AN INTERNATIONAL, MULTICENTER, PROSPECTIVE OBSERVATIONAL STUDY OF THE SAFETY OF MARAVIROC USED WITH OPTIMIZED BACKGROUND THERAPY IN TREATMENT-EXPERIENCED HIV-1 INFECTED PATIENTS

Compound:	UK-427,857
Compound Name:	Maraviroc
Protocol Number:	A4001067
Phase:	4
European Clinical Trial Database (EudraCT) Number:	2007-006148-24

[redacted]

Document History

Document	Version Date	Summary of Changes
Protocol Amendment #3	29 November 2010	This amendment outlines the change from enrolling 2000 maraviroc-exposed and 1000 maraviroc-unexposed patients to enrolling 1500 patients in each arm. AND To amend the procedures for ascertaining survival status of patients "switching to non-participating physicians" (Protocol Section 6.5).
Protocol Amendment #2	12 August 2010	See Appendix 5
Protocol Amendment #1	23 March 2009	See Appendix 4
Original protocol	16 January 2008	N/A

EPIDEMIOLOGY STUDY PROTOCOL
MARAVIROC

PROTOCOL NUMBER: A4001067

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1. INTRODUCTION

1.1. Indication

Maraviroc, in combination with other antiretroviral medicinal products, is indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable.

1.2. Background and Rationale

1.2.1. HIV Infection: Epidemiology and Treatment

AIDS has killed more than 25 million people since it was first recognized in 1981, making it one of the most destructive epidemics in recorded history. As of December 2006, WHO/UNAIDS estimated that there were 39.5 million (34.1–47.1 million) people living with HIV/AIDS. 4.3 million (3.6–6.6 million) people were newly infected with the virus in 2005.[1]

At present the only means of slowing HIV disease progression is the use of highly active antiretroviral therapy (HAART), with the preferred initial regimen containing a three or four-drug regimens consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI/r) plus two nucleoside reverse transcriptase inhibitors (NRTIs). Subsequent regimens frequently require more drugs, and become increasingly complex due to difficulty with adherence, tolerability due to adverse events and drug interactions with other required medications and the development of resistance to drugs in the failed regimen(s) or acquired resistant virus and class cross-resistance.[2-4] In the developed world, where antiretroviral drugs have been available since 1987, the unmet medical need is for new antiretroviral medications with unique resistance profiles, improved short- and long-term safety profiles, and convenient dosing to treat patients who have not achieved treatment success with multiple treatment regimens due to drug resistance, side effects, incomplete adherence, or some combination of these factors. Drugs that target novel steps of the HIV-1 life cycle are needed, as they do not share cross-resistance with currently available antiretroviral therapy.

1.2.2. HIV Tropism

An essential, early step in the replication cycle of HIV-1 is attachment to the CD4 receptor and to one of the chemokine coreceptors, CCR5 or CXCR4. Generally, sexually transmitted HIV uses CCR5 exclusively during primary infection. However, HIV that can use CXCR4 to enter CD4+ T lymphocyte cells can be detected in about 15% of treatment naïve patients and up to 50% of patients with late HIV disease or antiretroviral treatment experience in the developed world where Clade B virus predominates. In most cases the CXCR4-using HIV (X4 HIV) is present with CCR5-using virus (R5 HIV) as a single virus that can use either receptor (dual tropic) or a mixture of R5 and X4 HIV (mixed tropic). Infections with HIV-1 that exclusively use CXCR4 to enter CD4+ T lymphocyte cells are rare, and represent approximately 1% of treatment naïve and approximately 2-4% of treatment-experienced patients.[5, 6]

1.2.3. CCR5 Antagonists

Maraviroc is a member of a new class of antiretroviral compounds known as small molecule CCR5 antagonists that block R5 HIV-1 entry into CD4+ T lymphocyte cells. This group of molecules binds non-competitively to CCR5, causing a conformational change in the extracellular loops of CCR5 that renders it unrecognizable to wild type R5 HIV-1.

1.2.4. Safety Concerns with CCR5 Antagonists

1.2.4.1. Hepatotoxicity

The development program for aplaviroc (GSK 873140), another CCR5 antagonist, was terminated due to severe drug-induced hepatotoxicity. For a third drug in this class, vicriviroc, no severe hepatic-related adverse events have been reported in the ongoing clinical trials to date.

The clinical data to date do not indicate that maraviroc causes abnormalities in hepatic function relative to placebo. No clinically relevant difference in severity or nature of hepatic dysfunction was observed among the two active and the placebo control treatment arms in the Phase 2b/3 program of maraviroc. There was a slight difference in rates of hepatic adverse events which was driven by events related to laboratory abnormalities but this difference was not evident when the overall laboratory data were analysed. Based on the available data, including those observed with maraviroc in short and long-term studies, it appears that the hepatotoxicity observed with aplaviroc is most likely drug-specific and not a class effect.

1.2.4.2. Infections and malignancies

When a CCR5 antagonist binds to the CCR5 receptor on the surface of CD4+ T lymphocyte, it blocks the natural function of the CCR5 molecule, which is primarily associated with retention of mononuclear cells in areas of inflammation and injury. Individuals who are born with two copies of a mutant CCR5 gene (CCR5Δ32) (ie, homozygous for CCR5Δ32) and do not express CCR5 on the surface of their CD4+ T lymphocyte cells represent 1% of Caucasians of European descent. They appear to be essentially resistant to HIV-1 infection and have apparently normal immune function. Individuals with one normal CCR5 gene and one copy of the CCR5Δ32 gene (ie, heterozygous for CCR5Δ32), who comprise 10-15% of Caucasians of European descent, have a reduced concentration of CCR5 molecules on the surface of their CD4+ T lymphocyte cells and have essentially normal immune function. Relative to HIV-infected patients with two copies of the normal gene, the CCR5Δ32 heterozygote individuals have delayed CD4+ T lymphocyte decline, delayed progression to AIDS, and longer survival once infected.[7-10] However, whether blocking the CCR5 receptors in adults, who have had functioning CCR5 molecules throughout life, will have the same biologic effects as those observed in homozygotes or heterozygotes for CCR5Δ32 is unclear. It is theoretically possible that blocking CCR5 molecules after a critical period in immune development could result in increased or decreased immune surveillance, leading to increased frequency or severity of infections or malignancies.

Infection with West Nile Virus (WNV) is of particular scientific and clinical interest. Elderly and immunocompromised individuals have increased susceptibility to WNV, but genetic risk factors and immunologic control mechanisms have not been fully delineated. The monocyte and T lymphocyte chemokine receptor CCR5 have recently been identified as a key factor in viral clearance and survival in a mouse model of WNV encephalitis, in which the mechanism involved trafficking of leukocytes into the infected brain. Consistent with this, WNV induces expression of CCR5 ligands in WNV-infected mouse brain. To test whether this receptor is also protective in man, Glass and colleagues determined the frequency of *CCR5Δ32*, in two independent cohorts of patients, one from Arizona and the other from Colorado, who had laboratory-confirmed, symptomatic WNV infection.[11] The distribution of *CCR5Δ32* in a control population of healthy United States Caucasian random blood donors was in Hardy-Weinberg equilibrium and *CCR5Δ32* homozygotes represented 1.0% of the total group (n = 1,318). In contrast, *CCR5Δ32* homozygotes represented 4.2% of Caucasians in the Arizona cohort (odds ratios [OR] = 4.4 [95% confidence interval [CI], 1.6–11.8], P =0.0013) and 8.3% of Caucasians in the Colorado cohort (OR = 9.1 [95% CI, 3.4–24.8], P <0.0001). *CCR5Δ32* homozygosity was significantly associated with fatal outcome in the Arizona cohort (OR = 13.2 [95% CI, 1.9–89.9], P = 0.03). These authors concluded that CCR5 mediates resistance to symptomatic WNV infection. These findings may have important implications for the effect of CCR5-blocking agents on the incidence and severity of WNV infection.

On March 3, 2006 Schering-Plough announced that five cases of malignancy (four cases of lymphoma and one case of gastric adenocarcinoma) had been reported in 118 heavily pretreated patients participating in a Phase 2b clinical study of vicriviroc, AIDS Clinical Trial Group (ACTG) trial, A5211. The National Institute of Allergy and Infectious Disease (NIAID) Therapeutic DSMB overseeing the trial concluded that a causal association between vicriviroc and the lymphoma cases could not be established at that time. This experience is in contrast to findings of a 1999 article that reported a reduced risk of AIDS-associated lymphoma in HIV-infected CCR5Δ32 gene heterozygotes when compared to individuals without the polymorphism.[12] Currently, the data from clinical studies in treatment-experienced HIV-1 infected patients do not indicate a clinically meaningful alteration in the frequency or severity of infections or malignancy related to the use of maraviroc. In the phase 2b/3 trials of maraviroc (MOTIVATE 1, MOTIVATE 2) at 48 weeks no difference in rates of lymphoma was demonstrated between maraviroc and placebo treatment arms, despite the much longer exposure in the maraviroc treated patients.

1.2.4.3. Myocardial Infarction

Metabolic abnormalities associated with HIV-1 infection, including glucose homeostasis disturbances and dyslipidemia, are increasingly prevalent, and there is concern about the possibility of an association with accelerated cardiovascular disease. In addition, recent results from the D:A:D Study, an international collaboration of 11 cohorts following 23,468 HIV-infected patients prospectively in 21 countries situated in Europe, the USA, and Australia, indicated that the incidence of myocardial infarction (MI) increased by 26% per year of exposure to combination antiretroviral treatment, consistent with the hypothesis that atherosclerosis is a side-effect of combination antiretroviral treatment, generally attributed to

PIs dosed simultaneously with NRTIs.[13] The data from the Phase 2b/3 studies of maraviroc indicated a rate of MI and ischemic heart disease in keeping with that expected from the studied population. However there was an imbalance, with all the events occurring on maraviroc, most likely due to the design of the study and the limited follow up time in the placebo arm. Due to the relatively small data it is currently unknown whether the addition of maraviroc will modify the rate of MI occurrence in HIV-1 infected patients receiving HAART.

1.2.4.4. Rhabdomyolysis

Rhabdomyolysis is a condition associated with the injury of skeletal muscle. Rhabdomyolysis was initially described as a complication of traumatic injury particularly crush injuries however infections and most notably certain classes of drugs such as statins have been associated with this disorder. Myopathy has also been associated with nucleoside reverse transcriptase inhibitors (NRTIs), most notably zidovudine, which are commonly used in the treatment of patients with HIV. In the phase 2b/3 trials of maraviroc (MOTIVATE 1, MOTIVATE 2) subjects receiving maraviroc had a higher median change in creatine kinase compared to placebo. There was also a higher incidence of creatine kinase abnormalities (>2x ULN) in subjects receiving maraviroc: 30% and 29% on maraviroc QD and BID respectively, compared to 20% on placebo. Three patients in the MOTIVATE 1 and 2 studies reported adverse events of rhabdomyolysis or myositis and discontinued study drug. Two further patients receiving maraviroc QD in the MOTIVATE 2 study discontinued due to myalgia.

1.2.5. Study Rationale

There is limited information about the safety of long-term treatment with maraviroc. No signal for increased risk of hepatotoxicity, malignancy or infection has been observed in the clinical development program for maraviroc through 48 weeks of therapy. However, the concern that hepatotoxicity is a CCR5 antagonist class effect and the theoretical risk of altered immune function leading to altered rates or severity of malignancy or infections, including opportunistic infections (OI) remain to be fully addressed. Given the imbalance in the incidence of myocardial ischemic events in the ongoing clinical trials of maraviroc, data on long-term follow-up for MI and myocardial ischemia incidence in patients receiving maraviroc along with HAART would more fully characterize this potential safety risk. As most of these patients receive lipid-lowering agents that may be associated with a heightened risk of rhabdomyoloysis, it is of interest to examine the incidence of this event. All-cause mortality will also provide information regarding any possible long term implications of treatment with maraviroc.

The objective of this international, multicenter, prospective observational comparative study is to monitor the safety of long term use of maraviroc in a larger and more diverse patient population than that in which the phase 2b/3 clinical trials were conducted. By providing additional data regarding long-term use of maraviroc, this study will help further characterize the safety profile of the drug. This is a post-approval safety study (PASS) and is a

commitment to the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

1. To estimate the incidence rates of: (a) Centers for Disease Control and Prevention category C AIDS-defining opportunistic infections (OI), (b) viral encephalitis, (c) liver failure, and (d) rhabdomyolysis in treatment-experienced HIV-1 infected patients receiving maraviroc during time of use and for up to six months following discontinuation of maraviroc treatment, up to a total of five years since entry into the study.

2. To estimate the incidence rates of (a) myocardial infarction (MI) or ischemia, (b) all malignancies, (c) all cause mortality, and (d) liver related deaths in treatment-experienced HIV-1 infected patients receiving maraviroc for up to five years after entry into the study regardless of the actual duration of maraviroc use.

3. To compare the rates of the study endpoints in patients receiving maraviroc to those observed in an internal comparator group of treatment-experienced, HIV-1 infected patients not receiving maraviroc.

4. To compare the observed rates of the study endpoints in patients receiving maraviroc in this study to those observed in HIV-1 infected patients not receiving maraviroc in an appropriate external comparator cohort (eg, EuroSIDA).

2.2. Endpoints

The study endpoints are:

1. Centers for Disease Control and Prevention Category C AIDS-defining opportunistic infections (Appendix 1);

2. Viral encephalitis;

3. All malignancies;

4. Liver failure;

5. Myocardial infarction or ischemia;

6. Rhabdomyolysis;

7. Death from liver-related cause;

8. Death from any cause.

The operational diagnostic criteria of each endpoint are described in the endpoint adjudication manual for this study.

3. STUDY DESIGN

This is an international, multicenter, open-label, comparative, prospective observational epidemiologic study.

4. SUBJECT SELECTION

4.1. Study Population

The study will enroll 1500 HIV-1 infected, treatment-experienced adult patients who have been prescribed maraviroc along with an optimized background antiretroviral therapy (OBT) regimen in usual clinical practice following the approved local label of maraviroc.

The internal comparator group will consist of 1500 HIV-1 infected, treatment-experienced adult patients receiving OBT who received an HIV-1 tropism assay as a screening test for eligibility to receive maraviroc in usual clinical practice but were not prescribed maraviroc. This group may include patients infected with dual/mixed tropic or CXCR4 tropic HIV-1 as well as patients infected with CCR5 tropic HIV-1.

The subject enrollment scheme is presented in Appendix 2.

The study will be conducted at approximately 300 sites in multiple countries. Participating countries were chosen on the basis of extensive feasibility assessments and include: Belgium, Brazil, Canada, France, Germany, Greece, Italy, Portugal, Spain, United Kingdom, and United States. If required, additional countries may be added and some countries in this initially proposed list may be dropped. Countries will participate only after maraviroc is approved by Health Authorities in that country and is commercially available. Enrollment will be competitive and recruitment of subjects will terminate after the global target sample size is achieved. The expected numbers of subjects in the participating countries are provided in Table 1. Initial enrollment goals set for each country will be redistributed if necessary. Barring unforeseen circumstances (eg, significant delays in marketing authorization approval in countries, marked delays in regulatory approvals of the study protocol in countries, etc.), enrollment is expected to commence in 1Q2008 and is anticipated to continue for approximately 30 months. The enrollment status will be continuously monitored by the Sponsor and the external Scientific Steering Committee overseeing the study. If required, the enrollment period will be extended to enroll the necessary sample size.

Table 1. Enrollment targets by country

Countries	Expected number of study subjects	Projected launch date for commercial Maraviroc
Belgium	80	March 2008
France	200	April 2008
Germany	223	October 2007
Greece	40	March 2008
Italy	140	March 2008
Portugal	35	April 2008
Spain	250	May 2008
UK	161	November 2007
USA	1700	August 2007
Canada	80	October 2007
Brazil	91	May 2008

4.2. Inclusion Criteria

Subjects (male or female) must meet the following inclusion criteria to be eligible for enrollment into the study:

1. The subject is antiretroviral treatment experienced and is currently being considered for treatment with maraviroc;

2. Receive an appropriate HIV-1 tropism assay as a screening for eligibility to receive maraviroc within 14 weeks prior to enrollment (The 14-week window does not apply to patients who started maraviroc as participants of A4001050 or A4001063);

3. Provide signed and dated informed consent to enrolling physician indicating that the patient (or, legally acceptable representative) has been informed of all pertinent aspects of the study;

4. Of 18 years of age or older (or, minimum age as determined by local regulatory authorities or as dictated by local law) at the time of screening;

5. Provide signed and dated informed consent to allow the enrolling physician access to medical, hospital and vital statistics records as appropriate;

6. Provide information on at least one alternate contact person (preferably the legal next of kin) who can be contacted regarding the patient's whereabouts and survival status, should the patient be lost-to-follow-up over the course of the study;

7. Acknowledge that in case of his or her death, the next of kin may be approached for a medical records release form if needed;

8. Provide Social Security Number (applicable to U.S. participants) or other national identification number or national health insurance number, as available and allowed by local law. **This information will only be used to search appropriate national or regional cancer and vital status registries for incidences of malignancies and deaths.**

4.3. Exclusion Criteria

1. Pregnant or lactating;
2. Unable to provide informed consent;
3. Recipient of a small molecule CCR5 inhibitor other than maraviroc;
4. Previously enrolled in this study.
5. Already exposed to maraviroc (Except patients who started maraviroc as participants of either study A4001050 or study A4001063 and are still continuing the drug). These patients may constitute up to 15% of the target sample size in the maraviroc-exposed arm).

5. STUDY TREATMENTS

5.1. Drug administration and dosing

Patients receiving maraviroc:

All patients will receive maraviroc per the approved local label in combination with an optimized background antiretroviral therapy (OBT) regimen, composed of appropriate antiretroviral drugs prescribed by the enrolling physician according to the local standard of care of HIV infected patients. **Enrolling physicians should refer to the local package insert for maraviroc administration information.** There are no study-related restrictions on dose or OBT regimen prescribed by the physician.

Patients will obtain commercially available maraviroc as they would in routine clinical practice.

Patients not receiving maraviroc:

Subjects in the comparator group will receive appropriate antiretroviral drugs prescribed by the enrolling physician, according to the local standard of care of HIV infected patients. There are no study-related restrictions on dose or regimen prescribed by the physician. However, patients receiving any other CCR5 inhibitor are ineligible to participate.

Patients will obtain commercially available drugs as they would in routine clinical practice.

5.2. Concomitant medication(s)

All concomitant therapy as prescribed by the treating physicians is allowed as per the approved local label of maraviroc, with the exception of other CCR5 inhibitors.

5.3. HIV Tropism Assay

The Sponsor will cover the cost of tropism assay performed by the Monogram Biosciences, Inc., USA as a screening test for eligibility to receive maraviroc. The details of the sample collection, processing and shipping information will be made available to participating study sites as a separate document.

6. STUDY PROCEDURES

6.1. Study Period

All subjects will be followed for up to 5 years after enrollment in the study. The estimated length of time needed to complete the entire study, from enrollment of the first subject to completion of five years of observation of the last subject, is approximately 7.5 years, assuming enrollment will be complete in 2.5 years.

6.2. Follow-up Visits

There will be no protocol-mandated patient visits or laboratory tests in this observational, non-interventional study. Data on subject's vital status, continued use of maraviroc, and study endpoints will be obtained through follow-up with the treating physician according to the local HIV/AIDS treatment guidelines and routine medical practice. Medical records and other documentation, where applicable, will be obtained to adjudicate study endpoints according to the endpoint adjudication manual.

6.3. Follow-up of patients discontinuing maraviroc

If a patient discontinues maraviroc, the enrolling physician will record information on the date of and primary reason for discontinuation. Discontinuation of maraviroc due to adverse events should be distinguished from discontinuation due to insufficient response, and any serious adverse events (SAE) should be reported immediately to Pfizer, as the Sponsor's designated representative. A change in any of the components of OBT will not be considered as treatment discontinuation if the patient continues to receive maraviroc, but these changes in regimen will be recorded on patient questionnaires by enrolling physicians. Follow-up will continue after a patient discontinues maraviroc up to a total period of 5 years since enrollment, and safety data will be collected and reported for a total of 5 years following enrollment as well.

6.4. Patients lost to follow-up

A patient will be categorized as lost to follow-up if there has not been any contact with the patient for six months since last contact and attempts to reach the patient and/or his/her secondary contact person(s) fail.

In the situation where neither the patient nor the secondary contact person(s) can be reached, attempts will be made to ascertain the vital status of the patient by searching the appropriate national or regional vital status registry or other relevant databases, where available and allowable by local law. Depending on the local law, this search will be conducted by a designated CRO, or a professional search firm, or the enrolling physician or his/her designee at the study site. Medical records of these patients cannot be obtained or reviewed for adjudication of any death event. Therefore, the supplemental data on the un-adjudicated mortality events will not be included in the primary analyses of the study. It should be noted that there is usually a lag between calendar time of death and the time that data are available from vital status registries, due to the additional time necessary for government agencies to collate information from regional death registries and to check these data for accuracy. In the U.S. National Death Index, the delay is approximately 18 months.

6.5. Follow-up of patients switched to non-participating physicians

If for any reason (eg, relocation, insurance change) a patient switches to a physician who is not participating in the study, the patient will be discontinued from the study. The enrolling physician will complete a follow up questionnaire with the last available clinical data and the subject summary module of the questionnaire. If the patient does not withdraw consent to participate in the study, an attempt will be made to ascertain the vital status of the patient as mentioned in Section 6.4 for patients lost to follow up.

6.6. Termination of follow-up

Follow-up will terminate at the earliest of any of the following events:

- Withdrawal of consent by the patient;
- Death of the patient;
- Completion of five years since entry into the study;
- Switching to another CCR5 inhibitor medication (Applicable for maraviroc recipients);
- If a patient in the maraviroc-unexposed comparator group commences treatment with a CCR5 inhibitor other than maraviroc, study follow-up will terminate. If a patient in the maraviroc-unexposed comparator group commences treatment with maraviroc, the follow-up will continue as usual. However, the follow-up experience after commencement of maraviroc will be attributed to the maraviroc-exposed group;

- Discontinuation of the study by the Sponsor.

This study may be terminated or suspended by the Sponsor at any time. If the study is terminated or suspended, the Sponsor will promptly inform the enrolling physicians/institutions and the regulatory authorities. The IRB/IEC will be promptly informed and provided the reason(s) for the termination or suspension by the enrolling physician/institution, as specified by applicable regulatory requirement(s).

6.7. Subject Withdrawal

Subjects may withdraw their consent from study participation at any time at their own request, or they may be withdrawn at any time at the discretion of the enrolling physician or the Sponsor for behavioral or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made by the enrolling physician or site staff to contact the subject and his/her alternate contacts, as provided by the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The enrolling physician should inquire about the reason for withdrawal, request the subjects to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved serious adverse events and study endpoints.

The enrolling physician should determine the primary reason for withdrawal of consent, as well as any contributory factors, and record this information on the follow-up questionnaire. Withdrawal must be reported immediately if it is due to a serious adverse event.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.8. Transfer of Study Data

The study sites will report data without any personal identifiers other than the study identification number using an electronic data capture system.

Copies of all external documents (eg, hospital discharge certificates, death certificates, EKG tracings etc.) collected by the enrolling physician at the study sites will be de-identified, labeled with the patient's study identification number, and forwarded to a CRO designated by Sponsor. After ensuring that no personal identifiers are present, the CRO will forward the copies to the endpoint adjudication committee for validation of study end points.

7. BASELINE AND FOLLOW-UP DATA COLLECTION

7.1. Collection of Data

Several questionnaire forms will be used to collect information in this study. The Informed Consent and Alternate Contact Information forms will be completed by the subject at the time of screening. All other forms will be completed by the enrolling physician (or his/her

qualified representative), including the screening, enrollment and follow-up questionnaires, final disposition forms, adverse event monitoring forms, and endpoint notification forms.

7.2. Baseline Data

Once a patient has signed informed consent, baseline data will be collected at Screening and Enrollment visits. The enrolling physician will collect data from the patient interview and from relevant medical and laboratory records and will electronically complete baseline questionnaire pages without any personal identifiers. Data elements on the questionnaire pages will include but are not limited to:

- Study ID number;
- Date of birth;
- Sex;
- Race/ethnicity;
- Risk behavior(s) for HIV exposure;
- Duration of HIV infection;
- Diagnosis date and type of any current or past CDC category C AIDS-defining event;
- General medical history and relevant family history with specific emphasis on:
    - Malignancies: history of malignancies specifying the type and site;
    - Opportunistic infections: history of any opportunistic infection;
    - Past history of myocardial infarction (MI), ischemia and cardiovascular risk factors in general, including smoking history, family history and any significant EKG (ECG) finding if available;
    - History of any acute or chronic liver disease including viral hepatitis, alcoholic liver disease and alcohol use.
- Height, weight, systolic and diastolic blood pressure;
- Co-medications: including lipid-lowering agents, anti-hypertensive medication, anti-platelet medications, treatment for HCV/HBV, agents for OI treatment and prophylaxis and any potentially hepatotoxic medication;
- Components of OBT, including start dates and dose of each;

- Prior antiretroviral medication history with particular focus on the total duration of all antiretroviral therapy and number of failed regimens;

- Laboratory data: total, LDL and HDL-Cholesterol; serum triglycerides, liver enzymes: ALT, AST, bilirubin; Hepatitis B & C serology; CD4+ T lymphocyte cell count; nadir CD4+ T lymphocyte cell count; levels of HIV-1 RNA, HCV RNA from the most recent tests done per routine clinical care will be collected when available. During the screening and enrollment visits, historical data will be accepted for laboratory records up to 120 days prior to the visit date. (Please note: historical data on tests for viral hepatitis will be accepted up to 1 year prior to the visit date.) **There are no study mandated laboratory tests.**

- Result from the screening HIV-1 tropism assay;

- Starting date and dose of maraviroc;

- For the maraviroc non-user comparator group, the anchor drug in the OBT regimen will be identified according to the following hierarchy:

    - Raltegravir or other integrase inhibitor > Enfuvirtide or other fusion inhibitor >Etravirine or other 2nd generation NNRTI > Darunavir or other protease inhibitor.

- For subjects who participated in other studies involving maraviroc (eg, the Maraviroc Expanded Access Program, A4001050 or study A4001063), the name and/or protocol number of the study and the subject ID in that study will be collected.

In addition to these clinical data, the following information will be recorded on a separate form and stored separately from the questionnaire data.

- Contact information of primary care physician (if appropriate);

- Contact information of next of kin or other contacts (eg, primary care physician) who may be contacted if the patient is lost to follow-up;

- Social security number, national identifying number or national health insurance number as appropriate and allowed by local law to search national and state cancer and vital status registries to ascertain incidences of malignancies and death.

7.3. Follow-up Data

Follow-up information on the study outcomes, adverse events, laboratory tests, medication use, other relevant clinical information and the patient's vital status will be abstracted on follow-up questionnaires by the enrolling physician or a designated member of the clinical team from medical records and charts as well as from the patient, where applicable.

The complete follow-up questionnaires will be electronically submitted after a patient returns for follow-up according to local HIV treatment guidelines and routine medical practice (usually 3-4 monthly), and at least once every 6 months. At these visits, the physician will treat the patient per standard clinical practice and will conduct laboratory investigations as appropriate. **There will be no study-mandated tests or interventions.** Data on the patient's medications, recent laboratory test results and the study endpoints since the last visit/report will be recorded in the follow-up questionnaires based on the source medical records.

If a patient does not return for follow-up within six months from last contact, the enrolling physician will make at least three attempts to contact the patient to return for routine follow-up. If these initial attempts to directly contact the patient fail, the alternate contact person(s) recorded on file will be contacted to ascertain the whereabouts and survival status of the patient.

7.4. Endpoint Evaluation

At each visit after enrollment, the enrolling physician/investigator or designee will report all study endpoints for the subjects using an endpoint notification form. These endpoints may be identified by the enrolling physician at a follow-up visit or reported to the enrolling physician by other treating physicians or health care facilities. For subjects lost to follow-up, survival status may be identified through standard measures used in cohort studies, such as alternate contacts and tracking mechanisms (eg, national or regional death certificate data) however, endpoints will not be collected for adjudication.

When any of the study endpoints are identified or diagnosed, the enrolling physician will report the occurrence using an endpoint notification form and obtain the relevant medical records necessary to adjudicate the endpoint. The enrolling physician may request hospital discharge forms and medical records or their summary as needed. Where necessary and applicable, subjects will be contacted by the physician to assist in obtaining medical or hospital records.

These documents will be forwarded by the enrolling physician to the designated CRO for review by the Endpoint Committee (EC) in a de-identified format with the subject's study number added. The detailed process and timeframe for this endpoint data collection is described in the study Endpoint Manual.

De-identified copies of records, with translations into English where necessary, will be collated by the CRO for EC review. The EC will adjudicate the endpoint based on a review of the copies of relevant medical and hospital records. Two committee members will review each set of records individually and classify them according to the diagnostic algorithms described in the Endpoint Manual for the study. If the two adjudicators differ in their opinion, a third adjudicator will be assigned. The operational case definitions of the study endpoints as well as the operational aspects of the adjudication process are described in the study Endpoint Manual.

Study endpoints that are closely temporally related to drug exposures ie, CDC category C opportunistic infections, viral encephalitis, rhabdomyolysis and liver failure will cease to be adjudicated as study endpoints after six months following discontinuation of maraviroc. For patients in the maraviroc unexposed comparator group, adjudication of these events will cease after six months following discontinuation of the anchor drug in their OBT as identified at baseline (Section 7.2). If these events are diagnosed after this cut-off period, they will be considered as any other adverse event and reported per the Adverse Event Reporting guidelines described in Section 8, which requires the collection and reporting of all serious adverse events (SAE) and all adverse reactions. Occurrence of myocardial infarction or ischemia, malignancies, and death (all-cause and liver-related) will be reported and adjudicated as study endpoints for up to five years following enrollment.

The follow-up duration for malignancies may be extended beyond five years if, based on emerging safety data, the Scientific Steering Committee (SSC) overseeing the study recommends a longer period of observation. Due to the potentially prolonged time required for a malignancy to become clinically apparent, a search of national and state cancer and death registries will be performed to look for all episodes of malignancy within 10 years of study entry for all subjects in countries where such registries are available, are accessible for research purposes and where such search is allowed by local law. Active study participation of subjects will be for only 5 years, but informed consent will be obtained at enrollment allowing for passive subject follow-up beyond the 5 years of active participation through this additional search of cancer and vital status registries. This search will be conducted by a designated CRO or professional search firm using appropriate national identifiers collected at enrollment. The investigators will not have to do the search.

8. ADVERSE EVENT REPORTING

ViiV is the Sponsor of the study. Pfizer will conduct the study on behalf of ViiV. All adverse event reporting under this section will be to Pfizer, as the Sponsor's designated representative, using forms provided by Pfizer.

8.1. ADVERSE EVENTS

All observed or volunteered serious adverse events (SAE) regardless of treatment group or suspected causal relationship to maraviroc and all non-serious adverse events suspected by the investigator to be related to maraviroc (ie, adverse reactions) will be recorded on the adverse event page(s) of the case report form (CRF) as follows.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see section "Serious Adverse Events") requiring immediate notification to Pfizer as the Sponsor's designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to maraviroc, follow-up by the investigator is required until

the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer on behalf of the Sponsor concurs with that assessment.

8.2. Reporting Period

For serious adverse events, the reporting period to Pfizer, as the Sponsor's designated representative begins from the time that the subject provides informed consent or signed data privacy statement, which is obtained prior to the subject's participation in the study to 60 months from enrollment in the study regardless of the actual duration of the use of the study drug.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Extravasation;
- Exposure in during pregnancy;
- Exposure during breast feeding;

- Medication error.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator or the sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

8.7. Causality Assessment

The investigator's assessment of causality must be provided for all serious adverse events and non-serious adverse reactions. The investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that maraviroc caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether maraviroc caused the event, then the event will be handled as related to maraviroc for reporting purposes. If the investigator's causality assessment is unknown but not related to maraviroc *this* should be clearly documented in the CRF.

8.8. Exposure During Pregnancy

An exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) maraviroc, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to maraviroc (maternal exposure);

2. A male has been exposed, either due to treatment or environmental, to maraviroc prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with maraviroc, the investigator must submit this information to Pfizer, as the Sponsor's designated representative, within 24 hours of awareness of pregnancy, irrespective of whether an adverse event has occurred.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify Pfizer, as the Sponsor's designated representative, of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form.

8.8.1. Medication Error

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer).

- confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer within 24 hours of awareness, irrespective of whether an adverse event occurred:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors including potential medication errors or near misses that do not involve a patient directly. When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

    - An identifiable reporter;

    - A suspect product;

    - A medication error including potential medication error or near miss.

8.9. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.9.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

8.9.2. Non-serious Adverse Event Reporting Requirement

Non-serious adverse events are to be reported if they are suspected to be related to maraviroc (ie, adverse reaction) on the adverse event page, which is to be submitted to Pfizer, as the Sponsor's designated representative.

8.10. Communication of Issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of maraviroc, Pfizer, as the Sponsor's designated representative, should be informed immediately.

In addition, the investigator will inform Pfizer, as the Sponsor's designated representative, immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this non-interventional study protocol that the investigator becomes aware of.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan, which will be dated, filed, and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size

The sample size for the study was determined based on an extensive feasibility assessment in 28 countries, input from Pfizer country offices, and in consultation with the regulators. This number was estimated to be 3,000 subjects (1,500 patients receiving maraviroc and

1,500 patients not receiving maraviroc) to allow calculations of reliable and precise risk estimates.

Malignancies, myocardial ischemia or infarction and deaths (liver-related and all cause) occurring at any time during the 5-year follow-up period will be adjudicated and analyzed as study endpoints. Assuming up to 10% annual loss to follow-up, the 1,500 patients each receiving maraviroc or the anchor drug will contribute 5,836 person-years of observation for these study endpoints over a 5-year period (See Scenario 1 in Appendix 3 for details) in each treatment arm. It is assumed that the expected incidence rates are 12.7 per 1000 person-years for malignancies,[14] 3.5 per 1,000 person-years for myocardial infarction,[13] 2.35 per 1,000 person-years for liver-related deaths,[15] and 16 per 1,000 person-years for all cause mortality[15] in the internal comparator group of patients not receiving maraviroc.

CDC category C AIDS-defining opportunistic infections, viral encephalitis, rhabdomyolysis and liver failure will be adjudicated and analyzed as study endpoints if they occur during the use of maraviroc or the anchor drug in the OBT arm or within 6 months following maraviroc or anchor drug discontinuation. Accounting for the expected rates of drug discontinuation in the two treatment arms over time and a 10% annual loss to follow-up, each study arm will accrue 2,875 person-years of observation for these study endpoints (See Scenario 2 in Appendix 3 for details). It is assumed that the expected incidence rates are 3.5 per 1,000 person-years for liver failure,[16] and 160 per 1,000 person-years for AIDS-defining opportunistic infections[17] in the internal comparator group of patients not receiving maraviroc.

Based on these assumptions of equal person years of contribution in the maraviroc exposed and unexposed groups, using a two-tailed test with α=0.05, and a power of 80%, the minimum detectable relative rates for various study end points are reported in Table 2.[18]

Table 2. Minimum detectable relative rates using a two sided test, α =0.05, and a power of 80%

End Point	Expected number of events in the unexposed internal comparator group	Detectable Relative rates
Malignancies	74	1.572
AIDS-defining opportunistic infections	460	1.1955
Myocardial infarction	20	2.136
Liver failure	10	2.760
Liver-related deaths	14	2.410
All cause mortality	93	1.464

For example, results from Table 2 suggest that the study has 80% power to detect a relative risk of ≥1.527 for malignancies and ≥1.196 for AIDS-defining opportunistic infections, respectively for the patients receiving maraviroc. Similar conclusions can be drawn for other end points as well.

9.2. Analysis of Study Endpoint

This study is intended to provide descriptive and comparative data on the incidence rates of the selected study endpoints in the two study groups.

1. Descriptive statistics (ie, frequency, percent, mean, median, standard deviation as appropriate depending on data type) will be used to summarize baseline characteristics (clinical and demographic) of patients enrolled in the study. (Potential variables include but are not limited to age, gender, weight, BMI, race, smoking, alcohol consumption, HIV-1 RNA level, CD4+ T lymphocyte counts, duration of antiretroviral therapy, duration of HIV infection, number of failed regimens etc).

2. Cumulative incidence rates and incidence-density rates of the study endpoints in the two groups will be reported along with respective 95% confidence intervals.

3. Subject discontinuation, loss to follow-up and total person-time of follow-up accrued in the study will be summarized.

4. Depending on data availability, subgroup analyses may be performed to further describe the rates of the study endpoints stratified by age group, gender, baseline CD4+ cell counts, baseline viral load, hepatitis C/hepatitis B serology, duration of maraviroc use, total duration of antiretroviral use, components of OBT etc.

5. In addition to the selected study endpoints, SAEs and adverse reactions reported during the study will be summarized in summary tables and listings.

6. Crude and adjusted rate ratios with 95% confidence intervals will be calculated for each study endpoint comparing maraviroc-exposed patients to maraviroc-unexposed patients. Multivariate analysis techniques, including recurrent event analyses techniques, will also be used as appropriate to account for the baseline difference in the two study groups and recurrent events if any for a given subject, respectively.

In addition, incidence rates in patients receiving maraviroc in this study may be compared to those reported in comparable patients not using maraviroc in other HIV-1 infected cohort(s) such as EuroSIDA. The baseline characteristics of the patients (eg, number of failed regimens, CD4+ T lymphocyte counts) in this study will be used to identify comparable subjects from the external cohort(s).

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or Sponsor will conduct periodic monitoring visits of sites at least once a year to ensure that the protocol is being followed. The monitors may review source documents to confirm that the data recorded on questionnaire pages is accurate. The enrolling physician and institution will allow the Sponsor or its designated representatives and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by the Sponsor or its designated representative, and/or to inspection by appropriate regulatory authorities.

It is important that the enrolling physician(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Questionnaires

As used in this protocol, the term questionnaire refers to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

Baseline (screening and enrollment), follow-up, and final disposition questionnaires are required and should be completed for each included subject. The completed original questionnaires are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The enrolling physician has ultimate responsibility for the accuracy and authenticity of all clinical, safety, laboratory data entered on the questionnaires. The questionnaires must be signed by the enrolling physician or by an authorized staff member to attest that the data contained on the questionnaires is true. In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the questionnaires must match the data in those charts.

In some cases, the questionnaire, or part of the questionnaire, may also serve as source documents. In these cases, a document should be available at the enrolling physician's site as well as at the Sponsor and clearly identify those data that will be recorded in the questionnaire, and for which the questionnaire will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the enrolling physician agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, questionnaires and hospital records), all original signed informed consent forms, copies of all questionnaires, serious adverse event forms, source documents, and detailed records of treatment disposition. After the end of the study the records should be retained by the enrolling physician according to local regulations or as specified in the Clinical Study Agreement, whichever is longer.

If the enrolling physician relocates, retires, or for any reason withdraws from the study, Pfizer, as the Sponsor's designee should be prospectively notified. The study records must be transferred to an acceptable designee, such as another enrolling physician, another

institution, or to Pfizer. The enrolling physician must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the enrolling physician to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, eg, advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Enrolling Physician File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the enrolling physician must notify the IRB/IEC and the Study Team in writing within 5 working days after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the International Conference on Harmonization (ICH) guidelines. In addition, the study will be conducted in accordance with the protocol, the International Society for Pharmacoepidemiology's Good Pharmacoepidemiology Practices, and applicable local regulatory requirements and laws.

12.3. Subject Information, Consent and Confidentiality

All personal study subject data collected and processed for the purposes of this study will be managed by the enrolling physician and his/her staff with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/or local laws and regulations on personal data protection.

Only the enrolling physician and his/her designee, authorized agents of Pfizer, Inc., or of a CRO designated by Pfizer Inc. following the guidelines proposed by the ethics committees approving this research, will be granted direct access to the study subjects' original medical and hospital records for verification of study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. The Sponsor. will not have access to the study subject's address, phone number, social security number or any other national identification number or alternate contact information collected for the purpose of this study.

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Pfizer and Sponsor will maintain high standards of confidentiality and protection of subject personal data.

Informed consent must take place prior to enrollment of subjects in the study. Written, signed and dated informed consent will be obtained from each subject in accordance with local regulatory and legal requirements.

The informed consent form must be agreed to by the Sponsor or designee and the IRB/IEC and must be in compliance with local regulatory requirements and legal requirements.

The consent document will be available in English and in all applicable local languages depending on the site and country.

The completed and signed consent forms will be stored in a locked file cabinet at the study site. A separate document will include the secondary contact information provided by the subject and, where allowed by law, the social security number or any other national identification number or national insurance number. One copy of this contact form will be stored in a locked file cabinet at the study site. In countries where the CRO is allowed to contact the secondary contact person or the patient, a second copy of this contact form will be stored at the designated CRO office, separate from other data, and in locked file cabinets to insure confidentiality.

The enrolling physician must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The enrolling physician, or a person designated by the enrolling physician, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use. The enrolling physician will retain the original of each subject's signed consent form.

If the consent form is revised during the course of the study, it is the enrolling physician's responsibility to ensure that an amended consent receives approval/favorable opinion by the local IRB/IEC, and signed by all patients subsequently participating in the study.

13. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the Sponsor.

If a study is prematurely terminated or discontinued, the Sponsor or designee will promptly notify the enrolling physician. After notification, the enrolling physician must contact all participating subjects within one month. As directed by Pfizer, all study materials must be collected and all questionnaires completed to the greatest extent possible.

14. COMMUNICATION AND PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

Communication of Results

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Sponsor site or other mutually-agreeable location.

Sponsor will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to an internet-based study register at the time of the first regulatory approval or within 12 months of study completion or of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first regulatory approval or within 12 months of study completion or of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to an internet-based study register to supplement the results summary.

Publications by Investigators

ViiV Healthcare has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide ViiV Healthcare and/or designee an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to ViiV Healthcare /and/or designee at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for

Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

15. OVERSIGHT COMMITTEES

15.1. Scientific Steering Committee

The Scientific Steering Committee (SSC) is an external group of epidemiology, biostatistics, infectious disease/HIV medicine, hepatology, cardiology, and oncology experts that will serve two roles: (1) to safeguard the interests of study participants and (2) to monitor study conduct, in conjunction with the sponsor study team. The remit of the SSC will be described in the charter for the SSC. In summary, the role of the SSC will be to periodically monitor the progress of the study, including logistical and operational aspects, to establish acceptable performance criteria (eg, acceptable rates of withdrawn consent and loss to follow-up), to evaluate the quality of the data being collected in the study, and to assist the sponsor in the development of any remedial plans of action as necessary. The SSC may propose changes to the study design and conduct including follow-up duration, as the committee deems necessary based on emerging safety data. In the event of recommendations for a significant change by the SSC, the Sponsor will notify regulatory agencies where necessary, as per legal or regulatory requirements.

15.2. Endpoint Committee

The Endpoint Committee will review all study endpoints occurring over the course of the study. The EC will be comprised of an independent group of infectious disease specialists, hepatologists, cardiologists and oncologists experienced in the treatment of HIV-1 infection and/or the study of HIV in large observational study settings. The members of the EC will receive de-identified data gathered on subjects who are suspected to have experienced a study outcome and will be responsible for adjudicating and coding the endpoints as described in Section 7.4.

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Appendix 1. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults

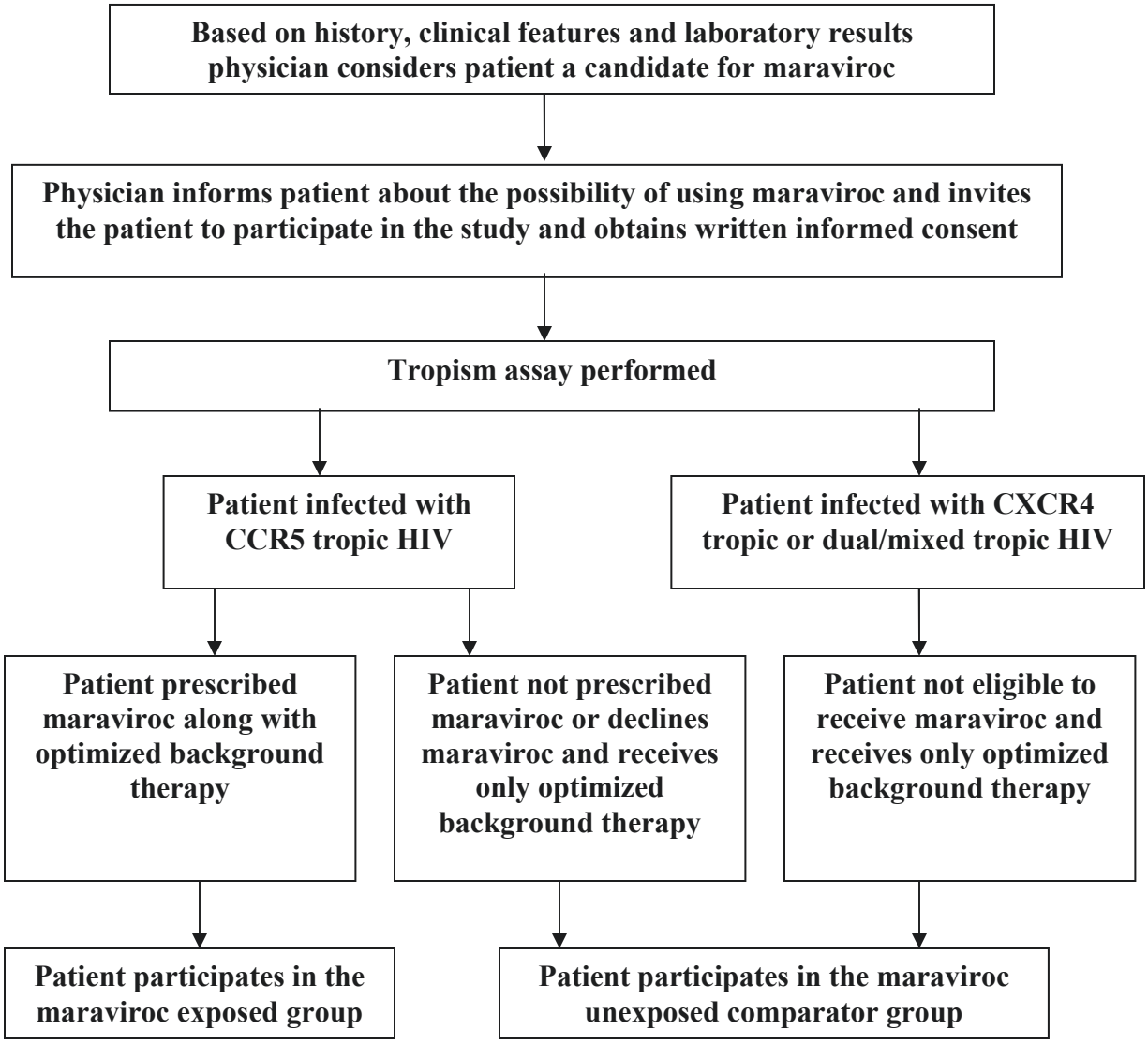
Category C AIDS-defining events

Category C includes the clinical conditions listed below. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Appendix 2. Enrollment procedure



Appendix 3. Calculation of person-time expected to be accrued in the study

Scenario 1

Endpoints: All cause mortality, Liver-related death, Malignancies, Myocardial ischemia and infarction

Expected person-time of observation in maraviroc exposed and unexposed groups: These events occurring at anytime during the 5-year follow up period will be adjudicated and analyzed as study endpoints. It is assumed that each year 10% patients will be lost to follow-up and that on average these losses will occur at the midpoint of the 12 months period.

Person-time accrual in the maraviroc exposed and unexposed groups for all cause mortality, Liver-related death, Malignancies, Myocardial ischemia and infarction				
	n at the beginning of period	**Lost to follow-up midway of the period (provide 6 months of follow-up)**	**n at the end of the period (provide 12 months of follow-up)**	**Person-Years accrued**
Year 1	1500	150	1350	1425.0
Year 2	1350	135	1215	1282.5
Year 3	1215	122	1093	1154.0
Year 4	1094	109	984	1038.5
Year 5	984	98	886	935.0
			Total person-years	5835.0

Based on the above assumptions, both these groups will accrue 5835 person-years of follow-up during the study for the assessment of all cause mortality, Liver-related death, Malignancies, Myocardial ischemia and infarction.

Scenario 2:

Endpoints: CDC category C AIDS-defining opportunistic infection, viral encephalitis, liver failure, rhabdomyolysis

Expected person-time of observation in:

These events will be adjudicated and analyzed as study endpoints if they occur during use of maraviroc or the anchor drug in the OBT, or within 6 months following their discontinuation

- Based on clinical experience, it is assumed that the rate of drug discontinuation will be higher in the earlier part of the study and will gradually decrease over time. To obtain a conservative estimate, it is assumed based on the observations from the 48-week clinical development program of maraviroc that the rate of discontinuation will be approximately 30% during the first 6 months of therapy, 25% between the 7th and 12th month, 20% between the 13th and 18th months and 15% in each 6 month

period thereafter. For the purpose of this calculation it is assumed that on average discontinuation occurs at the midpoint of each 6-month period.

- It is assumed that 5% of the patients (either continuing maraviroc or during the 6 months post discontinuation follow-up) will be lost every 6 months and on average these losses will occur at the midpoint of the 6-month period.

- Patients lost to follow-up during any 6-month period (either on or off maraviroc) will contribute only 3 months of follow-up time during that period. Patients who are being actively followed up at the end of each 6-month period will contribute 6 months of follow-up time.

Based on the above assumptions, both these groups will accrue 2875 person-years of follow-up during the study for the assessment of AIDS-defining OI, viral encephalitis, rhabdomyolysis and liver failure.

Appendix 4. Clinical Protocol Amendment #1

Current Amendment:			
Amendment No. 1	Date 23 March 2009	Country (ies) All	Site(s) All

SUMMARY

Reason(s) for Amendment

The A4001067 protocol is being revised to reflect the following administrative changes:

1. To update the list of countries participating in the study.

2. To modify the process of searching and establishing the survival status of patients who may have switched to a physician not participating in A4001067, or of patients who are lost to follow-up as defined in the protocol.

3. To include study A4001063 in addition to A4001050 in the examples of other Pfizer clinical studies where the patients may have started Maraviroc.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

- The "change from" section represents the current text in the protocol. **Bolded** text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.

- The "change to" section represents the revised text, with the revisions shown in the "change from" section in normal text.

1. SECTION 4.1. Study Population; Paragraph 4 (Sentences 1-3) and Table 1:

CHANGE FROM

The study will be conducted at approximately 300 sites in ~~13~~ **multiple** countries. Participating countries were chosen on the basis of extensive feasibility assessments and include: ~~Australia~~, Belgium, **Brazil**, Canada, France, Germany, Greece, Italy, ~~Malaysia, Mexico,~~ Portugal, Spain, United Kingdom, and United States. **If required, additional countries may be added and some countries in this list may be dropped.**

Table 1: Enrollment Targets by Country

Countries	Expected number of study subjects	Projected launch date for commercial Maraviroc
~~Australia~~	~~30~~	~~December 2008~~
Belgium	80	March 2008
France	200	April 2008
Germany	~~175~~ **223**	October 2007
Greece	40	March 2008
Italy	140	March 2008
Portugal	35	April 2008
Spain	250	May 2008
UK	~~200~~ **161**	November 2007
USA	~~1540~~ **1700**	August 2007
Canada	~~160~~ **80**	October 2007
~~Malaysia~~	~~102~~	~~January 2009~~
~~Mexico~~	~~80~~	~~June 2008~~
Brazil	**91**	**May 2008**

CHANGE TO

The study will be conducted at approximately 300 sites in multiple countries. Participating countries were chosen on the basis of extensive feasibility assessments and include: Belgium, Brazil, Canada, France, Germany, Greece, Italy, Portugal, Spain, United Kingdom, and United States. If required, additional countries may be added and some countries in this list may be dropped.

Table 1: Enrollment Targets by Country

Countries	**Expected number of study subjects**	**Projected launch date for commercial Maraviroc**
Belgium	80	March 2008
France	200	April 2008
Germany	223	October 2007
Greece	40	March 2008
Italy	140	March 2008
Portugal	35	April 2008
Spain	250	May 2008
UK	161	November 2007
USA	1700	August 2007
Canada	80	October 2007
Brazil	91	May 2008

2. SECTION 6.4. Patients lost to follow-up; Paragraph 2:

CHANGE FROM

In the situation where neither the patient nor the secondary contact person(s) can be reached, attempts will be made to ascertain the vital status of the patient by searching **the appropriate** ~~a~~ national or regional vital status registry **or other relevant databases**, where available and allowable by local law~~, by a designated CRO or a professional search firm~~**. Depending on the local law, this search will be conducted by a designated CRO, or a professional search firm, or the enrolling physician or his/her designee at the study site**. It should be noted that there is usually a lag between calendar time of death and the time that data are available from vital status registries, due to the additional time necessary for government agencies to collate information from regional death registries and to check these data for accuracy. In the U.S. National Death Index, the delay is approximately 18 months.

CHANGE TO

In the situation where neither the patient nor the secondary contact person(s) can be reached, attempts will be made to ascertain the vital status of the patient by searching the appropriate national or regional vital status registry or other relevant databases, where available and allowable by local law. Depending on the local law, this search will be conducted by a designated CRO, or a professional search firm, or the enrolling physician or his/her designee at the study site. It should be noted that there is usually a lag between calendar time of death and the time that data are available from vital status registries, due to the additional time necessary for government agencies to collate information from regional death registries and to check these data for accuracy. In the U.S. National Death Index, the delay is approximately 18 months.

3. SECTION 6.5. Follow-up of patients switched to non-participating physicians:

CHANGE FROM

If for any reason (eg, relocation, insurance change) a patient switches to a physician who is not participating in the study, the enrolling physician will complete a questionnaire with the last available clinical data. If the patient does not withdraw consent to participate in the study, **the patient or his/her current physician will be contacted** ~~the designated CRO will directly contact the patient (or the secondary contact person(s) if needed)~~ by telephone or mail every six months to ascertain survival status provided the local regulations allow such contact. **This communication will be conducted by the CRO or the enrolling physician or his/her designee at the study site as allowed by local law.** Where such contact is not allowed, attempts will be made to ascertain the vital status of the patient ~~by searching a national vital status registry, where available and allowable by local law~~ as mentioned in Section 6.4 for patients lost to follow up. Information on the occurrence of the

other study events (eg, MI, OI etc.) will not be sought, since patient-reported endpoints are not verifiable and are unable to be adjudicated by medical records in this situation. Therefore, in the analyses of the study endpoints except all cause mortality, such patients will be censored at the date of last clinical encounter with the enrolling physician.

CHANGE TO

If for any reason (eg, relocation, insurance change) a patient switches to a physician who is not participating in the study, the enrolling physician will complete a questionnaire with the last available clinical data. If the patient does not withdraw consent to participate in the study, the patient or his/her current physician will be contacted by telephone or mail every six months to ascertain survival status provided the local regulations allow such contact. This communication will be conducted by the CRO or the enrolling physician or his/her designee at the study site as allowed by local law. Where such contact is not allowed, attempts will be made to ascertain the vital status of the patient as mentioned in Section 6.4 for patients lost to follow up. Information on the occurrence of the other study events (eg, MI, OI etc.) will not be sought, since patient-reported endpoints are not verifiable and are unable to be adjudicated by medical records in this situation. Therefore, in the analyses of the study endpoints except all cause mortality, such patients will be censored at the date of last clinical encounter with the enrolling physicians.

4. SECTION 7.2. Baseline Data; List bullet 23:

CHANGE FROM

- For subjects who participated in other studies involving maraviroc (eg, the Maraviroc Expanded Access Program, A4001050 **or study A4001063**), the name and/or protocol number of the study and the subject ID in that study will be collected.

CHANGE TO

- For subjects who participated in other studies involving maraviroc (eg, the Maraviroc Expanded Access Program (A4001050 or study A4001063), the name and/or protocol number of the study and the subject ID in that study will be collected.

5. SECTION 12.3. Subject Information, Consent and Confidentiality; Paragraphs 2 and 7:

CHANGE FROM

Only **the enrolling physician and his/her designee,** authorized agents of Pfizer, Inc., or of a CRO designated by Pfizer Inc. following the guidelines proposed by the ethics committees

approving this research, will be granted direct access to the study subjects' original medical and hospital records for verification of study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. Pfizer, Inc. will not have access to the study subject's address, phone number, social security number or any other national identification number or alternate contact information collected for the purpose of this study.

The completed and signed consent forms will be stored in a locked file cabinet at the study site. A separate document will include the secondary contact information provided by the subject and, where allowed by law, the social security number or any other national identification number or national insurance number. One copy of this contact form will be stored in a locked file cabinet at the study site. **In countries where the CRO is allowed to contact the secondary contact person or the patient, a** ~~A~~ second copy of this contact form will be stored at the designated CRO office, separate from other data, and in locked file cabinets to insure confidentiality.

CHANGE TO

Only the enrolling physician and his/her designee, authorized agents of Pfizer, Inc., or of a CRO designated by Pfizer Inc. following the guidelines proposed by the ethics committees approving this research, will be granted direct access to the study subjects' original medical and hospital records for verification of study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. Pfizer, Inc. will not have access to the study subject's address, phone number, social security number or any other national identification number or alternate contact information collected for the purpose of this study.

The completed and signed consent forms will be stored in a locked file cabinet at the study site. A separate document will include the secondary contact information provided by the subject and, where allowed by law, the social security number or any other national identification number or national insurance number. One copy of this contact form will be stored in a locked file cabinet at the study site. In countries where the CRO is allowed to contact the secondary contact person or the patient, a second copy of this contact form will be stored at the designated CRO office, separate from other data, and in locked file cabinets to insure confidentiality.

Appendix 5. Clinical Protocol Amendment #2

Current Amendment:

Amendment No.	Date	Country (ies)	Site(s)
2	12 August 2010	All	All
Previous Amendments:			
Amendment No.	Date	Country (ies)	Site(s)
1	23 March 2009	All	All

SUMMARY

[redacted]

Reason(s) for Amendment

The A4001067 protocol is being revised to reflect the following changes:

- **To reflect the change of sponsor for this study from Pfizer Inc, to ViiV Healthcare. ViiV Healthcare as the sponsor ("ViiV" or "Sponsor") will continue to use Pfizer and Pfizer's designated agents ("Pfizer") to conduct the study.**

  ViiV Healthcare was formed in November of 2009. ViiV Healthcare is a global specialist HIV company established by GlaxoSmithKline and Pfizer to deliver advances in treatment and care for people living with HIV. The purpose of this amendment is to outline the changes that are relevant to ongoing clinical studies.

  On June 16th 2010, sponsorship of all maraviroc clinical trials including A4001067, was transferred from Pfizer Inc to ViiV Healthcare (980 Great West Road, Brentford, Middlesex, TW8 9GS. UK). There have been no changes to the study conduct or study team related to this transfer. Pfizer will continue to conduct maraviroc clinical trials on ViiV's behalf. Safety reporting procedures will continue to be managed as was done previously, and all AEs, SAEs and deaths must continue to be reported to Pfizer Inc.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

- The "change from" section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, text) is used to show the deletion of information from the current text.

- The "change to" section represents the revised text, with the revisions shown in the "change from" section in normal text.

1. Entire Protocol; Footer

Change From

Pfizer — Company Confidential

Change To

Confidential

2. Cover page

Change From

[redacted]

Change To

[redacted]

3. Contact Information

Change From

~~**PFIZER INC**~~

EPIDEMIOLOGY STUDY PROTOCOL
MARAVIROC

PROTOCOL NUMBER: A4001067

Sponsoring Group:	**ViiV Healthcare Ltd** ~~Pfizer Inc.~~ ~~Safety and Risk Management~~ ~~Epidemiology~~ ~~235 East 42nd Street~~ ~~New York, NY 10017~~
Pfizer Epidemiologist:	PPD MBBS, MHS, PhD PPD

235 East 42nd Street, MS 150/3/72
New York, NY 10017

Pfizer PPD :

PPD **MD**
PPD

235 East 42 Street MS 219/8/02
New York, NY 10017

PPD ~~MD~~
PPD

~~235 East 42 Street MS 235/3/38~~
~~New York, NY 10017~~

Pfizer Statistician:

PPD **MS**
PPD

NYO-219-08-02
219 East 42nd Street
New York, NY 10017

PPD ~~PhD~~
PPD

~~235 East 42 Street, MS 685/11/16~~
~~New York, NY 10017~~

Name and Title of Persons Authorized to Sign for the Sponsor:

PPD ScD
PPD

235 East 42 Street, MS 150/3/72
New York, NY 10017

PPD **MD**
PPD

235 East 42 Street, MS 219/8/30
New York, NY 10017

PPD ~~MD~~
PPD
PPD

~~235 East 42 Street, MS 235/3/38~~

~~New York, NY 10017~~

Change To

EPIDEMIOLOGY STUDY PROTOCOL
MARAVIROC

PROTOCOL NUMBER: A4001067

Sponsoring Group: ViiV Healthcare Ltd

Pfizer Epidemiologist:

PPD MBBS, MHS, PhD
PPD
235 East 42 Street, MS 150/3/72
New York, NY 10017

Pfizer PPD :

PPD MD
PPD
PPD
235 East 42 Street MS 219/8/02
New York, NY 10017

Pfizer Statistician:

PPD MS
PPD
NYO-219-08-02
219 East 42nd Street
New York, NY 10017

Name and Title of Persons Authorized to Sign for the Sponsor:

PPD ScD
PPD
235 East 42 Street, MS 150/3/72
New York, NY 10017

PPD MD
PPD
235 East 42 Street, MS 219/8/30
New York, NY 10017

4. Section 5.3; HIV Tropism Assay

Change From

Paragraph

~~Pfizer~~ **The Sponsor** will cover the cost of tropism assay to determine the viral tropism as a screening test for eligibility to receive maraviroc. The details of the sample collection, processing and shipping information will be made available to participating study sites as a separate document.

Change To

The Sponsor will cover the cost of a tropism assay performed by the Monogram Biosciences, Inc., USA as a screening test for eligibility to receive maraviroc. The details of the sample collection, processing and shipping information will be made available to participating study sites as a separate document.

5. Section 6.7; Subject Withdrawal

Change From

1st paragraph

Subjects may withdraw their consent from study participation at any time at their own request, or they may be withdrawn at any time at the discretion of the enrolling physician or the Sponsor for behavioral or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made **by the enrolling physician or site staff** to contact the subject and his/her alternate contacts, as provided by the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The enrolling physician should inquire about the reason for withdrawal, request the subjects to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved serious adverse events **and study endpoints**.

Change To

Subjects may withdraw their consent from study participation at any time at their own request, or they may be withdrawn at any time at the discretion of the enrolling physician or the Sponsor for behavioral or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made by the enrolling physician or site staff to contact the subject and his/her alternate contacts, as provided by the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The enrolling physician should inquire about the reason for withdrawal, request the subjects to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved serious adverse events and study endpoints.

6. Section 6.8; Transfer of Study Data

Change From

2nd paragraph

Copies of all external documents (eg, hospital discharge certificates, death certificates, EKG tracings etc.) collected by the enrolling physician at the study sites will be de-identified, labeled with the patient's study identification number, and forwarded to a CRO designated by ~~Pfizer~~ **Sponsor**. After ensuring that no personal identifiers are present, the CRO will forward the copies to the endpoint adjudication committee for validation of study end points.

Change To

Copies of all external documents (eg, hospital discharge certificates, death certificates, EKG tracings etc.) collected by the enrolling physician at the study sites will be de-identified, labeled with the patient's study identification number, and forwarded to a CRO designated by Sponsor. After ensuring that no personal identifiers are present, the CRO will forward the copies to the endpoint adjudication committee for validation of study end points.

7. Section 8; Adverse Events

Change From

Paragraph added

Change To

ViiV is the Sponsor of the study. Pfizer will conduct the study on behalf of ViiV. All adverse event reporting under this section will be to Pfizer, as the Sponsor's designated representative, using forms provided by Pfizer.

8. Section 8.1; Adverse Events

Change From

2nd paragraph

For all **reportable** adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see section "Serious Adverse Events") requiring immediate notification to Pfizer ~~or a Pfizer-designated representative~~ **as the Sponsor's designated representative**.. For all **reportable** adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to maraviroc, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer **on behalf of the sponsor** concurs with that assessment.

Change To

For all reportable adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (see section "Serious Adverse Events") requiring immediate notification to Pfizer or a Pfizer-designated representative. For all reportable adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to maraviroc, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer on behalf of the sponsor concurs with that assessment.

9. Section 8.2; Reporting Period

Change From

Paragraph

For serious adverse events, the reporting period to Pfizer**,** ~~or its~~ **as the Sponsor's** designated representative**,** begins from the time that the subject provides informed consent or signed data privacy statement, which is obtained prior to the subject's participation in the study to 60 months from enrollment in the study regardless of the actual duration of the use of the study drug.

Change To

For serious adverse events, the reporting period to Pfizer, as the Sponsor's designated representative, begins from the time that the subject provides informed consent or signed data privacy statement, which is obtained prior to the subject's participation in the study to 60 months from enrollment in the study regardless of the actual duration of the use of the study drug.

10. Section 8.4; Abnormal Test Findings

Change From

Last bullet

- Test result is considered to be an adverse event by the investigator or ~~sponsor~~ **the Study Team**.

Change To

- Test result is considered to be an adverse event by the investigator or the Study Team.

11. Section 8.8; Exposure in Utero

Change From

From 2nd paragraph

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with maraviroc, the investigator must submit ~~this~~ **the required** information to Pfizer**, as the Sponsor's designated representative**, irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify Pfizer**, as the Sponsor's designated representative,** of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form.

Change To

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with maraviroc, the investigator must submit the required information to Pfizer, as the Sponsor's designated representative, irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (eg, induced abortion) and then notify Pfizer, as the Sponsor's designated representative, of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form.

12. Section 8.9.1; Serious Adverse Event Reporting Requirements

Change From

Last paragraph, last sentence

. . . In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to ~~Pfizer~~ **the Sponsor** or its designated representative.

Change To

. . . In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

13. Section 8.9.2; Non-serious Adverse Event Reporting Requirement

Change From

Paragraph

Non-serious adverse events are to be reported if they are suspected to be related to maraviroc (ie, adverse reaction) on the adverse event page, which is to be submitted to Pfizer**, as the Sponsor's designated representative.**

Change To

Non-serious adverse events are to be reported if they are suspected to be related to maraviroc (ie, adverse reaction) on the adverse event page, which is to be submitted to Pfizer, as the Sponsor's designated representative.

14. Section 8.10; Communication of Issues

Change From

From 1st paragraph

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of maraviroc, Pfizer**, as the Sponsor's designated representative,** should be informed immediately.

In addition, the investigator will inform Pfizer**, as the Sponsor's designated representative,** immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this observational plan that the investigator becomes aware of.

Change To

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of maraviroc, Pfizer, as the Sponsor's designated representative, should be informed immediately.

In addition, the investigator will inform Pfizer, as the Sponsor's designated representative, immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this observational plan that the investigator becomes aware of.

15. Section 10; Quality Control and Quality Assurance

Change From

First 2 paragraphs

During study conduct, Pfizer or ~~its agent~~ **Sponsor** will conduct periodic monitoring visits of sites at least once a year to ensure that the protocol is being followed. The monitors may review source documents to confirm that the data recorded on questionnaire pages is accurate. The enrolling physician and institution will allow ~~Pfizer monitors or their agents~~ **the Sponsor or its designated representatives** and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by ~~Pfizer~~ **the Sponsor or its designated representative**, and/or to inspection by appropriate regulatory authorities.

Change To

During study conduct, Pfizer or Sponsor will conduct periodic monitoring visits of sites at least once a year to ensure that the protocol is being followed. The monitors may review source documents to confirm that the data recorded on questionnaire pages is accurate. The enrolling physician and institution will allow the Sponsor or its designated representatives and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by the Sponsor or its designated representative, and/or to inspection by appropriate regulatory authorities.

16. Section 11.1; Questionnaires

Change From

2nd paragraph; 1st sentence

Baseline (screening and enrollment), follow-up, and final disposition questionnaires are required and should be completed for each included subject. The completed original questionnaires are the sole property of **the Sponsor** ~~Pfizer~~ and should not be made available in any form to third parties, except for authorized representatives of **the Sponsor** ~~Pfizer~~ or appropriate regulatory authorities, without written permission from **the Sponsor** ~~Pfizer~~.

Change To

Baseline (screening and enrollment), follow-up, and final disposition questionnaires are required and should be completed for each included subject. The completed original questionnaires are the sole property of the Sponsor and should not be made available in any

form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

17. Section 11.2; Record Retention

Change From

1st and 2nd paragraphs

To enable evaluations and/or audits from regulatory authorities or ~~Pfizer~~ **the Sponsor**, the enrolling physician agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, questionnaires and hospital records), all original signed informed consent forms, copies of all questionnaires, serious adverse event forms, source documents, and detailed records of treatment disposition. After the end of the study the records should be retained by the enrolling physician according to local regulations or as specified in the Clinical Study Agreement, whichever is longer.

If the enrolling physician relocates, retires, or for any reason withdraws from the study, Pfizer**, as the Sponsor's designee** should be prospectively notified. The study records must be transferred to an acceptable designee, such as another enrolling physician, another institution, or to Pfizer. The enrolling physician must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

Change To

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the enrolling physician agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, questionnaires and hospital records), all original signed informed consent forms, copies of all questionnaires, serious adverse event forms, source documents, and detailed records of treatment disposition. After the end of the study the records should be retained by the enrolling physician according to local regulations or as specified in the Clinical Study Agreement, whichever is longer.

If the enrolling physician relocates, retires, or for any reason withdraws from the study, Pfizer, as the Sponsor's designee should be prospectively notified. The study records must be transferred to an acceptable designee, such as another enrolling physician, another institution, or to Pfizer. The enrolling physician must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

18. Section 12.1; Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Change From

2nd paragraph, last sentence

. . . In that event, the enrolling physician must notify the IRB/IEC and ~~Pfizer~~ **the Study Team** in writing within 5 working days after the implementation.

Change To

. . . In that event, the enrolling physician must notify the IRB/IEC and the Study Team in writing within 5 working days after the implementation.

19. Section 12.3; Subject Information, Consent and Confidentiality

Change From

From 2nd paragraph

Only the enrolling physician and his/her designee, authorized agents of Pfizer, Inc., or of a CRO designated by Pfizer Inc. following the guidelines proposed by the ethics committees approving this research, will be granted direct access to the study subjects' original medical and hospital records for verification of study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. ~~Pfizer, Inc.~~ **The Sponsor** will not have access to the study subject's address, phone number, social security number or any other national identification number or alternate contact information collected for the purpose of this study.

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Pfizer **and Sponsor** will maintain high standards of confidentiality and protection of subject personal data.

Informed consent must take place prior to enrollment of subjects in the study. Written, signed and dated informed consent will be obtained from each subject in accordance with local regulatory and legal requirements.

The informed consent form must be agreed to by ~~Pfizer~~ **the Sponsor or designee** and the IRB/IEC and must be in compliance with local regulatory requirements and legal requirements.

8th paragraph

The enrolling physician must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible

risks associated with participation. The enrolling physician, or a person designated by the enrolling physician, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and ~~Pfizer~~ **the Sponsor** before use. The enrolling physician will retain the original of each subject's signed consent form.

Change To

From 2nd paragraph

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20. Section 13; Sponsor Discontinuation Criteria

Change From

From 1st paragraph

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of ~~Pfizer~~ **the Sponsor**.

If a study is prematurely terminated or discontinued, ~~Pfizer~~ **the Sponsor or designee** will promptly notify the enrolling physician. After notification, the enrolling physician must contact all participating subjects within one month. As directed by Pfizer, all study materials must be collected and all questionnaires completed to the greatest extent possible.

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21. Section 14; Communication and Publication of Study Results

Change From

~~**Communication of results by Pfizer:**~~

~~Pfizer fulfils its commitment to publicly disclose the results of studies through postings on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:~~

- ~~Studies that Pfizer registered on **www.clinicaltrials.gov**, (ClinicalTrials.gov) regardless of the reason for registration; **OR**~~
- ~~All other studies for which the results have scientific or medical importance as determined by Pfizer.~~

~~For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed.~~

- ~~For studies involving products already approved in any country and for studies that do not involve a Pfizer product, Pfizer posts results within one year after study completion, defined as last subject, last visit (LSLV);~~

- ~~For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within one year after the first regulatory approval of the product;~~

- ~~For studies involving products whose drug development is discontinued before approval, Pfizer posts the results of already-completed studies within one year after such discontinuation.~~

~~Pfizer's posting on ClinicalStudyResults.org includes the following elements:~~

- ~~Protocol title, study phase, and indication;~~

- ~~A link to approved product labeling, if applicable;~~

- ~~The synopsis of study results;~~

- ~~Citations of known study publications;~~

- ~~Legal disclaimer.~~

~~If posting of study results to ClinicalStudyResults.org jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has issued or two years have elapsed, whichever occurs first.~~

~~Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.~~

Publication of study results is discussed in the Clinical Study Agreement.

Communication of Results

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Sponsor site or other mutually-agreeable location.

Sponsor will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to an internet-based study register at the time of the first regulatory approval or within 12 months of study completion or of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first regulatory approval or within 12 months of study completion or of any decision to terminate development.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to an internet-based study register to supplement the results summary.

Publications by Investigators

ViiV Healthcare has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide ViiV Healthcare and/or designee an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to ViiV Healthcare /and/or designee at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

Change To

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For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for

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22. Section 15.1; Scientific Steering Committee

Change From

Last sentence

. . . In the event of recommendations for a significant change by the SSC, ~~Pfizer~~ **the Sponsor** will notify regulatory agencies where necessary, as per legal or regulatory requirements.

Change To

. . . In the event of recommendations for a significant change by the SSC, the Sponsor will notify regulatory agencies where necessary, as per legal or regulatory requirements