UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Gilead Sciences, Inc
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A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

PHARMACOKINETIC/PHARMACODYNAMIC RESEARCH SUBSTUDY CONSENT

Your contacts for this study at the Hospital of the University of Pennsylvania [HUP] are:

Site address: 502 Johnson Pavilion, Philadelphia, PA 19104

Principal Investigator:	Pablo Tebas, MD	(215) 349-8092
Manager:	Joseph Quinn, RN, BSN	(215) 349-8092
Study Nurses:	Jenna Lewis, RN, BSN	(215) 349-8092
	Wayne Wagner, RN, MSW	(215) 349-8092

24 Hour Emergency Number (215) 662-6059 Ask for the Immunodeficiency Program Doctor on call

INTRODUCTION

You have already agreed to take part in a research study involving an experimental combination medication named E/C/F/TAF STR for the treatment of HIV-1 infection. An experimental medication means that the United States Food and Drug Administration (FDA) has not approved it for use by the general public.

An optional research substudy will take place in some of the subjects in the main study requiring additional blood sample(s). These blood sample(s) will be used for a research substudy to help understand markers of health and disease. If you would like, you can also be part of this **optional** substudy. This consent form tells you about this study.

Your Study Doctor or study nurse will go over this consent form with you and answer any questions you may have regarding this substudy. Before you agree to take part in this study, ask your Study Doctor or study nurse to explain any words or information in this consent form you do not clearly understand. You should understand the purpose of the substudy and this optional blood sampling, how your participation may help you, any potential risks to you, and what is expected of you during the substudy.

If you agree to take part in this substudy, you will be asked to sign and date this consent form and will be given a signed and dated copy to keep for your records. No one can force you to take part in this substudy. Even if you agree to participate, you are free to change your mind and stop at any time without penalty or loss of benefits which you would have otherwise. You can still continue to participate in the main study even if you do not agree to participate in this substudy. You must have reviewed and signed the main study consent form before signing this consent form. This consent form is not meant to replace the main study consent, and the contents of the main study consent apply to this substudy.

PURPOSE OF THE SUB STUDY

Blood will be drawn to determine the concentration of the study drugs in your body. This type of testing is called pharmacokinetics (PK) and measures the amount of the study drug in your blood and tells the researchers how much time it takes for the study drug to be absorbed into your body and how long it stays in your body after it has been absorbed. There will also be pharmacodynamics (PD) testing done. This type of testing measures how the drug works in the body and the relationship between the amount of the drug taken and the effect on the body. A small portion of subjects

(approximately 30 subjects out of 150 enrolled in the main study) will be asked to participate in the PK/PD substudy.
The purpose of this sub-study is to assess how the administration of the combination pill containing three experimental medications [elvitegravir (EVG), cobicistat (COBI) and tenofovir alafenamide (TAF)] and one medication that is approved by the FDA for the treatment of HIV-1 infection affects blood levels of a chemical, creatinine (a measure of kidney function), measured before, during and after dosing. The FDA approved medication included in the experimental combination tablet is Emtriva® (emtricitabine) and will be referred to in this informed consent form as FTC. The experimental combination medication will be referred to as E/C/F/TAF.

Iohexol (such as Omnipaque™) is an FDA approved contrast dye used for radiologic (x-ray) procedures. Iohexol is a useful agent for the measurement of kidney function. If you sign this consent form, you will give your permission to receive Iohexol at three visits as part of this research study to measure your kidney function. Iohexol is given as an intravenous (IV) injection and then blood is drawn at multiple time points to measure how much Iohexol is still in your blood. How quickly the Iohexol is cleared gives us a measure of how well your kidneys are working. You MUST NOT participate in this study if you are allergic to iodine, shellfish or have had a bad reaction to contrast dyes in the past.

This consent form details the PK/PD substudy, during which additional procedures will be performed on you if you agree to participate in the substudy. Your Study Doctor or study staff will go over this with you and answer any questions you may have regarding this research substudy.

PROCEDURES
If you are asked to participate in the PK/PD substudy and you agree, you will have extra evaluations for the substudy at three of your main study visits. You will have the following procedures performed Baseline (visit 1), at or between the Week 2, Week 4, or Week 8 (visit 2) and Week 24 (visit 3) visits. Visit 2 will be scheduled at one of these time points based on your convenience. In addition to the following procedures, you will be asked to record your study drug dosing information for 14 days prior to your visit to the clinic for the PK/PD substudy visit, which may occur anytime at or between your Week 2, Week 4, or Week 8 and Week 24 study visits. You will be provided with a dosing diary at the Baseline (Day 1) visit to record your study drug dosing information. The Study Doctor or study nurse will tell you how to complete the diary.

Day 1 (baseline) Visit #1:
Following your overnight fast, you will be given a meal on the morning of the PK/PD substudy visit. It is important for you to eat the entire meal. Your "fast" means that you will be restricted from food or liquid (except water) intake for 8 hours before your PK/PD substudy visit. At the Baseline visit, only PD samples will be collected. Within 5 minutes of consuming your meal, the first PD blood draw will be collected (pre-iohexol injection/0). You will then receive a single 1500 mg IV (intravenous – inserting a needle into a vein in your arm) dose of Iohexol which takes about 1 to 2 minutes. Additional blood draws will be collected at 5 mins, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8 hours post Iohexol injection. You will be given your study drug and you will be asked to return to the clinic 24 hours after taking the study drug for the 24 hour post dose collection.

A tube may be inserted into your vein and used for repeated blood draws. Using this tube allows the research staff to draw multiple blood samples with only a single needle stick.

At or between Week 2, 4 or 8/ Visit #2

At or between Week 2, 4 or 8, both PK and PD samples will be collected. Within 5 minutes of consuming your meal, the first PK/PD blood draw is shortly before (within 30 minutes) of receiving a single the dose of Iohexol and study drug (pre-dose/0) and additional blood draws will be collected at 5 mins, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8 and 24 hours after dosing.

Additional blood samples to determine the amount of study drug in certain types of your blood cells called peripheral blood mononuclear cells (PBMCs) for the PBMC portion of PK substudy will be collected. Your Study Doctor will discuss this in more detail with you. If you participate in this additional PBMC portion, additional blood draws will occur shortly before (within 30 minutes) taking the study drugs (pre-dose/0) and then at 2, 4, 8 and 24 hours after dosing.

Week 24 /Visit#3

At the Week 24 visit, only PD samples will be collected. Within 5 minutes of consuming your meal, the first PD blood draw is shortly before (within 30 minutes) of receiving a single the dose of Iohexol and study drug (pre-dose/0) and additional blood draws will be collected at 5 mins, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 8 and 24 hours after dosing.

Food and Drink Restrictions During the Visits

You will not be allowed to eat any food until after the 4-hour blood draw. In addition, you will not be allowed any water for 1 hour before and 2 hours after study drug dosing, except for the 240 mL (8 ounces) of water given with your dose of study drugs.

Time Requirements for Visits

You will have to stay at the study center for about 12 hours after the morning dose of study drugs. After your last blood draw on the evening of the PK/PD substudy visit, you may leave the study center when the Study Doctor or study staff believes it is safe for you to do so. You will be required to return to the study center the next morning for the 24-hour blood draw.

Blood Volumes

At each visit, you will have blood taken a total of 13 times (8 mls or approximately 1 ½ teaspoons at each time); this is approximately 156 mL (about 31 teaspoons) of blood during a 24 hour period. If you also participate in the PBMC portion, in addition to the 156 mLs, you will have approximately 80 more mLs (about 16 teaspoons) removed during these 24 hours.

RISKS

Whenever possible, efforts will be made to reduce additional blood draw risk (e.g. placement of central line to draw samples from participants so you will not have to be re-stuck as referenced on page 2). The PK sub-study visit with the main study visit will occur on the same day so that the risk of extra needle sticks for the blood draws are reduced.

BLOOD DRAWS

In addition to risks associated with the study drug, drawing blood from a vein may cause local pain, bruising, occasional lightheadedness, fainting, and very rarely, infection at the site of the blood draw. Please note that if the PK substudy is completed during your regularly scheduled visit at Week 2, Week 4, or Week 8, no additional needle sticks will be required. However, if your substudy visit is on another day (between your regularly scheduled study visits), it will require an additional needle stick.

Iohexol

During the injection of iohexol, you may experience a sensation of warmth or pain. Other adverse events include pain, blurred vision, headache, abnormal taste, nausea, vomiting, hives, itching and bruising. The administration of contrast dyes, like iohexol, are rarely associated with serious cardiovascular complications and death.

If you are allergic to iodine or shellfish or if you have had a serious reaction to contrast dyes in the past, you MUST NOT participate in this study.

You may experience some, all, or none of these side effects. However, life-threatening and even fatal side effects could occur. You will be monitored for all side effects. You must tell the study doctor about any new health problems that develop while you are participating in this study. You will be informed in a timely manner of any significant new information that may affect your willingness to continue to participate in this study.

POSSIBLE BENEFITS OF THE STUDY

There is no direct benefit to you, although your participation in this substudy may eventually help people with HIV-1 infection or people who are treated with E/C/F/TAF and medicines like it in the future.

WITHDRAWAL FROM STUDY AND REFUSAL TO PARTICIPATE

Like your participation in the main research study, the substudy is completely voluntary. **You may participate in the main research study EVEN IF YOU ARE NOT PART OF THE SUBSTUDY.** Your decision will not affect future treatment you may receive or your rights as a research subject.

The results of your tests from this substudy will NOT be available to you or your Study Doctor and you will not be notified of any findings related to your sample since the testing is only for research. Because these results will not be available to you or your Study Doctor, no genetic counseling will be offered or reimbursed by the Sponsor.

If you consent to the substudy and decide at a later date that you would like to withdraw your consent, you will need to do so in writing to your Study Doctor.

Withdrawing consent will result in destruction of your substudy sample(s). However, if you withdraw your consent after the sample(s) has (have) been tested, the test results and research study/sample-related information must remain in any database(s) that were created for the research study. The reason for this is to comply with regulations that require us to make data available for review by the United States Food and Drug Administration (FDA) or other appropriate regulatory authorities, or if this research is used to support an application for FDA approval to market the study drug(s).

If you withdraw consent for participation in the main study or are discontinued from the main study, the sample you provided for PK testing will continue to be available for testing unless you also withdraw your consent for the substudy as stated above.

PAYMENT FOR PARTICIPATION IN SUB STUDY

You will be paid $91 for your participation in the sub-study for each visit. The maximum compensation you will receive for the substudy participation is $273. This compensation will need to be provided as a check; therefore it must be processed through the University's accounts payable

system and can take 4-6 weeks to be received in the mail. In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

STATEMENT ABOUT PRIVACY

Records identifying you will be kept confidential and, to the extent permitted by applicable laws and/or regulations, will not be made publicly available. In the event of any publication regarding this study, your identity will remain confidential.

To further protect your confidentiality on the study, you will be assigned a code number. This code number will be used to label all your samples for testing and the information collected about you as part of your study visits will be entered into a database by this code number. Records that have your name and personal information will have restricted access and stored in locked cabinets in a secure facility.

Representatives from government agencies, including the U.S. Food and Drug Administration ("FDA"), institutional review boards, the Sponsor and/or the Sponsor's authorized representatives may need access to your original medical records and study records for the purpose of checking data collected for this study. By signing this consent form, you authorize this access.

Your coded study information and samples may also be used for additional unanticipated medical and/or scientific research projects in the future relating to HIV-1 or the development of the E/C/F/TAF STR (but at all times in compliance with applicable law and regulation). Your stored samples will be labeled with a study identification number, a bar coded number, and your initials. If your stored samples are shared with other researchers, they will only contain an identification number that does not identify you.

AUTHORIZATION TO USE AND DISCLOSE RECORDS

The authorization part of the consent gives more detailed information about how your personal health information may be used and disclosed by the University of Pennsylvania Health System (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What personal health information is collected and used in this study and might also be disclosed?

The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, email address, date of birth
- Social Security Number (needed for by UPENN to process payments by check); medical record number
- Personal and family medical history
- Current and past medications or therapies
- Results of physical exams, laboratory tests and procedures you will undergo during this research study

Why is your personal contact and health information being used?

Your personal contact information is important for the research team to contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study. In some situations, your personal health information might be used to help guide your medical treatment.

Which of our personnel may use or disclose your personal health information?
The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.).

Who, outside of UPHS and the School of Medicine, might receive your personal health information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- Pharmaceutical sponsor (Gilead Sciences): This is the company that supplies drugs for the study. Information regarding safety and adverse effects needs to be collected and monitored.
- Contract Research Organization: Monitors will visit the site on a regular basis to review data and assure accuracy and completeness of information before the data are analyzed.
- BioClinica: This is the central reading facility that will review your DEXA scan for the sponsor. It is important that one team review all the scans for all of the participants for quality control purposes.

Regulatory and safety oversight organizations

- The Food and Drug Administration and regulatory agencies in other countries
- The Office of Human Research Protections
- The Study Monitoring Committee

Once your personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by federal privacy protection regulations. Data are reported to the sponsor on Case Report Forms that identify you by your unique study number and not your name or medical record number. Information regarding your health, such as side effects of the study medications you experience will be reported only by code number. All samples collected for analysis will be labeled with your study number, visit number and date of your visit.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose your personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research repository (database). However, UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Will you be able to access your records?
Since this is an open-label study, you will be able to access some or all of your medical records after the study is over. The Principal Investigator is not required to release research information to you that is not part of your medical record.

Can you change your mind?
Yes, at any time you may withdraw your approval to allow the use and disclosure of your personal health information as described here. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your personal health information, you will also be withdrawn from the research sub-study.

If you withdraw your permission to use any blood or tissue obtained for the study, the Sponsor may need to retain and use any samples that have already been collected to comply with its legal obligations and to maintain the scientific integrity of the study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

COMMERCIAL ISSUES
You should also know that the Sponsor and other researchers who may study your medical information have an economic interest in developing new drugs and medical tests. The results of this research may lead to a commercial product for the diagnosis, cure, mitigation, treatment, or prevention of disease. You understand and agree that by signing this consent form you authorize the use of your sample, the by-products of the sample, and any products developed from the sample as described in this form. The Sponsor or other researchers or research companies may patent or sell discoveries that result from this research. Neither the Sponsor nor the Study Doctor has any plans to compensate you if this happens.

WHAT IS AN ELECTRONIC MEDICAL RECORD?
An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study,

results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

WHO CAN I CALL WITH QUESTIONS, COMPLAINTS OR IF I'M CONCERNED ABOUT MY RIGHTS AS A RESEARCH SUBJECT?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

CONSENT FOR OPTIONAL PBMC SUBSTUDY:

☐ **Yes, I consent to participate in the optional PBMC Substudy**

☐ **No, I do not wish to participate in the optional PBMC Substudy**

AGREEMENT TO BE IN THE OPTIONAL PK/PD SUBSTUDY

By signing this informed consent form, I acknowledge that:

(1) I have carefully read and understand the information presented in this consent document.
(2) The purpose and procedures related to this research study have been fully explained to me and I have had the opportunity to ask questions and all of my questions were answered to my satisfaction.
(3) I have been informed of the parts of the program that are experimental and of the possible discomforts, symptoms, adverse events and risks that I might reasonably expect, and the possible complications, if any, that I might reasonably experience from both known and unknown causes as a result of my participation.
(4) I understand that I am free to withdraw this authorization and to discontinue my participation in this substudy any time. The consequences and risks, if any, of withdrawing from the substudy while it is ongoing have been explained to me.
(5) I understand that such withdrawal will not affect my ability to receive medical care to which I might otherwise be entitled.

CONSENT FOR OPTIONAL PK/PD SUBSTUDY:

Subject

Subject Printed Name	Signature	Date

Person Obtaining Consent
I have carefully explained to the subject the nature and purpose of the above study. There has been an opportunity for the subject to ask questions about this research study. I have been available to answer any questions that the subject has about this study.

Printed Name & Title	Signature	Date

Witness (if applicable)
My signature indicates that I was present during the entire informed consent process interview and that the information in the form was presented and reviewed with the subject and that informed consent was freely given by the subject.

Witness Printed Name	Signature	Date