervention. Overall, 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.

There have been reports of muscle aches or weakness associated with an increase in an enzyme, CPK found in the blood. Increases in CPK may indicate potential muscle damage. The CPK levels have been shown to return to normal with the discontinuation of the drug. If you experience muscle pain or weakness, inform the study doctor or staff immediately.

Some patients experience an increase in liver enzyme laboratory test values, an indication of possible liver damage. In rare instances patients have experienced a yellowing of their skin or the whites of their eyes.

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

All antibiotic treatment may result in the overgrowth of organisms that are not susceptible to the antibiotic. Therefore, you may be at greater risk for developing a fungal or yeast infection of the mouth (thrush) or vagina.

The following adverse events occurred infrequently across all clinical studies sponsored by Cubist; however, you should be aware of these specific events.

Cardiac failure occurred in less than 2% of 1400 subjects and the events were generally considered to be a result of the subject's prior illness.

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

One subject who received daptomycin was diagnosed with Bell's Palsy (facial droop). Although the subject's physician thought that the event was not related to treatment with daptomycin, we feel this information is important to communicate.

In addition, all antibiotics increase the risk of developing a dangerous and potentially life threatening condition called pseudomembranous colitis. This condition is characterized by severe diarrhea that is often filled with blood and/or mucous. Inform the study doctor or study staff if you develop severe diarrhea during or after the study.

The incidence and severity of the adverse events associated with daptomycin may increase with increased doses.

During the collection of blood samples, you may experience pain and/or bruising at the needle insertion site. Although rare, localized clot formation and infections may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

The test that measures the speed at which electrical impulses travel through your nerves will involve a sensor being placed on your wrist. When the test begins, you will feel slight electrical pulses that will cause a short, mild tingling sensation in your hand or wrist. These pulses will increase in strength until they cause your thumb or fingers to twitch. The pulses will be repeated about 15 times with about 5 seconds between each one. The discomfort that you experience during these procedures is anticipated to be minimal.

UNKNOWN/UNFORESEEABLE RISKS

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of this medication or interaction with another medication. You will be informed verbally and in writing of any new information, findings or changes to the way the research will be performed that might influence your willingness to continue your participation in this study.

Version : 01/18/05
Protocol DAP-ADT-04-02



Initials: _____
Date: _____

BIRTH CONTROL AND PREGNANCY

The effect of daptomycin on infants and unborn children has not yet been determined and may be harmful. You may not participate in this program if you are pregnant or breast-feeding. If you are a woman who can become pregnant, you must avoid becoming pregnant while receiving daptomycin treatment and for at least 30 days after treatment is stopped. For that period you must use a reliable method of birth control (oral contraceptive pills, also known as birth control pills, or a barrier method of contraception such as condoms or diaphragm together with spermicidal foam or gel). If you become pregnant while receiving daptomycin treatment, you will be withdrawn from treatment and provided alternative treatment for your infection. Your doctor will determine what follow-up visits are necessary during your pregnancy. You must see your doctor as requested and provide information about the outcome of the pregnancy.

BENEFITS

It is understood that participation in this study is purely for research purposes, and that no therapeutic benefit may be derived.

COST

There will be no cost to you for your participation in this study.

PAYMENT

The total payment for your participation in this study is \$2,435.00 for groups 1 and 2 and \$800 for group 3. If you choose to withdraw from the study prior to completion, you will be entitled to payment for the portion of the study that you have completed based on the following payment schedules:

Group 1 and 2

	Total Visit	Stipend per Visit	Total
Screening Visits	1	\$0.00	\$0.00
Inpatient Visits	17	\$130.00	\$2,210.00
Follow-up Visit	1	\$150.00	\$150.00
Discharge Visit	1	\$75.00	\$75.00
Total			\$2,435.00

Group 3

	Total Visit	Stipend per Visit	Total
Screening Visits	1	\$0.00	\$0.00
Inpatient visits	5	\$130.00	\$650.00
Follow-up visit	1	\$150.00	\$150.00
Total			\$800.00

All volunteers will be paid within 10 business days of the completion of their participation in the study.

In agreeing to participate in this study, you will be acting as an independent contractor, not as an employee of Comprehensive NeuroScience, Inc. Because payments made to you for participating in this study may be reported to the IRS

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

as income, you are required to provide your social security number. No deductions for any state or federal withholding or any other similar taxes will be made. It is the responsibility of the participant to report this compensation on state and federal tax returns and for the payment of any taxes that are due on this compensation.

TREATMENT ALTERNATIVE

Since this study is not intended to provide any therapeutic or other health-related benefit, your alternative is to not participate in this study.

RESEARCH-RELATED INJURIES

In the event of any illness or injury resulting directly from participation in this research project, Dr. Maria Gutierrez will provide medical treatment at Comprehensive PhaseOne. Medical treatment will be paid for (in excess of insurance payments) by Cubist for any injury that is determined by the Investigator and Cubist to be a direct result of receiving daptomycin in accordance with the protocol, first appearing while you are receiving daptomycin. No other compensation is offered by Cubist Pharmaceuticals, Inc. or by Comprehensive Phase One.

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

If you have any adverse reaction (side effect) to the study medicine or changes in your physical or mental condition during the course of the study, you should immediately contact Maria Gutierrez, M.D., at (954) 467-1960.

RIGHT TO WITHDRAW OR REMOVAL FROM STUDY

You understand that you are free to withdraw from this study at any time, and you agree to inform the physician immediately if you intend to withdraw. It is understood that your decision to participate in this study or to withdraw from this study will not influence the availability of your future medical care and will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time.

You agree that the physician in charge of the study can remove you from this study without your consent for any reason, including, but not limited to:

- a. His/her judgment that any condition or circumstance may jeopardize my welfare or the integrity of the study.
- b. Your failure to follow the instructions of the investigator(s).
- c. If the study is stopped by the sponsor and/or doctors participating in the study prior to completion.

We require that you wear a study identification bracelet on your ankle that will tell other clinics that you are in a study at Comprehensive NeuroScience, Inc. If you remove or change the bracelet in any way, you will not be allowed to stay in the research study.

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

CONFIDENTIALITY

Information from this study, medical records which identify you and the consent form signed by you, may be submitted to, inspected and or copied by; the study Sponsor (Cubist Pharmaceuticals, Inc.), the Sponsors representatives (such as contract research organizations), the FDA, governmental agencies in other countries where the study drug may be considered for approval, and the Independent Investigational Review Board, Inc. Because of the need to release information to these parties, absolute confidentiality can not be guaranteed. The results of this research study may be presented at meetings or in publications, however, your identity will not be disclosed in these presentations. Your research and medical records will be available for review for at least two years following completion of the study and possibly much longer. If you are transferred to another facility prior to the end of your participation in this study, you will be requested to fully cooperate with obtaining records from that facility. If you medical records are not obtained, it may not be possible to reimburse you for your care.

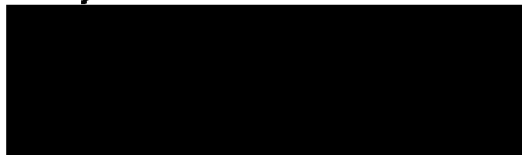
AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION IN A CLINICAL INVESTIGATION

You have agreed to take part in the study mentioned above. Under a federal law called the Health Insurance Portability and Accountability Act of 1996, medical information collected during research studies cannot be used, except in certain circumstance, without an authorization from the individual to whom the health information relates. By signing in the space provided below, you agree to permit Comprehensive NeuroScience, Inc., your doctors, and your other health care providers (together, "Providers"), as well as [REDACTED] and the investigator's staff (together, "Researchers"), to use and disclose health information that identifies you for the purposes described below.

1. **The health information that may be used and disclosed includes:**
 - All information collected during the research described in the Informed Consent Form that references the study; and
 - Health information in your medical records that is relevant to the research described in the Informed Consent Form.
2. **Your Providers may disclose health information in your medical records:**
 - To the Researchers;
 - To the study sponsor, Cubist Pharmaceuticals, Inc., and its agents, contractors, and other business partners, including laboratories involved with the study (together, "Cubist"); and
 - As required by law and to representatives of government agencies, independent review boards, and other persons who watch over the safety, effectiveness, and conduct of research.

3. **The Researchers may:**

Version : 01/18/05
Protocol DAP-ADT-04-02



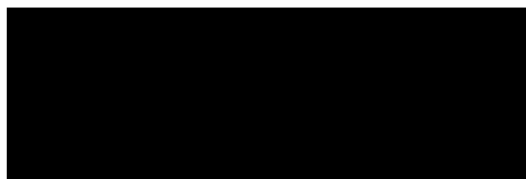
Initials: _____
Date: _____

- Use and share your health information to conduct the research;
 - Disclose your health information to Cubist;
 - Disclose your health information as required by law and to representatives of government agencies, independent review boards, and other persons who watch over the safety, effectiveness, and conduct of research; and
 - Remove from your health information your name and other information that could be used to identify you.
4. **Cubist may use and share your health information:**
- to conduct the research and confirm the research results
 - to assure the safety, effectiveness and quality of the research and of medical products or therapies developed through the research;
 - to develop new medical research and proposals for new medical products or therapies; and
 - as required by law.
5. **Once information that could be used to identify you has been removed**, the information that remains is no longer subject to this Authorization and may be used and disclosed as permitted by law, including for other research purposes.
6. **Once your health information has been disclosed to a third party**, federal privacy laws may no longer protect it from further disclosure. However, the Researchers and Cubist agree to protect your health information by using and disclosing it only as permitted by you in this Informed Consent Authorization. These limitations continue even if you revoke (take back) this Authorization.
7. **You do not have to sign this Authorization**, but if you do not, you will not be allowed to participate in the study. Refusing to sign this authorization will not affect your ability to obtain treatment outside of this study, or receive benefits for which you are entitled.
8. **You may change your mind and revoke (take back) this Authorization at any time.**
To revoke this Authorization, you must write to:



However, if you revoke this Authorization, you will no longer be allowed to participate in the research. Also, even if you revoke this Authorization, the information already obtained may continue to be used and disclosed to protect the integrity of the research.

Version : 01/18/05
Protocol DAP-ADT-04-02



Initials: _____
Date: _____

9. While the research is in progress, you may not be allowed to see your health information that is created or collected in the course of the research. After the research is finished, however, you may see this information in accordance with applicable laws.

10. This Authorization does not have an expiration (ending) date.

PERSONS TO CONTACT

You have the right to ask any questions concerning the potential and/or unknown hazards of this study at any time. If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study medication, contact [REDACTED]

If you have any questions regarding your rights as a research volunteer, please contact [REDACTED] Chairman of the Independent Investigational Review Board, Inc. at toll free [REDACTED] during regular working hours. The Independent Investigational Review Board is a Committee established for the purpose of protecting the rights of volunteers in a research study.

Do not sign this form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

CLOSING STATEMENT

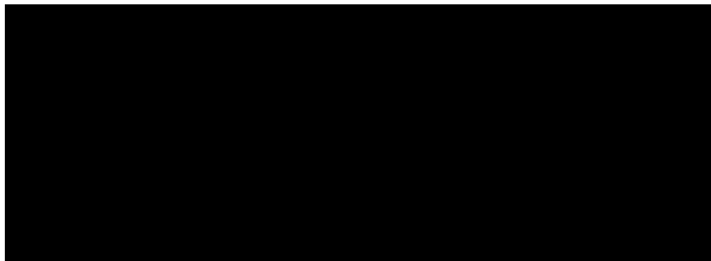
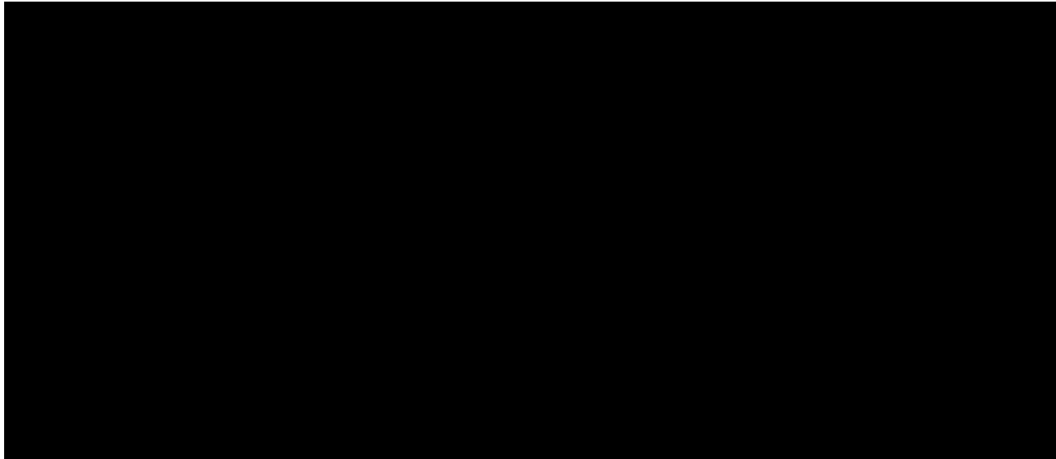
You have read and understood the information which has been stated above and have received satisfactory answers to all of the questions which you have asked and you willingly sign this consent form. You will receive a copy of the signed informed consent. You hereby consent to be a participant in this study.

Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

SIGNATURES

I have read the above information in a language that I understand well. The content and meaning of this information has been explained to me. I hereby voluntarily consent and offer to take part in this study and authorize the release of my personal health information.



Version : 01/18/05
Protocol DAP-ADT-04-02

Initials: _____
Date: _____

