Protocol *A4001067*

An International, Multicenter, Prospective Observational Study of the Safety of Maraviroc used with Optimized Background Therapy in Treatment-Experienced HIV-1 Infected Patients

Statistical Analysis Plan (SAP)

Version: 2

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[redacted]

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

This amendment outlines the change implemented in protocol amendment #3 of Nov 29 2010, from enrolling 2000 maraviroc-exposed and 1000 maraviroc-unexposed patients to enrolling 1500 patients in each arm.

2. INTRODUCTION

NOTE: ***Italicized*** text within this document has been taken verbatim from the Protocol.

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

2.1. Study Design

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

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*

There will be no protocol-mandated patient visits or laboratory tests in this study. Therefore, visits are scheduled following the local guidelines and/or clinical practices. However, most guidelines recommend follow-up visits at weeks 2-4 after initiating a new therapy to assess initial viral response and address issues affecting adherence, then again at weeks 8 and 12, and then every 12 weeks thereafter. All subjects will be observed for five years.

2.2. Study 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 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).*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Periodic review of the study progress and assessment of collected data will be conducted by the Scientific Steering Committee (SSC) once in every six months. The data to be reviewed by the Steering Committee will be outlined in a separate analysis plan. In addition, yearly progress reports will be provided to the regulatory agencies throughout the duration of the study. The analyses as outlined in Section 8.2 will be adopted for reporting these results. There are no formal stopping rules for the study; however, the SSC may recommend stopping the study for safety issues at any time.

Full final analysis will follow the official database release. Since this is an open label study, no formal un-blinding of the randomization is needed.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

None

4.2. Statistical Decision Rules

4.2.1. 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, (*Beral, V. et al, 2000)[1] *5 per 1,000 person-years for myocardial infarction, (*Friis-Moller, N, et al, 2003)[4] *2.35 per 1,000 person-years for liver-related deaths, (*Weber, R, et al 2006)[12] *and 16 per 1,000 person-years for all cause mortality (*Weber, R, et al 2006) *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, (*Friis-Moller, N., Kirk O, Reiss P, 2003)[5] *and 160 per 1,000 person-years for AIDS-defining opportunistic infections* (Kaplan, J.E., et al., 2000)[8] *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*. (McMahon, A.D. and T.M. MacDonald, 1997).[9]

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.

4.2.2. Estimation of follow up time

Patients enrolled in the maraviroc-exposed group: all follow up time accrued in the study will be contributed to the "maraviroc-exposed" group regardless of the actual duration of maraviroc use.

Patients enrolled in the maraviroc-unexposed group: all follow up time accrued in the study will be contributed to the "maraviroc-unexposed" group regardless of the actual duration of the use of the anchor drug in the OBT. If a patient starts maraviroc during the study, the follow up time accrued before starting maraviroc will be applied to the "maraviroc-unexposed" group and the follow up time accrued after starting maraviroc will be applied to the "maraviroc-exposed" group.

For the maraviroc unexposed group, the anchor drug in the OBT regimen is identified according to the following hierarchy:

- ► Raltegravir or other integrase inhibitor
  - ► Enfuvirtide or other fusion inhibitor
    - ► Etravirine or other second generation NNRTI
      - ► Darunavir or other protease inhibitor

The following are the currently commercially available drugs in each class at the time of the finalization of the SAP:

Protease Inhibitors (PI):
- ► tipranavir, indinavir, saquinavir, lopinavir, fosamprenavir, ritonavir, darunavir, atazanavir, nelfinavir

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI):
- ► emtricitabine, lamivudine, zalcitabine, zidovudine, didanosine, tenofovir disoproxil fumarate, stavudine, abacavir

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI):
- ► delavirdine, efavirenz, nevirapine, etravirine

Fusion Inhibitors:
- ► enfuvirtide

Entry Inhibitors:
- ► maraviroc

Integrase Inhibitors:
- ► raltegravir

Patients starting CCR5 inhibitors other than maraviroc: In both groups, follow up will be terminated if a patient starts using any CCR5 inhibitor (either experimental or commercially available) other than maraviroc.

Patients switching to a non-participating physician: If the patient does not withdraw consent, follow up will continue. In these cases, only the mortality endpoints will be collected via direct patient contact by a CRO.

4.2.3. Survival Bias

It is anticipated that up to 15% of the patients in the maraviroc-exposed group will comprise of patients who started maraviroc prior to enrollment in this study as participants in the maraviroc expanded access program (A4001050) and are still continuing the drug. The exact therapy start date and baseline covariates for these patients are documented in the A4001050 study database and will be used. Appropriate statistical analytical techniques (Muñoz, Wang et al. 1989; Hoover, Muñoz et al. 1991; Tarwater, Mellors et al. 2001; Cole, Li et al. 2004)[10, 6, 11, 2] that account for staggered entry of exposed subjects into study will be utilized to address the theoretical concern of survival bias from enrolling patients who were already exposed to the drug at study entry. In addition, sensitivity analyses will be performed to determine whether inclusion of such subjects substantially alters the findings of this study and the results will be reported.

The study will not enroll patients who started maraviroc in regular clinical practice outside of a clinical study since reliable data on the date of first exposure and baseline characteristics at that time may not be consistently available. Also, the study will not enroll into the maraviroc-unexposed arm any individual with prior exposure to maraviroc.

4.2.4. Scientific Steering Committee

A Scientific Steering Committee (SSC) with external experts from epidemiology, biostatistics, infectious disease/HIV medicine, hepatology, cardiology, and oncology will be constituted for this study. The role of this external body is (1) to safeguard the interests of study participants and (2) to monitor the 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 monitor the progress of the study on a regular basis, 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. In the event of recommendations for a significant change (eg, study stoppage) by the SSC due to safety issues, Pfizer will notify regulatory agencies where necessary, as per legal or regulatory requirements.

4.2.5. Endpoint Committee

The Endpoint Committee (EC) will review in a blinded manner 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. Details of these activities are described in greater detail within the endpoint adjudication manual for the study.

5. ANALYSIS SETS

All tables and figures will be based on the safety analysis set population as described below.

5.1. Full Analysis Set

Same as in Section 5.3: *Safety Analysis Set.*

5.2. Per Protocol Analysis Set

None

5.3. Safety Analysis Set

All subjects who enroll in the study will be included in the safety analyses and listings.

5.4. Other Analysis Sets

None

5.5. Treatment Misallocations

Not applicable.

5.6. Protocol Deviations

If applicable, a full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to official database release.

6. ENDPOINTS AND COVARIATES

6.1. Study Endpoint(s)

The study endpoints are:

1. Centers for Disease Control and Prevention Category C AIDS-defining opportunistic infections will be considered as study end points up to 6 months post-discontinuation of maraviroc or the anchor drug in the OBT (Appendix 1). After 6-months, these clinical events will be handled as AE.

2. All malignancies up to five years of follow-up will be considered as study endpoints.

3. Liver failure will be considered as study endpoints up to 6 months post-discontinuation of maraviroc or the anchor drug in the OBT. After 6-months, these clinical events will be handled as AE.

4. Myocardial infarction or ischemia up to five years of follow-up will be considered as study endpoints.

5. Death from liver-related cause up to five years of follow-up will be considered as study endpoints.

6. Death from any cause up to five years of follow-up will be considered as study endpoints.

In addition, the following will be considered as study end points up to 6 months post-discontinuation of maraviroc or the anchor drug in the OBT:

- viral encephalitis
- rhabdomyolysis

After 6-months, these clinical events will be handled as AE.

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

6.2. Covariates

In the multivariate analyses comparing the two treatment groups, age, gender, weight, BMI, race/ethnicity, smoking classification collected as current smoker, ex-smoker, or non-smoker, alcohol usage (yes/no), hepatitis status, history of cardiovascular disease, screening HIV-1 RNA levels, and screening CD4+ cell counts will be used as covariates as appropriate. If data is available for other relevant covariates (for example: the use of lipid lowering agents), these will also be utilized.

7. HANDLING OF MISSING VALUES

For the analysis of safety, Pfizer Data Standards (PDS) rules for imputation will be applied. Missing dates for study medication, and adverse events (AE's) will be imputed using the PDS algorithm.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Efficacy and Pharmacokinetic Analysis

None

8.2. Safety Analyses

All safety data will be subjected to clinical review and summarized according to Pfizer Data Standards and using the Safety Analysis Set. The format and algorithms described in Pfizer Data Standards documentation will be followed to produce summary tables and listings.

This study will provide data to calculate incidence rates on each of the study endpoints in the two study groups and will be analyzed as given below:

1. Descriptive statistics (ie, frequency, percent, mean, median, standard deviation as appropriate depending on data type) will be used to summarize characteristics (clinical and demographic) of patients enrolled in the study. (Potential variables include but are not limited to age, gender, weight, BMI, race, smoking classification, alcohol use (yes/no), 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, appropriate 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 study endpoints, SAEs and drug-related adverse reactions reported during the study will be summarized in 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 will be used as appropriate (e.g., Poisson regression model) to account for the baseline difference in the two study groups via propensity score technique. Specifically, since subjects are not randomized to treatment, there is a potential for imbalance in the above-mentioned important demographic and baseline characteristics between groups. To account for the imbalance between the two groups on the clinically important demographic and baseline characteristics, the confidence intervals will be adjusted for propensity score quintile. Specifically, propensity score for treatment membership (maraviroc exposed vs. maraviroc un-exposed) will be calculated for each subject from a logistic regression with the above mentioned covariates as predictors and study group membership as the outcome. Participants with similar propensity scores generally have similar distribution of the covariates on which the score is based. Participants will then be categorized into quintiles according to their propensity score. Four indicator variables will be created to represent the propensity score quintiles and will be used in the multivariate model as covariates along with the primary exposure variable i.e., exposure to maraviroc. Adjusting for propensity score quintile in this manner helps account for imbalances at baseline as discussed in D'Agostino (1998).[3]
7. Appropriate survival analyses techniques (eg, Kaplan-Meier survival curves, Cox proportional hazards model) will be used to further analyze the data. The multivariate models will incorporate appropriate techniques referred to in section 4.2.3 to adjust for

potential survival bias.

8. In addition, incidence rates in patients receiving maraviroc in this study may be compared to those reported in comparable patients (ie, those with similar propensity scores and with the smallest Mahalanobis' distance between baseline values (D'Agostino, 1998)[3] 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).

The following data will be presented in standard safety summaries:

- *adverse events*
- *laboratory data (to the extent available)*
- *vital signs data (pulse rate, systolic and diastolic blood pressure)*

8.2.1. Treatment and Disposition of Subjects

Subject evaluation groups will show the end of study subject disposition and will report which subjects were analyzed for safety (adverse events). Frequency counts will be supplied for subject discontinuation(s).

8.2.2. Demographic and Clinical Examination Data

Demographic information including age, gender, weight, BMI, race/ethnicity, smoking classification, alcohol use, percentage of patients with AIDS defining events, HIV-1 RNA level, and CD4+ cell counts at screening/baseline or at the time of entry into the study will be described. Age will be derived from the visit date and the date of birth according to the Pfizer Data Standards algorithm.

Continuous measurements like age, height, weight, and duration of HIV-1 will be summarized using the descriptive statistics (N, mean, standard deviation, median, range).

Categorical data like gender, race, smoking classification, and alcohol use (yes/no) will be summarized by counts (N, frequency, and percent).

8.2.3. Discontinuation(s)

Discontinuation of maraviroc or the anchor drug (as applicable) due to adverse events or abnormal laboratory test results will be detailed and summarized by maraviroc exposed and un-exposed groups. In addition, subjects who permanently withdrew from the study will also be summarized.

8.2.4. Adverse Events

All serious adverse events regardless of their association with maraviroc will be collected and summarized by the treated group.

Maraviroc related non-serious adverse events (AE's) are collected in this observational study and will be reported according to the Pfizer Data standards (PDS).

- Maraviroc related study emergent AE's by Body System
- Incidence and Severity of maraviroc related study Emergent AE's
- Discontinuation of maraviroc due to Adverse Events

Note: If for some reason an investigator reports non-serious adverse events in the maraviroc un-exposed group, these will be summarized descriptively (if applicable).

8.2.5. Laboratory Data

None

8.2.6. Vital Signs (Pulse Rate, Systolic and Diastolic Blood Pressure)

The baseline measurement is measurement taken at enrollment.

At each post-baseline time point available, baseline values and change from baseline scores may be summarized with descriptive statistics (N, mean, SD, median, minimum and maximum).

Categorization of post-baseline vital sign measurements may be summary tabulated by criteria for values 'outside the reference range' that are of potential clinical concern (see Section 9.4: *Criteria for Safety Values of Potential Clinical Concern*).

Listings of observed values and categorical placement will be provided.

8.2.7. ECG Data

None

8.2.8. Other Safety Data

None

8.2.9. Prior and Concomitant Treatments

All prior and concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.2.10. Screening and Other Special Purpose Data

None

8.3. Exploratory Analyses

None

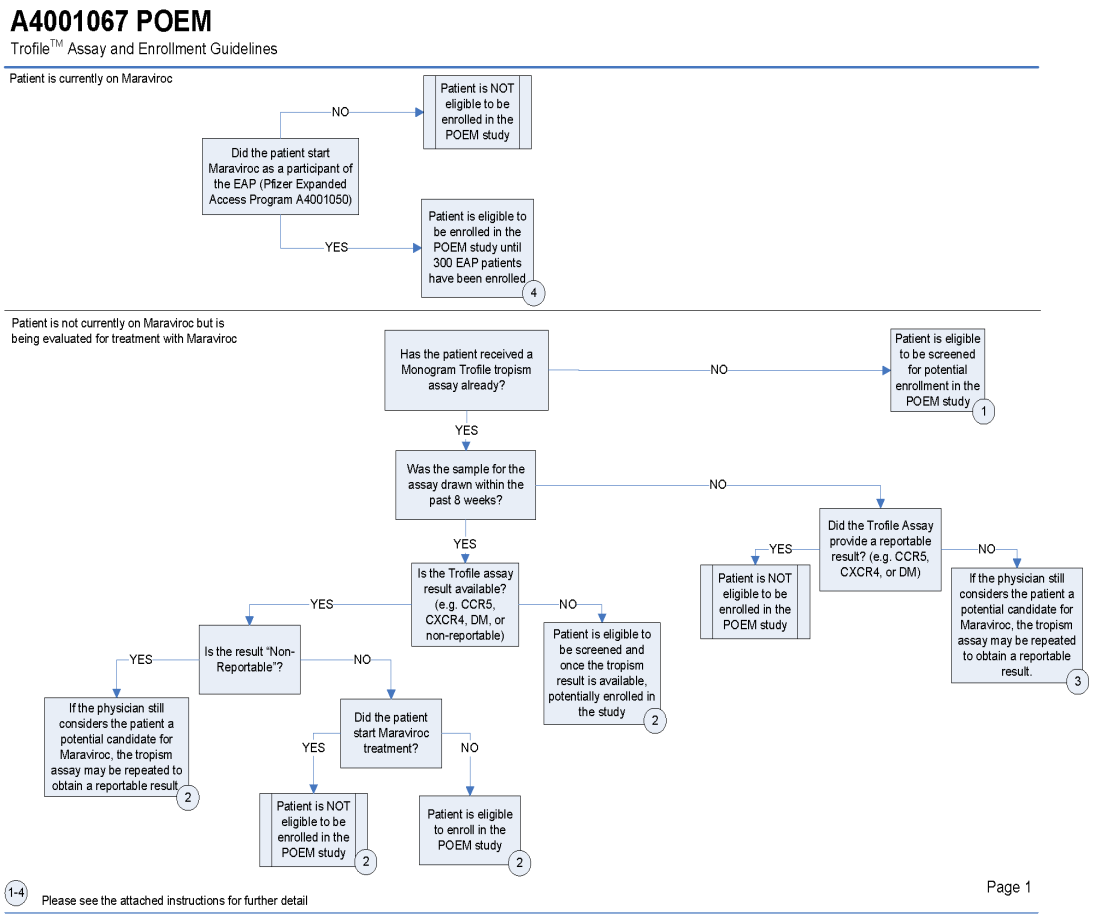
9. LIST OF APPENDICES

9.1. 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

9.2. Appendix 2: Enrollment Procedure



Detailed Eligibility Criteria

1

Patients being considered for treatment with maraviroc who have not received the Trofile™ assay yet:

These patients are eligible to be screened and enrolled in the POEM (A4001067) study. Please inform the patient about the study, obtain informed consent and send the sample to Monogram for the Trofile™ assay. Once the result becomes available, enroll the patient in the appropriate study arm.

2

A patient who has received the Trofile™ assay within 8 weeks prior to screening:

If the result of the test is not yet available, the patient is eligible to be screened and enrolled and a repeat Trofile™ assay is not necessary. Please inform the patient about the study and obtain informed consent. When the result becomes available, enroll the patient in the appropriate study arm, enter the viral tropism in the CRF and fax the report from Monogram to Kendle.

If the test result is already available and shows a reportable HIV tropism (i.e., CCR5, CXCR4 or dual/mixed tropic) the patient is eligible to enroll provided he or she has **not** yet started maraviroc. Inform the patient about the study, obtain informed consent and enroll the patient in the appropriate study arm, enter the viral tropism in the CRF and fax the report from Monogram to Kendle.

If the test result was non-reportable, but based on your clinical judgment you still consider him a potential candidate for maraviroc and would like to repeat the tropism assay to get a reportable result, you can screen and enroll the patient. Please inform the patient about the study, obtain informed consent and send the sample to Monogram for the Trofile™ assay. Enroll the patient in the appropriate study arm when the result becomes available.

Kendle Fax # 866-470-4465

3

A patient who received the Trofile™ assay more than 8 weeks prior to screening:

If the assay provided a reportable result (i.e.,CCR5, CXCR4 or dual/ mixed tropic HIV) this patient will **not** be **eligible** to be screened and enrolled regardless of exposure to maraviroc.

If the test result was non-reportable, but based on your clinical judgment you still consider him a potential candidate for maraviroc and would like to repeat the tropism assay to get a reportable result, you can screen and enroll the patient. Please inform the patient about the study, obtain informed consent and send the sample to Monogram for the Trofile™ assay. Enroll the patient in the appropriate study arm when the result becomes available.

4

A patient who is already exposed to maraviroc:

Patients who started taking maraviroc in the maraviroc expanded access program (EAP, A4001050) and are still continuing the drug at the time of screening will be eligible to enroll in POEM (A4001067). These patients will not need a repeat Trofile™ assay. Please inform the patient about the study and obtain informed consent. In the screening module of the CRF please complete the section on prior study participation with the relevant information. Please note that the FDA has allowed the inclusion of up to 300 such patients in A4001067 and we will inform you once that number is reached.

Patients who started maraviroc from any source other than the EAP (A4001050) are not eligible to enroll in POEM (A4001067). Please note that patients who started taking maraviroc in the Pfizer clinical trials A4001027 and A4001028 will be followed for long term safety under a separate program being run by Pfizer. These patients are not eligible to enroll in POEM (A4001067).

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9.3. 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 7^{th} and 12^{th} month, 20% between the 13^{th} and 18^{th} 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.

9.4. Appendix 4: Criteria for Safety Values of Potential Clinical Concern

Vital Signs

Pulse Rate	Supine/Sitting: <40 or >120 bpm Erect: <40 or >140
Blood Pressure	Systolic ≥30 mm Hg change from baseline in same posture Systolic <90 mm Hg Diastolic ≥20 mm Hg change from baseline in same posture Diastolic <50 mm Hg

[redacted]

[redacted]

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