PROTOCOL #066-155

INFORMED CONSENT
AUTHORIZATION TO PARTICIPATE IN A RESEARCH PROJECT

A DOUBLE-BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, MULTICENTER STUDY OF THE USE OF WEEKLY AZITHROMYCIN AS PROPHYLAXIS AGAINST THE DEVELOPMENT OF *MYCOBACTERIUM AVIUM COMPLEX* DISEASE IN HIV INFECTED PEOPLE

PATIENT NAME: _____

1. THE NATURE AND PURPOSE OF THIS STUDY

You are being asked to volunteer for a research study. The drug to be used in this study, azithromycin, has been approved for use in a number of bacterial diseases. It has only been tested in a few HIV-infected people for prophylaxis or prevention of disease and has not been approved for this use. The aim of this study is to find out if azithromycin in HIV infected people like yourself can prevent infection with a number of microorganisms known as Mycobacterium avium complex or MAC. Because this study is designed to test azithromycin for a new use, the study is investigational research.

You have been diagnosed as being infected with the Human Immunodeficiency Virus (HIV). HIV infection causes you to lose certain white cells of your immune system known as CD4 cells. As a result, you are less able to naturally protect yourself from infection with other microorganisms. Since you have been HIV-infected for some years, the number of the CD4 white cells in your blood is now about 100 per cubic millimeter, and you are susceptible to many infections. In general, it is better to prevent these infections rather than wait until you become ill and then treat you.

One microorganism to which you are now susceptible is the Mycobacterium avium complex (MAC) of organisms. Up to 25% of HIV-infected persons with CD4 counts less than 100 per cubic millimeter, become infected with MAC. Until recently, there were virtually no drugs effective for MAC. Azithromycin is a new drug that is active for MAC in animals. However, although azithromycin is on the market for the treatment of some infections it has <u>not</u> been <u>approved</u> for use in treating MAC as only a few patients with MAC have received azithromycin and only as part of research. Therefore a careful study or test is needed to find out if it is useful in preventing MAC before azithromycin can be more widely tested and used.

The purpose of this study is to determine if azithromycin protects you from getting infected with MAC. This is a prophylaxis or disease prevention study, not a treatment study. We think that azithromycin might protect you better than no prophylaxis at all (the present standard of care). However, we can not presently be sure that azithromycin will be to your benefit. To make sure, in this study equal numbers of people will take

azithromycin or a placebo (an inactive dummy pill). As this is an experimental study you cannot expect to routinely continue on azithromycin after the study.

2. EXPLANATION OF PROCEDURES TO BE FOLLOWED

A. EXPERIMENTAL PROCEDURES OR THERAPY

If you decide to enter into this study, you will first have laboratory tests to make sure that you are not already infected with MAC or have some other disease, other than HIV. You will also have a chest X-ray and your hearing will be tested. Then you will be randomly assigned (like flipping a coin) to receive placebo or azithromycin. Neither you nor your doctor will know which material you are receiving. You will then take your pills (either azithromycin or placebo) once a week. Each month, you will have to come back to the clinic for blood tests to see if the medication is working and to determine whether or not you have side effects. If you do have side effects, we might stop the medication for a while, and restart the medication if the side effects go away. If you then again get side effects due to the drug, the drug would be permanently stopped. Your participation in the study will end if you become infected with MAC, you desire to stop the study or if you get side effects which require you to end the study. Other reasons why you may need to leave the study are also explained in section 9 of this form.

B. DRUG ADMINISTRATION:

You will take four tablets as a single dose once a week. A small calendar or diary card will be provided to remind you when to take your medication.

C. EXPECTED DURATION OF THE STUDY AND NUMBER OF PEOPLE EXPECTED TO PARTICIPATE

You will be part of this study for up to twenty four months or longer unless you need to discontinue treatment for any reason. Causes for you having to leave the study could include development of other infections that need treatment that will interfere with this study, or if you develop MAC that needs treatment, or because of drug toxicity. If, during the study you you develop MAC you will be removed from the study and offered the best available treatment by your personal physician. This treatment will include the opportunity to enroll in an azithromycin compassionate use protocol if it is available. The total number of people who will be asked to enter this study will be approximately 200.

3. FORESEEABLE RISKS AND DISCOMFORTS

Based on animal studies and the experience of other people who have received azithromycin some adverse effects related to treatment may occur. The medication may not work, and your clinical condition could worsen. To date, approximately 5,000 patients including over 300 children have participated in short-term azithromycin studies at other hospitals and clinics. In patients where detailed information is available approximately 0.7% of non-AIDS patients discontinued therapy because of adverse effects. The most commonly reported adverse effects were gastrointestinal in nature with nausea, abdominal pain, and diarrhea being the most common.

Of AIDS patients who have received higher doses of azithromycin for longer periods of time than non-AIDS patients upset stomach, diarrhea abdominal cramping and rash have been seen. No consistent effect on blood tests have been seen thus far, but there is not enough information available to reach any conclusions in this regard. Toxic effects from long-term administration of azithromycin will be evaluated as a part of this study.

Some patients receiving high doses of azithromycin every day for periods of time in excess of a week have shown a partial loss of hearing. It is not known whether or not the hearing loss may or will be permanent. When a hearing loss has been noted and treatment stopped, the loss has typically reversed toward normal hearing. This problem has not been reported in patients taking large single doses. However a hearing test will be performed at the start of the study and again if you notice any problems.

Although animal tests have not shown harmful effects of azithromycin on fetuses, there is no data on the use of azithromycin during pregnancy in humans. If you are pregnant, taking this drug may expose your unborn child to a potential hazard. If you are a woman of childbearing potential, you will agree to use effective contraception during the treatment period, and for three months after the end of treatment.

If you are being treated with azithromycin and nevertheless get infected with MAC, there is a possibility that your MAC will be resistant to azithromycin. Azithromycin would not then be used in you for treatment even though it is under investigation as a treatment for MAC. However, the likelihood of resistance developing is unknown, other drugs may be available for its treatment, and you may consider that the possibility of a disease free period outweighs the possible problems of resistant organisms.

There are discomforts associated with the tests needed to conduct the study. Prior to entry into the study and each month during the study, blood will be drawn to make sure you do not have MAC infection and to make sure you do not have drug toxicity. On each of these visits, we will draw about 15 ml of blood (3 teaspoons). This may cause some discomfort, bruising and possibly faintness. Since we do not know how long you will be in the study, we can not state how much total amount of blood we will draw in the study.

A drug similar to azithromycin is known to interact with widely used drugs including terfenadine (Seldane) and ketoconazole (Nizoral). If you need to take any of these medicines during the study let your doctor know so the dose can be monitored.

4. UNFORESEEABLE RISKS TO SUBJECT:

It is not known whether this drug might harm an unborn child. Pregnancy while you are taking these drugs may expose your unborn child to a potential hazard of deformity. Therefore, you should not participate in this study if you are pregnant or become pregnant during the course of the study. Any women of child-bearing potential will have a pregnancy test performed and evaluated before entering the study and again every 3 months whilst you are being treated. Therefore, if you agree to enter this study, you will also agree to abstain from sexual intercourse, or use barrier contraception (diaphragm, condom, and foam) during treatment. If you do become pregnant while in this study, you must agree to immediately inform your doctor.

5. SIGNIFICANT NEW FINDINGS TO CONTINUE PARTICIPATION:

Any significant new findings that develop during the study which could affect your willingness to continue participation will be made available to you. The results of the research will be made available to you if you so desire.

6. POSSIBLE BENEFITS OF THE STUDY

The possible benefit from participation in this study is that if you are randomly selected to receive azithromycin, you may receive a treatment that may prevent MAC infection. Everyone in the study will be checked monthly, so if MAC does occur it will be caught early. Others may benefit from the overall conclusions to be drawn from the results of this study.

7. ALTERNATIVES TO PARTICIPATION IN THE STUDY:

If you decide not to participate in the study, your situation will be as if you were in the placebo group (no prophylaxis for MAC). Your decision not to take part in this study will have no effect on your future medical care.

8. CONSEQUENCES OF DECIDING TO WITHDRAW FROM STUDY:

Your participation in this research study is voluntary, refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled, and you may discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled.

9. CIRCUMSTANCES UNDER WHICH PARTICIPATION MAY BE TERMINATED WITHOUT YOUR CONSENT:

Your participation may be terminated without your consent if health conditions or other conditions occur that might be dangerous or detrimental to you or your health; or, if military contingency requires it; or, if you become ineligible for military medical care as authorized by army regulation.

10. CONFIDENTIALITY OF SUBJECT/RESEARCH RECORDS:

Research records of your participation in this study will be maintained by the principal investigator. All volunteers will receive study numbers that are known only to the investigators. Clinical and research records may be reviewed by (i) the Department of Clinical Investigation and/or the Human Use Committee/Institutional Review Board; (ii) the US Army Medical Research and Development Command; (iii) the collaborating pharmaceutical company (Pfizer); and (iv) the Federal Food and Drug Administration, as part of their responsibilities for insuring the protection of research volunteers. Every effort

will be made to keep the records as confidential as possible, within the limits of the law. Research and clinical information relating to you will be shared with other investigators, the scientific community through presentation and/or publication; however, you will not be identified by name in any publications or presentations resulting from this study.

11. LIMITATIONS TO MEDICAL CARE:

Medical care is limited and will be within the scope authorized for Department of Defense health care beneficiaries. Necessary medical care does not include domiciliary care.

12. SAFEGUARDS.

You will be monitored for drug side effects or lack of efficacy by clinical examinations, blood tests, and X-rays. You will be asked to leave the protocol for lack of efficacy, pregnancy, anemia, very low white count or platelet count, severe bleeding tendency, severe liver toxicity, or other drug reactions.

13. ADDITIONAL COSTS THAT MAY-RESULT FROM PARTICIPATION IN STUDY:

There is no additional cost to you for your participation in this study

14. TREATMENT AND COMPENSATION FOR RESEARCH-RELATED INJURY:

Your entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations. Details of who you should contact about your rights or if you believe you have received a research related injury are given in section 15. below. If you are injured because you take part in this study, medical care will be made available to you by <NAME> and <NAME> Medical Center. Financial compensation for such things as lost wages, disability or discomfort due to an injury is not available. You will not give up any legal rights by signing this form. If you experience any symptoms which you think might be related to receiving azithromycin, or any other medical problems, be sure to report them promptly to the Principal Investigator.

_____ Duty tel No:_____

Off duty tel No:_____

15. OFFER TO ANSWER QUESTIONS ABOUT THIS STUDY

If you have questions about the conduct of this study, you should contact:

_____ Telephone Number:_____

If you have questions concerning patient's rights, you should contact:

_____ Telephone Number:_____

If you have questions concerning adverse drug effects, you should contact:

_____ Telephone Number:_____

16. CONSENT

I have read, or had read to me, the above information before signing this consent form. I have been offered ample opportunity to ask questions and have received answers that fully satisfy those questions. If I do not participate or if I discontinue my participation in this study I will not be penalized and I will not give up any of my legal rights.

I have received a copy of this informed consent agreement.

_____ _____

Signature of Patient Date

_____ _____

Patient's name (printed) Patients address

_____ _____

Witness Date

_____

Witness name (printed)