Elvitegravir (EVG) Cerebrospinal Fluid (CSF) Pharmacokinetics in HIV-Infected Adults

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

Elvitegravir (EVG) Cerebrospinal Fluid (CSF) Pharmacokinetics in HIV-Infected Individuals

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

Elvitegravir (EVG) Cerebrospinal Fluid (CSF) Pharmacokinetics in HIV-Infected Individuals

The study will be conducted locally at the UCSD AntiViral Research Center (AVRC), 220 Dickinson Street, Suite A, San Diego, CA 92103 and the HIV Neurobehavioral Research Program (HNRP), 220 Dickinson St, Suite B, San Diego, CA 92103.

Document Date: 7/2/2014

4. ESTIMATED DURATION OF THE STUDY

The enrollment period is anticipated to be approximately 18 months with final results approximately 24 months after study initiation. Subject participation will be approximately 24 weeks.

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The proposed project is a single dose, single arm, open-label, multicenter, phase IV pharmacokinetic study with the primary aim of describing cerebrospinal fluid (CSF) concentrations of elvitegravir (EVG), an HIV integrase inhibitor. Stribild is an FDA-approved, multiclass combination drug with potent antiretroviral activity against HIV-1. Stribild is a tablet containing four drugs, one of which is EVG. The study population will be HIV-1 infected study subjects who are naive to EVG. The study will enroll 14 subjects at three sites in the United States, who will be given Stribild over a period of approximately six months. Blood draws, urine collection and lumbar punctures will be performed after screening, to generate 22 on-treatment CSF-blood specimen pairs. Pharmacokinetic (PK) analysis will provide a small-sample estimate of distribution of EVG into CSF. HIV Dementia Scale scores will also be measured. The study will recruit approximately 7 subjects at UCSD.

6. SPECIFIC AIMS

Primary:

1) To describe the CSF concentrations of elvitegravir (EVG).

Secondary:

1) To determine the effects of Stribild on HIV RNA levels in CSF.
2) To evaluate the effects of Stribild on blood-brain barrier permeability as estimated by the CSF-to-serum albumin ratio.
3) To determine the effects of Stribild on HIV Dementia Scale scores.

7. BACKGROUND AND SIGNIFICANCE

Stribild™ (elvitegravir/cobicistat/emtricitabine/tenofovir) was approved by U.S. Food and Drug Administration (FDA) in August 2012 as a new multiclass combination drug with potent antiretroviral activity against HIV-1.[1]

Two randomized double-blind phase III clinical trials have demonstrated the non-inferiority as well as the tolerability and safety of Stribild™ compared to Atripla™ and ritonavir-boosted atazanavir plus Truvada™.[2,3] Similar results have been found between ritonavir-boosted elvitegravir and raltegravir in treatment-experienced patients.[4] The safety assessment of Stribild™ based on the pooled data from two comparable clinical trials with a total of 701 subjects in the Stribild™ arms suggested that it distributes into the central nervous system (CNS) because 11-12% of participants reported relevant adverse events, such as somnolence, headache, dizziness, insomnia, or abnormal dreams.[5]

HIV-associated neurocognitive disorder (HAND) is a common disease complication and is thought to be due to neurotoxic events that result from HIV replication in perivascular macrophages and microglia and immune and glial activation.[6] Most data have supported the notion that antiretroviral regimens possessing better estimated distribution into the CNS result in more favorable neurologic and cognitive outcomes. The CNS penetration effectiveness (CPE) score is one approach that estimates a drug's effectiveness in the CNS.[6,7] CPE values range from 1 (below average) to 4 (much above average) and raltegravir, an integrase strand transfer inhibitor, has an above average CPE value of 3. Higher CPE values are associated with lower CSF viral loads, better neurocognitive function, and better survival,[7-10] although some studies have had inconsistent findings. Prior studies have reported significantly higher concentrations of raltegravir in CSF than the 50% inhibitory concentration for wild-type HIV-1, suggesting that raltegravir –and perhaps other integrase inhibitors – reach therapeutic concentrations in the brain.[11]

During suppressive ART, persistent systemic and neuro-inflammation appears to be associated with HAND. HIV injures gut-associated lymphoid tissue early in the course of HIV disease, leading to translocation of microbial products, such as elevated plasma bacterial lipopolysaccharide (LPS) into blood. LPS binds to CD14 and can result in activation of myeloid cells. Higher soluble CD14 concentrations in blood are associated with HAND.[12] Other soluble CSF and blood biomarkers reflecting monocyte activation (e.g., MCP-1) and inflammation (e.g., IL-6) have also been linked to HAND. HAND has also been associated with cardiovascular disease biomarkers such as soluble vascular adhesion molecule-1 (sVCAM-1).[13] This may be important since switching to an integrase inhibitor, raltegravir, was associated with decreased inflammation- and cardiovascular disease-associated biomarkers, suggesting that these processes may be responsive to elvitegravir.[14]

8. PROGRESS REPORT

Not Applicable.

9. RESEARCH DESIGN AND METHODS

The proposed project is a single dose, single arm, open-label, multicenter, phase IV pharmacokinetic study. This study plans to enroll 7 HIV-infected, EVG Naïve subjects at our site and 14 at all sites.

The goals of the study are to (1) describe the population pharmacokinetics of elvitegravir in CSF, and (2) determine the impact of Stribild™ on suppressing HIV RNA in CSF, blood-brain barrier permeability, and HIV Dementia Scale scores. No published studies have addressed the following questions: 1) What are the concentrations of elvitegravir in the CSF in patients with HIV-1 disease? 2) Do these concentrations exceed the 95% inhibitory concentration (IC_{95}) for wild-type HIV-1? 3) How does Stribild™ affect blood-brain barrier permeability and HIV Dementia Scale scores? We will address these questions in a prospective, open-label treatment trial of HIV-infected, treatment-naive patients.

Even though this is primarily a pharmacokinetic study of FDA-approved drugs, adverse events will likely occur. According to the package insert, the most common adverse reactions are nausea (16%), diarrhea (12%), abnormal dreams (9%), headache (7%), fatigue (4%), rash (3%), insomnia (3%), and dizziness (3%).

Laboratory abnormalities can also occur, including elevations in creatine kinase (7%), elevated amylase (3%), and hematuria (3%). Serious adverse events, including lactic acidosis and severe hepatomegaly, have been reported but are uncommon. The standard regimen of Stribild™ will be used. If a regimen change occurs during the course of the project, participation will be discontinued. Patients will be carefully screened and those with pre-conditions, such as morbid obesity or hepatitis B virus co-infection, will be excluded.

HIV-1 infected patients who are willing to initiation antiretroviral therapy and who are naive to the components of Stribild™ will be the study population. Stribild™ has been recently added into the DHHS Guidelines as an option for the first-line therapy. The study will enroll 14 subjects to generate 22 on-treatment CSF-blood specimen pairs, which is sufficient to provide a small-sample estimate of distribution of EVG into CSF. A tabular schedule of assessments is provided below.

Assessment	**Screening**	**Baseline**	**Week 2**	**Week 8**	**Week 16**	**Week 24**
Time window (days)	-28 to -1	0	12-20	49-63	105-119	161-175
Informed consent	x					
Brief assessment	x		x			
Eligibility assessment	x					
Full assessment		x				x
Telephone assessment				x	x	
HIV RNA, Plasma	x	x	x			x
CD4+ T-cell count	x		x			x
Drug resistance testing	x					
HIV RNA, CSF		x	x			x
HIV Dementia Scale		x				x
Study drug dispensing		x	x	x	x	x
Safety assessment			x			x
PK assessment			x			x

Signs and symptoms, laboratory results, and toxicities ≥ Grade 2 will be recorded on the appropriate case report forms (CRFs).

Screening and Entry Evaluations

1) **Screening Evaluations will occur within 28 days of study entry**

a) Details of the study will be carefully discussed with subjects during screening and the subject asked to read and sign an informed consent approved by the IRB at the participating institutions.
b) Documented presence of HIV infection, as specified in Section 3.1.1 of the master protocol, prior to study entry.
c) A brief medical history will be obtained and will include:

i) Previous diagnoses including liver disease, renal disease, fracture, osteoporosis, allergies, drug reactions, and most recent menses.
ii) Current prescription and non-prescription medications taken within 14 days prior to entry.
iii) Recent use of drugs of abuse or unprotected sexual contacts. Past use of needles.
iv) A signs-and-symptoms assessment, including: vital signs, height, and weight. Vital signs will include temperature, blood pressure, and pulse rate.

d) 35 mL of blood and 15 mL of urine will be collected using standard methods.

2) The following laboratory tests must be performed within 28 days prior to study entry, unless otherwise noted:

a) Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count, differential white blood cell count, and platelet count.
b) Blood chemistries: electrolytes, blood urea nitrogen (BUN), creatinine, glucose, phosphorus, and calcium.
c) Liver function tests: total bilirubin, AST, ALT, alkaline phosphatase, and albumin.
d) Coagulation: prothrombin time, international normalized ratio, partial thromboplastin time
e) Urinalysis, including urine glucose and protein
f) Estimated glomerular filtration rate (eGFR)
g) For women of childbearing potential: Serum or urine pregnancy test.
h) HIV RNA in blood plasma
i) Lymphocyte subsets in blood (including CD4+ and CD8+ T-cell absolute counts and percentages)
j) Hepatitis C and hepatitis B serologic testing
k) Rapid plasmin reagent (RPR)
l) Drug resistance mutation genotyping in blood
m) 5 mL of blood plasma will be stored at -80C.

3) Baseline (Entry) Evaluation: Within 28 days of the screening evaluation, eligible and consenting subjects will enter the study. Additional assessments will be performed and study drug will be dispensed.

a) A complete medical history and physical examination will be performed:

   i) Prior diagnoses including liver disease, renal disease, fracture, osteoporosis, allergies, drug reactions, and most recent menses.
   ii) Current symptoms including those of an active systemic illness (e.g., fever) and bleeding or easy bruising.
   iii) Prescription and non-prescription medications taken within 14 days prior to entry.
   iv) Vital signs, including temperature, blood pressure, and pulse rate, height, weight, and waist circumference.

b) The HIV Dementia Scale will be performed.

c) 45 mL of blood and 15 mL of urine will be collected by standard methods. 15 mL of cerebrospinal fluid (CSF) will be collected by lumbar puncture using aseptic technique and an atraumatic needle.

d) The following laboratory tests will be performed:

   i) HIV RNA in blood plasma
   ii) HIV RNA in CSF
   iii) CSF total leukocyte count and differential, CSF erythrocyte count, CSF total protein, CSF albumin, CSF glucose
   iv) For women of childbearing potential: Serum or urine pregnancy test.

e) 5 mL of blood serum, 10 mL of blood plasma, 5 mL of whole blood, 5 mL of urine, and 8 mL of CSF

will be stored at -80C. An aliquot of peripheral blood mononuclear cells will be stored at -150C.

f) A three-week supply of Stribild will be dispensed from the research pharmacy.

On-Treatment Evaluations

4) Two-Week Assessment: Subjects will return at day 14 (one-week window) for safety and pharmacokinetic assessments that will include:

a) Brief, safety-focused clinical assessment:

i) Vital signs including temperature, blood pressure, and pulse rate.
ii) A medical history assessment including symptoms and signs of adverse reactions
iii) Study drug adherence assessment
iv) For women of childbearing potential: serum or urine pregnancy screen.

b) 75 mL of blood and 15 mL of urine will be collected by standard methods. 15 mL of CSF will be collected by lumbar puncture using aseptic technique and an atraumatic needle. Collection will follow a specific schedule as detailed in detailed in the *PK Sample Collection and Processing Document* and summarized in section 4.2.2 of the Master Protocol.

c) The following laboratory evaluations will be performed:
i) Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count, differential white blood cell count, and platelet count.
ii) Blood chemistries: electrolytes, blood urea nitrogen (BUN), creatinine, glucose, phosphorus, and calcium.
iii) Liver function tests: total bilirubin, AST, ALT, alkaline phosphatase, and albumin.
iv) Urinalysis, including urine glucose and protein
v) Estimated glomerular filtration rate (eGFR)
vi) For women of childbearing potential: Serum or urine pregnancy test.
vii) HIV RNA in blood plasma
viii) HIV RNA in CSF
ix) CSF total leukocyte count and differential, CSF erythrocyte count, CSF total protein, CSF albumin, CSF glucose
x) Lymphocyte subsets in blood (including CD4+ and CD8+ T-cell absolute counts and percents)

d) Pharmacokinetics: Detailed instructions for performing the pharmacokinetic studies are detailed in the *PK Sample Collection and Processing Document*. Briefly:

Stribild™ containing elvitegravir (EVG) 150 mg will be administered in the morning after breakfast, *e.g.* 9:00 am, for study days 1-14. The precise times of dosing on days 11, 12 and 13 will be recorded.

On the morning of study day 14, subjects will hold their morning dose and will report to the clinical research center at approximately 8:00 a.m. An indwelling catheter will be placed in one arm of the subject for serial PK sampling. Stribild™ will be administered later that morning immediately after a meal and the precise time of drug administration will be recorded.

Blood samples will be collected prior to Stribild™ dosing, and at 2, 4, and 6 hours following Stribild™ administration. The catheter will then be removed and a lumbar puncture will be performed within 1 hour of the last blood sampling (~ 7 hours after Stribild™ dosing). Subjects will then be discharged from the clinical

research center.

e) Drug dispensing: Six additional weeks of study drug will be dispensed from the research pharmacy.

f) Specimen storage: In addition to specimens collected for the required PK assays, 5 mL of blood serum, 10 mL of blood plasma, 5 mL of whole blood, 5 mL of urine, and 8 mL of CSF will be stored at -80C.

5) Events Between Week 2 and Week 24 Visits

a) The study coordinator will call study subjects at Weeks 8 and 16 (and more often at their discretion) to inquire about signs or symptoms of adverse effects as well as medication adherence. Results will be recorded on a CRF. If any symptoms are reported, the subject will be asked to come to the clinic to be evaluated by the study nurse and investigator (see Section 6.6 of the master protocol).

b) Drug dispensing: Eight weeks of study drug will be dispensed at Weeks 8 and 16.

c) HIV RNA in plasma: Study subjects will be asked to return to their primary care provider to obtain a measurement of HIV RNA in blood plasma per routine clinical care. This is anticipated to occur after approximately 12 weeks of treatment. Study subjects will be asked to bring a copy of the lab report to the research center. Alternatively and with the consent of the study subject, the research nurse will obtain the value from the clinic.

6) Week 24 Assessments

a) A complete medical history and physical examination will be performed:

i) Prior diagnoses including liver disease, renal disease, fracture, osteoporosis, allergies, drug reactions, and most recent menses.
ii) Current symptoms including those of an active systemic illness (e.g., fever) and bleeding or easy bruising.
iii) Prescription and non-prescription medications taken within 14 days prior to entry.
iv) Vital signs, including temperature, blood pressure, and pulse rate, height, weight, and waist circumference.

b) The HIV Dementia Scale will be performed.

c) 75 mL of blood and 15 mL of urine will be collected by standard methods. 15 mL of cerebrospinal fluid (CSF) will be collected by lumbar puncture using aseptic technique and an atraumatic needle. Collection will follow a specific schedule as detailed in detailed in the *PK Sample Collection and Processing Document* and summarized in section 4.2.2 of the master protocol.

d) The following laboratory tests will be performed:

i) Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count, differential white blood cell count, and platelet count.
ii) Blood chemistries: electrolytes, blood urea nitrogen (BUN), creatinine, glucose, phosphorus, and calcium.
iii) Liver function tests: total bilirubin, AST, ALT, alkaline phosphatase, and albumin.
iv) Coagulation: prothrombin time, international normalized ratio, partial thromboplastin time

v) Urinalysis, including urine glucose and protein
vi) Estimated glomerular filtration rate (eGFR)
vii) For women of childbearing potential: Serum or urine pregnancy test.
viii) HIV RNA in blood plasma
ix) HIV RNA in CSF
x) CSF total leukocyte count and differential, CSF erythrocyte count, CSF total protein, CSF albumin, CSF glucose
xi) Lymphocyte subsets in blood (including CD4+ and CD8+ T-cell absolute counts and percentages)

e) Pharmacokinetics: Detailed instructions for performing the pharmacokinetic studies are detailed in the *PK Sample Collection and Processing Document*. Briefly:

Stribild™ containing elvitegravir (EVG) 150 mg will be administered in the morning after breakfast, *e.g.* 9:00 am, for study days 1-14. The precise times of dosing on days 11, 12 and 13 shall be recorded.

On the morning of study day 14, subjects will be instructed to hold their morning dose and will report to the clinical research center at approximately 8:00 a.m. An indwelling catheter will be placed in one arm of the subject for serial PK sampling. Stribild™ will be administered later that morning immediately after a meal and the precise time of drug administration will be recorded.

Blood samples will be collected prior to Stribild™ dosing, and at 2, 4, and 6 hours following Stribild™ administration. The catheter will then be removed and a lumbar puncture will be performed within 1 hour of the last blood sampling (~ 7 hours after Stribild™ dosing). Subjects will then be discharged from the clinical research center.

f) 5 mL of blood serum, 10 mL of blood plasma, 5 mL of whole blood, 5 mL of urine, and 8 mL of CSF will be stored at -70°C. An aliquot of peripheral blood mononuclear cells will be stored at -150C.

g) Subjects will be strongly encouraged to have an appointment with a primary care provider scheduled within a week prior to the final study visit to obtain a prescription and allow for clinical dispensing of continuing antiretroviral therapy.

Premature Discontinuation

Subjects who prematurely discontinue study treatment will undergo an assessment similar to the one detailed for Week 24 with the following exceptions.

a) The visit will not include lumbar puncture.
b) The visit will not include PK assessment.
c) The visit will not include drug dispensing.
d) Following up with a primary care provider will be discussed with the study subject.

Off-Drug Requirements

Additional safety monitoring and reporting of Serious Adverse Experiences (SAEs) continues to be required upon completion or discontinuation of study treatment regardless of whether a protocol follow-up period is scheduled to occur. Adverse experiences occurring during the immediate 8-week period after the last dose of study treatment which meet SAE Reporting Requirements must be reported to the sponsor and the Institutional Review Board (IRB). If the study subject discontinues study treatment, after 8 weeks OFF study treatment,

there are 4 types of events which must be reported to the sponsor and the IRB if the relationship to the study treatment is assessed by the site physician as definitely, possibly, or unable to judge: DEATHS, NEW ONSET CANCERS, CONGENITAL ANOMALIES, PERMANENT DISABILITIES. The study nurse will call the study subject eight weeks after the last study visit to determine if an SAE has occurred.

STATISTICAL CONSIDERATIONS

General Design Issues

The first objective of this study is to evaluate the CSF pharmacokinetics of EVG. This will be accomplished by evaluating HIV-1 infected, treatment-naive subjects. In this single arm, open-label study, within-subject differences in pharmacokinetics parameters at week 2 and 24 will be analyzed, as each subject will serve as his/her own control. For the secondary objective, which is to evaluate the effect of Stribild™ on the permeability of the blood-brain barrier and HIV Dementia Scores, we will consider within-subject differences in a similar manner to analyses for the primary objective.

Pharmacokinetic analysis

Two methods, one model-independent and one model-dependent analyses, will be undertaken in this study. The use of these two methods of analysis will serve as validation. For the model-independent method, total and unbound plasma concentrations and total CSF concentrations will be used to calculate a CSF/plasma ratio, based on individual subject concentration-time profiles. The model-dependent method will fit a population hierarchical mixed-effect model to the data including clinical outcomes. Relevant hypotheses can be tested using the likelihood ratio test. Individual pharmacokinetic parameters can be estimated by empirical Bayesian methods.

Endpoints

Primary endpoints

a) Plasma and CSF total/unbound concentrations of EVG over 2- and 24-week treatment periods

Secondary endpoints

a) Proportion HIV RNA levels below the lower limit of quantitation in CSF and plasma from 2- and 24-week assessments.
b) Changes in CD4+ T-cells at baseline and week 24.
c) Changes in blood-brain-barrier permeability as indicated by CSF-to-serum albumin ratio between baseline and either week 2 or week 24.
d) Changes in HIV Dementia Scale scores between baseline and week 24.

Sample Size and Accrual

Based on estimates from ING116070, assuming within-subject coefficients of variation between 30 and 40%, with a type I error of 0.05 and 90% power, a sample size of 14 would be sufficient to detect a minimum of 50% change in the CSF concentration of EVG using a two-sided paired t-test.

Any subject who prematurely discontinues study participation prior to completing at least one on-treatment PK assessment will be replaced by another subject.

Drug Regimens, Administration and Duration:

Days 1-14: Give Stribild™ (150 mg EVG, po q AM)
Day 14: First PK assessment (PK1)
Days 15-168: Continue Stribild™ (150 mg EVG, po q AM)
Day 168: Second PK assessment (PK2)

Stribild™ (150 mg EVG, po q AM). With the exception of PK days, can be administered as a single dose in the morning, immediately after breakfast.

At PK assessment visits, subjects will be asked to hold all study drugs. Doses will then be administered in the clinical research center under direct observation by study staff.

Drug Formulations

a. Stribild™ (150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine, and 300 mg tenofovir disoproxil fumarate): green, capsule-shaped, film-coated tablets. Store at room temperature (15-30 °C) (59-86 °F)

Drug Supply, Distribution and Pharmacy

Dispensing and monitoring drug-taking behavior

a. Adherence will be self-reported and documented by project staff on appropriate CRFs. Subjects will be asked to bring medication bottles to each visit.

Study supply acquisition

a. The study treatment will be supplied by Gilead Sciences to each study site and will then be dispensed by each site's research pharmacy.

Accountability

a) The study pharmacist will maintain complete records of all study medications received and subsequently dispensed.
b) All unused study medication will be returned to the study pharmacy and discarded following standard operating procedure.

Concomitant Medications

Precautions

a) STRIBILD is NOT recommended for coadministration with: emtricitabine or tenofovir DF (ATRIPLA, COMPLERA, EMTRIVA, TRUVADA, VIREAD); products containing lamivudine (COMBIVIR, EPIVIR, EPIVIR-HBV, EPZICOM, TRIZIVIR) or adefovir dipivoxil (HEPSERA); or ritonavir (NORVIR, KALETRA).

Contraindications

a) Coadministration of STRIBILD is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, *e.g.* alfuzosin, rifampin, ergo derivatives, cisapride, St. John's wort, lovastatin, simvastatin, sildenafil, triazolam, oral midazolam. Specific case-by-case exemptions may be considered by the study investigators.

Management of Selected Toxicities

New Onset or Worsening Renal Impairment

a) Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with the use of STRIBILD™. If renal impairment occurs as indicated by a decrease of estimated creatinine clearance below 50 mL/min, study treatment will be discontinued. Subjects will be followed off treatment with evaluations as per section 4.2 of the master protocol.

Lactic Acidosis/Severe Hepatomegaly with Steatosis

a) Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of tenofovir DF, a component of STRIBILD, in combination with other antiretrovirals. Treatment with STRIBILD should be suspended in any subject who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

Bone Effects, Fat Redistribution, and Immune Reconstitution Syndrome

a) Decreases in bone mineral density, redistribution/accumulation of body fat, and immune reconstitution syndrome have been reported in patients treated with STRIBILD™, which may necessitate further evaluation and treatment.
b) Any Grade 2 or higher symptoms or laboratory abnormalities will result in termination of the subject from the study (see Section 4.2 of the master protocol for post-treatment evaluations).
c) If a subject discontinues the study drugs prior to the pharmacokinetic sampling on day 14, s/he will be replaced in the original sample size.

Criteria for Treatment Discontinuation

a) The subject or legal guardian refuses further treatment and/or follow-up evaluations.
b) The investigator determines that further participation would be detrimental to the subject's health.
c) The subject fails to comply with the study requirements so as to cause harm to self or seriously interfere with the validity of the study results.
d) The subject requires treatment with medications that are disallowed while on this study (Section 6.5.2 of the master protocol).
e) Drug toxicity as defined in Section 6.6 of the master protocol.
f) Pregnancy.

10. HUMAN SUBJECTS

HIV-1 infected subjects will be recruited via IRB-approved posters and flyers and advertisements in local publications. All necessary precautions will be taken to ensure participant confidentiality. Participants will be informed in the informed consent document that their participation will be confidential and their information

will be protected.

Inclusion Criteria

- Adult men or women aged 18-60 years. Able and willing to provide informed consent.
- Presence of HIV-1 infection as documented by a licensed ELISA test kit and confirmed by Western blot or HIV RNA.
- Naive to EVG
- Screening plasma HIV-1 RNA ≥ 5,000c/ml and CD4+ T-cell count ≥ 200cells/mm^3.

Exclusion Criteria

- Presence of primary drug resistance mutations for EVG, tenofovir, or emtricitabine.
- Use of drugs of abuse or alcohol which would interfere with adherence or completion of this study. While on-study, subjects will be instructed not to consume alcohol for 48 hours prior to PK sampling days.
- Pregnancy or breast-feeding. Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to study entry and day of entry.
- History of chronic illnesses such as hypertension, coronary artery disease, arthritis, diabetes, hepatitis B or C virus infection, or gastrointestinal conditions that might interfere with drug absorption.
- Medical conditions that, in the opinion of the investigator, would interfere with the subject ability to participate in the protocol.
- Use of prohibited protocol-specified drugs, prescription, or over-the-counter (see Section 6.5.2 of the master protocol) within 14 days prior to study entry.
- Bleeding abnormality or other contraindication to lumbar puncture.
- Moderate or severe cognitive impairment by history or based on HIV Dementia Scale testing.
- Laboratory parameters documented within 21 days prior to study entry that would increase the risk for adverse events:
    a. Hemoglobin < 12.5 g/dL for men; < 11.5 g/dL for women;
    b. Platelet count < 100,000 platelets/mm^3;
    c. AST (SGOT) or ALT (SGPT) > 1.5 x the upper limit of normal (ULN);
    d. Creatinine clearance < 70 ml/min;
    e. Weight less than 50 kg;
    f. Weight more than 20% over ideal body weight.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

If needed, the AVRC Outreach Department will develop recruitment tools, i.e., flyers/posters, and e-mails to community doctors which will be submitted to the IRB for review and approval prior to posting.

As this is a multicenter study, recruitment of HIV-1 infected subjects will be done through IRB-approved flyers posted in approved areas of the UCSD, University of Rochester (NY), and Erie County Medical Center (Buffalo, NY). All necessary precautions will be taken to ensure participants confidentiality. Participants will be informed in the informed consent document that their participation shall be confidential and their information shall be protected.

12. INFORMED CONSENT

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Institutional Review Board at each participating institution. Written informed consent will be obtained from the subject. Subjects who are unable to provide consent due to neurocognitive impairment or

other causes will not be enrolled. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or legal guardian). If the potential subject is still interested in participating, a clinic visit will be scheduled. The subject will be informed of the time that needs to be allotted for their first visit in which the informed consent will be administered.

The informed consent will describe the purpose of the study, the procedures to be followed, and the risks, and benefits of participation. This information will be explained to the study subject in a face-to-face setting by the individual consent the subject. Subjects will be encouraged to ask questions throughout the consent process and encouraged to discuss their participation with trusted advisors, such as family members, close friends, etc. Subjects will be allotted sufficient time to consider whether or not to participate in the research study. After allowing the potential subject time to read the informed consent the study staff and/or investigator will answer and address any questions or concerns the subject may have. Once all questions and concerns have been addressed and the subject wishes to participate, they will be asked to sign the informed consent.

Also, during the consent process, the Health Insurance Portability and Accountability Act (HIPAA) Authorization will addressed. A copy of the consent and HIPAA Authorization form as well as the Notice of Privacy Practices booklet will be given to the subject. A subject's bill of rights will also be given to the subject.

13. ALTERNATIVES TO STUDY PARTICIPATION

The subject's alternative to participation is to not join the trial or to discontinue the study and continue to receive care for their HIV from their doctor. Subjects can also enroll in other clinical trials that may be ongoing that the subject may be eligible to enroll

14. POTENTIAL RISKS

Risk of Social Harm: Although we make every effort to protect the subject's privacy and confidentiality, it is possible that the subject's involvement in the study could become known to others. If this was to happen, the subject's family and/or communities may have problems accepting the subject's status. This could cause the subject to become labeled as HIV-infected or at high risk for HIV infection causing them to be treated unfairly or to be discriminated against, such as affect their employment and ability to obtain insurance.

Risks of Fasting: Some people find fasting to be difficult. It may make some people feel anxious, irritable, or hungry. Fasting may also cause dizziness, headache, stomach discomfort or fainting.

Risks of Test Results: Getting test results may make some participants feel worried or nervous. Because some tests are experimental, tests results cannot always be given to the subject. Laboratory results (e.g. tests that check the fats in your blood) will be given to the subject, when possible, after the study.

Unknown Risks: There may be unknown risks that are unforeseen, or at this time cannot be predicted. The subject will be told of any significant new risks.

Risks of Lumbar Puncture*:*
Risks include headache, vision problems such as blurred or double vision (rare), hearing problems (rare), pain, lowered blood pressure, allergic reaction to the anesthetic used to numb the skin for the spinal tap, fever, problems with urination or bowel movements, nerve injury (rare), infection (rare), bleeding (rare). This allergic reaction could include itching, hives, swelling, shortness of breath, difficulty breathing, changes in blood pressure and heart rhythm, loss of consciousness, or in a rare case, death.

Occasionally (about 5 in 100 times), participants may experience leaking of cerebrospinal fluid into the tissues of back after the procedure which is known as post-LP headaches. The headache is not dangerous, but can be uncomfortable. You will be given instructions on how to contact the on-call research clinician (7 days a week, 24 hours a day) if you experience this type of headache. Rarely (about 1 in 100 times) the headache pain may be severe and persistent enough to require an epidural blood patch. A blood patch is a procedure in which 1-3 teaspoons of blood is drawn from your arm and injected into your lower back. Your blood clots there to stop the fluid leakage that is causing the headache. The blood patch is performed by an anesthesiologist physician at the hospital.

Reporting Requirements:
If a subject is tested for Hepatitis B and C, there may be a chance they will be diagnosed with one of these infections. The study staff will talk with them about their options and provide them with referrals of doctors and/or facilities that can provide treatment for their hepatitis infection if they are found to have one of these infections.

Efforts will be made to keep their personal information confidential, however, all cases Hepatitis B or C must be reported to the public health department. According to California state law, study staff is required to report their name, contact information and treatment records if their tests show evidence of active Hepatitis B or C.

Risk of Blood Draws
Risks include pain, bruising, fainting, swelling, dizziness or possible infection at the blood withdrawal sites (rare).

Risks of Stribild
Common adverse drug reactions in clinical studies (incidence ≥5%; all grades) nausea (16%), diarrhea (12%), abnormal dreams (9%), headache (7%), fatigue (4%), rash (3%), insomnia (3%), and dizziness (3%). Laboratory abnormalities can also occur including elevations in creatine kinase (7%), elevated amylase (3%), and hematuria (3%). Serious adverse events, including lactic acidosis and severe hepatomegaly, have been reported but are uncommon.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

We will implement the following procedures to safeguard the patients against risk. In order to maintain subject confidentiality all laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number only. All records will be kept in a locked file cabinet. Any information obtained as part of this study will not be released without written permission of the subject, except as necessary for monitoring by the UCSD IRB or for monitoring by the FDA. Please see the data security plan in section 16 for more information.

Experienced phlebotomists will obtain blood specimens.

Risks and reported adverse events of Stribild will be clearly explained to each subject during the informed consent process. At each study visit the study nurses will ask participants to report any symptoms they experience while taking Stribild. During PK visits, a temporary intravenous catheter will be placed in the subject's arm to facilitate multiple blood draws and minimize pain and swelling associated with repeated venipuncture. The intravenous catheter will be removed at the end of the 6-hour blood collection. Participants will be instructed to contact the Clinical Trials Unit in the event of adverse events by telephone 24 hours a day/7 days a week. Following a telephone interview, the Clinical Trials Unit will schedule a visit for an additional assessment as necessary. For serious adverse events participants, will be instructed to immediately discontinue Stribild and to go the closest emergency room. Any Grade 3 or higher symptoms or laboratory abnormalities will result in termination of Stribild. Subjects who experience renal function abnormalities with

estimated creatinine clearance below 50 ml/min will also have the study drug terminated and complete the evaluations listed in Section 4.2. Subjects will also have the study drug terminated in cases of suspected drug-related toxicity, taking prohibited concomitant medications (see section 4.2 of the master protocol), if a female subject is pregnant or breast-feeding, if the subject is judged by the investigators to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results, at the discretion of the investigator, institutional review board (IRB), Food and Drug Administration, pharmaceutical sponsor; or if the subject requests to withdraw from the study. In case of injury or serious adverse events, the investigators will assist the subject in obtaining appropriate medical treatment.

***Lumbar Punctures*:** Experienced research clinicians (either a physician or a nurse) will perform all lumbar punctures. Local back pain will be minimized by injection of an anesthetic, 1% lidocaine into the subcutaneous tissue surrounding the needle puncture site. Oral analgesics and anti-inflammatory medications will be provided when necessary. Following LP, patients will be observed for 10-15 minutes. Over 3,000 LPs have been performed at the HNRC using non-cutting or "pencil point" spinal needles that reduce the risk of post-LP cephalgia. A site clinician will be available by pager 24 hours-per-day to respond to problems, should they occur. If post-LP headache occurs, initial conservative management will include recumbency, hydration, and oral analgesics. When headaches are prolonged, a blood patch, involving an epidural injection of a sample of the subject's own blood, may be performed by consulting anesthesiologists.

UCSD AVRC will serve as the lead/coordinating site for this study. Clinics at the Erie County Medical Center and University of Rochester will be subordinate sites, as outlined in the master protocol team roster. All adverse events, protocol deviations, and other study related reports will be reviewed by the PI as outlined in section 5.0 of the Master Protocol. All data transfers and other study related information will be performed in accordance with the Data Security Plan.

The safety and tolerability of the study medications will also be monitored closely by the protocol team. In addition, a Data Safety Monitoring Board (DSMB) will be convened at two timepoints (after 50% enrollment, after completion of enrollment) to review the project's safety data. At least three experts will comprise the DSMB: a statistician with experience in clinical trials, an expert in HIV clinical trials, and an expert in neurologic HIV disease research. Reports will be prepared by the DSMB and responses will be prepared by the protocol team.

Case report forms (CRF) will be provided for each subject. Subjects must not be identified by name on any study documents. Subjects will be identified by the Patient Identification Number (PID) and Study Identification Number (SID).

All data on the CRF must be legibly recorded in black ink or typed. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to it. The correction must be initialed and dated by the investigator or a designated, qualified individual. Any requested information that is not obtained as specified in the protocol should have an explanation noted on the CRF as to why the required information was not obtained.

Monitoring

The investigators will review the research records for accuracy, completeness, and legibility. The investigators will also regularly inspect regulatory files to ensure that regulatory requirements are being followed.

The investigator will make study documents (e.g., consent forms, drug distribution forms, case report forms)

and pertinent hospital or clinic records readily available for inspection by the Food and Drug Administration (FDA), as required, for confirmation of the study data.

Serious Adverse Experience (SAE) Reporting

Serious Adverse Experiences will be documented on the Serious Adverse Experience (SAE) Reporting Form and submitted to the sponsor and the IRB within 24 hours of the investigator becoming aware of the event.

Safety Monitoring Plan

A safety monitor will be designated to review safety reports.

Data to be reviewed

On a quarterly basis, the monitor will be provided with reports of the following data:

- All hypersensitivity (e.g., rash) and renal events regardless of grade or causality;
- All ALT grades, concurrent ALT + bilirubin, eosinophilia, rash, and other data that could be associated with drug hypersensitivity reactions;
- Study drug discontinuations and reasons for discontinuation
- Serious adverse events (SAEs), grade 3-4 AEs
- Grade 3-4 laboratory abnormalities

Within 24 hours of the event, the IRB, the sponsor, and the independent safety monitor will be provided with reports on all SAEs or grade 4 lab abnormalities

Stopping Guidelines

Stribild™ has previously been used in phase III clinical trials, has an excellent safety profile, and has received marketing approval from the US Food and Drug Administration. The safety in this small, investigator-initiated study is expected to reflect those in larger registration trials. In the event that an unexpected and serious safety signal emerges, such as more than 33% of subjects having SAEs requiring treatment discontinuation, the investigators will present the data to the DSMB and will strongly consider temporarily suspending or prematurely ending the trial.

Biohazard Containment

As the transmission of bloodborne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control.

All infectious specimens will be sent using the ISS-1 SAF-T-PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Please refer to individual carrier guidelines (e.g., FedEx, Airborne) for specific instructions.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

The AVRC research staff has undergone the CITI Biomedical Human Research, and Good Clinical Practice

(GCP) training along with the HIPAA training.

The research staff will protect Patient Protected Health Information (PHI) or other Personal Identification Information (PII) of any individual in general, obtained from as part of the University or Healthcare or other work-related records, for whatever purpose, as private and confidential, and will make every effort to safeguard such information from unauthorized access or dissemination. Steps in place to protect this information are outlined below (Data Security).

Consent Process/Study Visits
For confidentiality purposes the consent process and questionnaire will be conducted in an exam room by one of the study staff members.

Data Security
Any data collected as part of this study that is stored at the AVRC and/or is transferred via the internet will follow our data security process as outlined below.

With the fast-developing technology, dependable and comprehensive data security measures are key components to defy the perceived threats of Internet hackers and accidental disclosure of confidential information. In the following we provide a summary of the key features pertinent to this project.

- An anonymous participant identification number is used for all data collection, recording and submission to the project database.
- Data that contain any participant identifiers (e.g., name or contact information) other than the unique identifier are password protected and accessible only to staff members whose job requires knowledge of such data.
- Laboratories are instructed not to disseminate any participant identifiers in any communications with, or data submissions to, any other AVRC collaborators. Any data transfer over the Internet uses encryption.

Data transfer and all Web-based utilities use secure access (user and server authentication, 128-bit SSL encryption). This type of encryption is the same as is used for Web-based transactions that involve credit cards or Web banking

*Research Laboratory Specimen Identification Policy**:***
All research laboratory specimens leaving the AVRC to an outside laboratory will be de-identified.

Procedures:
The Lab Manager will create a study specific AVRC internal lab requisition. The requisition will be saved and accessible via the AVRC internal computer system's shared drive.

Each research nurse will access and print the study specific requisition(s) via the shared drive.

Each research nurse will then complete the study specific requisition with the subject's name, date-of-birth (DOB), medical record number (MR#), PID, AVRC number and study week .

The requisition will then be delivered by the research nurse to the AVRC lab.

The AVRC laboratory staff will then complete the appropriate form for the corresponding laboratory to which the specimen will be sent, using two coded identifiers, the subject's PID number (in the name field) and AVRC number (in the medical record number field)

The AVRC laboratory staff will prepare and label specimen tubes using the same two coded identifiers, the subject's PID number (in the name field) and AVRC number (in the medical record number's field). No personal health identifiers will be included on the specimen label (e.g., name, initials, DOB, MR#).

Prior to the blood draw, the phlebotomist will verbally verify the subject's name and DOB. The phlebotomist will confirm the coded specimen tube(s) identifiers with the coded form identifiers.

Prior to the lumbar puncture, the LP research clinician will verbally verify the subject's name and DOB. Pre-LP screening will be performed and Post-LP instructions will be reviewed.

Coded specimens are transported to the appropriate lab either by AVRC staff or shipped via FedEx , under IATA regulations.

All study specific completed AVRC internal lab requisitions will be retained in a locked and secured area for a period of six months and thereafter shredded.

17. POTENTIAL BENEFITS

A direct benefit to subjects participating in the study is unlikely. They may also receive no indirect benefit from participating in this study. However, information learned from this study may help others who are infected with HIV.

18. RISK/BENEFIT RATIO

The opinion of the investigators is that the benefits outweigh the risks for the proposed project and that the privacy risks are reasonable relative to the anticipated benefits of the research.

19. EXPENSE TO PARTICIPANT

There will be no costs to the subject associated with participation in the study.

20. COMPENSATION FOR PARTICIPATION

Subjects will be reimbursed $25 for phlebotomy (no more than once per visit), $75 for lumbar puncture, and $25 for completion of forms. Subjects who completes all assessments will be compensated a total of $425. By visit, subjects who complete all assessments will receive $50 at screening, $125 at entry, and $125 at each PK visit at weeks 2 and 24.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Drs. Scott Letendre, Richard Haubrich, Constance Benson, Susan Little, Sheldon Morris, Ronald Ellis, and Davey Smith currently have privileges at UCSD Medical Center in the Department of Medicine; Division of Infectious Disease and are licensed and certified by the State of California to perform all the medical procedures discussed in the protocol at UCSD. In addition to having privileges with UCSD Medical Center, Drs. Susan Little, and Davey Smith have privileges at the VA Medical Center.

The nurses at the AVRC will be involved with the consent process and study visits. The study nurses are all licensed by the State of California. Prior to the study opening at the AVRC, one of the study nurses will be assigned to the study and provide any in-service necessary to the other AVRC nurses who will be here back-up when the main study nurse is absent due to illness or vacations. The HNRC nurse and nurse practitioner are credentialed to perform lumbar punctures and perform well over 500 a year.

Leticia Muttera, Pharm.D. is the investigational pharmacists for this study and responsible for accounting and dispensing the study drug. The pharmacist is licensed by the State of California.

Helene Le, CPhT and Joseph Lencioni, MABMH, will serve as the regulatory contacts for this study. Both Helene and Joseph will have access to the HRPP submission webpage.

The PI, co-PIs, pharmacist, regulatory staff, and nurses at the AVRC have completed the required UCSD research training to include CITI Human Subjects and GCP training along with the UCSD IRB HIPAA tutorial.

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23. FUNDING SUPPORT FOR THIS STUDY

In 2013, Gilead Sciences approved a donation of $208,731 USD in support of this study. The financial contact for this study at UCSD AVRC is Fernando Mares. He can be reached at 619-543-8178.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not Applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

This drug used in this study, Stribild, was approved by the US FDA in August of 2012.

26. IMPACT ON STAFF

The AntiViral Research Center (AVRC) is an HIV/AIDS research facility. The nurses and other study

personnel assigned to this study are funded in part by the Gilead donation for this study.

27. CONFLICT OF INTEREST

No conflict of interest exist for this study.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not Applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

None.

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable.

In order for a subject to be eligible for this study they must not be cognitively impaired and must be able to communicate effectively with the study staff; therefore, the subjects enrolling/participating in this study will have the ability to:

1. Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, as well as the risks and benefits of participating versus not participating;
2. Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for their own situation and condition;
3. Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternative, and
4. The ability to express a choice about whether or not to participate.

If for any reason, the study staff finds that the subject does not understand, appreciate, have reasoning ability and/or cannot express his/her choice to participant in the study, the subject will not be enrolled and provided with the options that may be available to them.

Version date: May 11, 2011