The Safety and Efficacy of Lopinavir in Combination with Standard Drugs in the Treatment of HIV + Individuals

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A. Study Introduction

Highly active antiretroviral treatment (HAART) combining 2 or more drugs is now the standard of care for HIV infection. One important, newer class of drugs is the protease inhibitors, which work by preventing the cleavage of protein precursors essential for HIV maturation, infection of new cells, and replication. Since 1995, numerous studies have shown that in patients with advanced HIV infection, use of a protease inhibitor in combination with other classes of drugs has led to marked clinical improvement and prolonged survival. Most PI's potently suppress HIV in vitro, However, all protease inhibitors have different efficacies in vivo, based largely on pharamacokinetic differences. All PI's have side effects, including gastrointestinal intolerance and increased liver function tests. Among the 6 different PI's there are different side effects related to fat redistribution and diabetes.

There are currently 6 PI's currently licenced or available through compassionate-use programs in the U.S. Each was designed to be an improvement over Saquinivir, the first protease inhibitor; The subject of my research proposal is to Lopinavir or ABT-378, which is the newest investigational drug, and it is not yet FDA approved, Lopinavir, which is chemically related ritonavir, is extremely potent, 10 times more potent than ritonavir, as evidenced in in vitro studies. No large clinical studies have been published yet. The objective of my study will be to determine the safety and efficacy of Lopinavir in combination with standard drugs of choice, namely the two nucleosides lamivudine and zidovudine.

B. Study Design

This will be a phase 2, randomized, placebo controlled study of Lopinavir versus placebo. After being randomized by computer, subjects will be stratified into three treatment arms: Lopinavir 200mg bid, 400mg bid, or placebo bid. All subjects will receive the standard treatment of larnivudine and zidovudine

The subjects will be consenting adult patients infected with HIV. They will be either recently diagnosed HIV patients or patients naive to the above therapy. The population will come from the HP6 clinic, which includes a large number of women and minorities. Inclusion criteria for the study: age greater than 18, CD4 <200, plasma HIV RNA >10K. Patients must not have had previous treatment with protease inhibitors or 3TC or zidovudine; Exclusion criteria include malabsorption, acute infections, elevated Lfts, or peptic ulcer disease

We will measure the effect of Lopinavir at 200mg bid versus 400mg bid versus placebo on a relative reduction in plasma HIV Rna from baseline, the proportion of subjects with plasma IRV RNA <400 copies/n-fl; and in increase in CD4 cell count from baseline after 3 months of treatment;

The measurements will be made by blood sample every four weeks, and standard techniques for measuring CD4 and HIV RNA will be employed. During these measurements, patients will also have similar measurements of blood and urine chemistries, along with a history and physical to assess safety profile and potential side effects.

C. Statistical Analysis

To detect a 25% relative decrease in the HIV RNA after three months of therapy, an enrollment of about 100 patients would be necessary, stratified among the three treatment arms. The three arms would be compared in efficacy after three months. At the end of three months, we will analyze the proportion of patients in each treatment arm that had undetectable plasma FHV RNA. This would be conducted on an as treated basis (only patients on randomized therapy) and on a strict intention to treat basis that will include data on all patients randomized and all available follow up data. Missing data and failures after a month will be accounted for considered a treatment failure.

D. Study Subjects

"Vulnerable patients" will not be used.

The patient's primary BP6 physician will identify the potential subject based on the above criteria. This physician will ascertain from the patient that he or she is willing to discuss the study with the PI or the research team

The number of patients that will be needed: As this drug is investigational; there is only enough medicine to treat about 500 patients, as per Abbott Laboratories; Similar Phase 2 studies that measure a relative decrease in FHV RNA employed about 100 patients to see a relative decrease of 25%, which is powered at 90%

E. Miscellaneous

Each subject will receive a unique code number that ensures confidentiality

There is no potential conflict of interest with the investigator. There is no relationship between Abbott Laboratory, which will supply the drug, and myself.

The location of the study will be within the confines of the Infectious Disease Division.

Potential Discomforts to the patients include venipuncture monthly. There is a risk that the treatment may not be as efficacious as the placebo or that the patient may receive placebo. This drug is investigational; Previous smaller studies, not published, have shown that known side effects are small and include mild gi distress and headache, at an estimated frequency of 2%; There may also be worsening blood chemistries. The method and route of the drug is po bid, and this is its standard use

Potential Benefits: are that the patient will have a marked slowing of AIDS defining events and longer survivability with no adverse effects.

Alternative Therapies:

Compensation to Subjects: Each subject win receive $ 10,000 for completing the study and for compliance by check after the completion of the study;

Minors and Radiation will not be used in this study.