Janssen Research & Development*

Epidemiology Study Protocol

Observational Cohort Study to Assess Rilpivirine (RPV) Utilization According to the European SmPC

Amendment INT-1

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NOTE

The outline of this template is consistent with the Guidelines for Good Pharmacoepidemiology Practices (GPP) and The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	06 SEP 2011

Amendments are listed beginning with the most recent amendment.

Amendment INT-1 (30 AUG 2013)

The overall reason for the amendment: The protocol was updated to remove the collection of data on the required intake of rilpivirine (RPV) with food, in view of the feedback obtained from the HIV cohorts that collecting these data within the Drug Utilization Study (DUS) is not considered feasible. Therefore, the effect of RPV intake with food on the risk of virologic failure will not be evaluated in the DUS. Furthermore, for the assessment of risk factors for virologic failure, the analytical method has been modified from a nested case-control study to a Poisson regression analysis further to the selection of EuroSIDA and in line with their proposed analysis plan. Additionally, the protocol was updated to expand the DUS to include 800 instead of 600 patients in the RPV and comparator arms and to specify EuroSIDA as the HIV cohort for implementation of the DUS.

Applicable Section(s)	Description of Change(s)
Rationale: The collection of data on the required intake of RPV with food was removed given feedback from the HIV cohorts that collecting these data within the DUS is not considered feasible due to logistical issues and data validity concerns. Therefore, the effect of RPV intake with food on the risk of virologic failure will not be evaluated in the DUS. It was agreed with the CHMP that data on food intake with RPV-containing regimens would be collected through another study.	
Synopsis; 1.1 Background; 5 Limitations	Text on collection of data on the required intake of RPV with food was deleted.
Synopsis; 1.1 Background; 1.3.1 Primary Objectives; 2.1 Study Design; 4.3 Analyses; 4.5 Statistical Analysis Plan; 5 Limitations	Evaluation of the effect of RPV intake with food on virologic failure was removed.

Applicable Section(s)	Description of Change(s)
Rationale: After methodological discussions with the EuroSIDA cohort researchers, the assessment of risk factors associated with virological failure among those treated with RPV-containing regimens was changed from a nested case-control study to Poisson regression analysis. The EuroSIDA cohort provides longitudinal data and captures all the variables of interest (except intake with food, see above) to assess the rate of virologic failure with respect to potential predictors. A Poisson regression model optimizes the analysis of the data and provides maximal statistical power. In a case-control study, the process of matching cases to controls on various factors can prove limiting when the population is small. Further, any factors that are matched on cannot be analyzed in relation to risk of virologic failure. In a Poisson regression analysis, rather than matching cases and controls, all patients treated with RPV are included and patient demographics, clinical characteristics, and length of time enrolled in the cohort are included as covariates in the model to adjust for confounding. This provides maximal statistical power by including the total RPV population while also being able to assess the risk of virologic failure according to all factors included in the model by comparing the incidence of virologic failure in each subgroup. This is of particular benefit when the likely number of cases (i.e. virologic failures) is small. Utilization of a Poisson regression analysis rather than a nested case-control study equally allows for the planned assessment of risk factors associated with virologic failure among those treated with RPV-containing regimens.	
Title; Synopsis; 1.1 Background; 2.1 Study Design; 2.2 Study Design Rationale; 4.1 Sample Size; 4.2 Measurement; 4.3 Analyses; 4.5.3 Additional analysis on virologic failure	Text was modified to remove the nested-case control study and reflect the change in analysis of risk factors for virologic failure to Poisson regression.
Rationale: As was agreed with the CHMP, the target sample size in the DUS has been expanded from 600 to 800 patients in both the RPV and efavirenz (EFV) treatment groups to assess more thoroughly the adherence to the EU SmPCs and to follow-up on any development of resistance in real-life settings.	
Synopsis; 2.1 Study Design; 3.1 Patient Selection; 7.2.1 Study Completion	Text was modified to reflect the expansion of sample size from 600 to 800 patients in each treatment group.
4.1 Sample Size	Study precision table was modified to show proportion of appropriate use and associated 95% CI error rate with the revised sample size of 800 patients.
Rationale: An evaluation of several HIV cohorts in Europe for their suitability for meeting the study objectives was conducted and the EuroSIDA study cohort was selected for implementation of the DUS.	
Synopsis; 1.1 Background; 1.2 Overall Rationale of Study; 2.1 Study Design; 2.2 Study Design Rationale; 3.1 Patient Selection; 3.1.1 Inclusion Criteria; 3.1.2 Exclusion Criteria	Text was modified to clarify that the DUS will be implemented in EuroSIDA.

Applicable Section(s)	Description of Change(s)
3.1.3 Data Sources	Given the decision to implement the DUS in EuroSIDA, the list of HIV cohorts initially assessed for feasibility was deleted. Description of the EuroSIDA study cohort was added.
Rationale: In view of the Committee for Medicinal Products for Human Use (CHMP) request to assess whether RPV-containing regimens are used in accordance with their approved Summaries of Product Characteristics (SmPCs), clarification has been added regarding the inclusion of only those countries in the EuroSIDA cohort where RPV has been granted marketing authorization through the centralized procedure.	
3.1.3 Data Sources	Text was added to clarify that only those countries in the EuroSIDA cohort which are member states of the EU/European Economic Area will be included in the DUS.
Rationale: Clarification was added regarding data on antiretroviral (ARV) treatment adherence in the EuroSIDA cohort database. Treatment adherence data in EuroSIDA are collected qualitatively and graded as "Poor: <70%", "Excellent: >95%" or "Anything in between: 70%-95%". According to the EuroSIDA cohort researchers, these data will only be available for a subset of patients and data quality and quantity will vary by geographic region. If sufficient ARV treatment adherence data accrue over the course of the DUS, ARV treatment adherence will be assessed as a potential risk factor for virologic failure; otherwise, available data will be summarized descriptively for RPV and EFV treatment groups.	
3.1.3 Data Sources; 4.2.3 Potential Confounders	Description of ARV treatment adherence data in EuroSIDA was added.
4.2.3 Potential Confounders; 4.5.3 Additional analysis on virologic failure; 5 Limitations	Text was modified to clarify that ARV treatment adherence will be included in the assessment of risk factors for virologic failure if sufficient data are available.
Rationale: Updates were made to Outcome Definition and Potential Confounders in line with the EuroSIDA definitions, data collection, and analysis methods.	
4.2.2 Outcome Definition	Definition of virologic failure was changed to the definition used in the EuroSIDA cohort and as defined by the European AIDS Clinical Society. Drug resistance to NRTIs, in addition to NNRTIs, was added as an outcome to be captured. Clarification was provided that concomitant medication refers to only those medications contraindicated for RPV as per the SmPC.
4.2.3 Potential Confounders	List of covariates was updated with the patient demographic and clinical characteristics specified for inclusion by EuroSIDA: age, sex, ethnicity, geography, weight, CD4 cell count, HIV viral load, route of HIV transmission, coinfection with hepatitis B/C, prior AIDS diagnoses, prior non-AIDS diagnoses, hypertension, diabetes, chronic kidney disease, smoking, length of time enrolled in EuroSIDA, and ARV treatment adherence.

Applicable Section(s)	Description of Change(s)
	Depression was deleted from list of covariates as it is not captured in EuroSIDA.
Rationale: Minor administrative and textual changes were made.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved in the European Union (EU) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a baseline viral load ≤ 100,000 HIV-1 ribonucleic acid (RNA) copies/mL. RPV is available as two formulations on the European market: a single agent tablet, marketed by Janssen-Cilag International NV (Edurant®), and a single tablet regimen (STR) containing emtricitabine (FTC)/RPV/tenofovir disoproxil fumarate (TDF), marketed by Gilead Sciences International Ltd (Eviplera®).

The Committee for Medicinal Products for Human Use (CHMP) has requested further assessment of the development of resistance with RPV-containing regimens and whether RPV-containing regimens are used in accordance with their approved Summaries of Product Characteristics (SmPCs).

The development of resistance with RPV-containing regimens and the utilization of RPV-containing regimens according to their SmPCs will be assessed through a drug utilization study (DUS) conducted in the EuroSIDA cohort. Additionally, the DUS will provide context to the observed rates of virologic failure and development of resistance for patients initiating RPV treatment by describing the treatment outcomes in a control group of patients initiating efavirenz (EFV). The relative risk of virologic failure and emergence of resistance-associated mutations (RAMs) after initiating RPV-containing regimens will be estimated separately by comparing the incidence rates of virologic failure and RAMs among RPV-treated patients to the incidence of virologic failure and RAMs among EFV-treated patients. For all study objectives, frequency and rates will be reported for the RPV and EFV-treated groups separately, as well as for RPV relative to EFV.

The objectives of the DUS are to describe the following in the context of routine clinical practice:

Primary objectives:

- To describe the proportion of patients treated with RPV-containing regimens in accordance with their SmPCs
  The proportion of patients treated with RPV-containing regimens in accordance with their SmPCs will be described by estimating a proportion separately for each recommendation of patient treatment. The denominator for each proportion will consist of the number of all patients initiating RPV-containing regimens included in the study. Proportions will be estimated separately using the following numerators:
    - The number of patients naïve to HIV treatment regimens
    - The number of patients with documented pre-treatment screening for ARV RAMs
    - The number of patients initiating RPV-containing regimens with a baseline viral load ≤ 100,000 HIV-1 RNA copies/mL
- To describe treatment emergent RAMs in patients treated with RPV or EFV-containing regimens
- To describe virologic failure in patients treated with RPV or EFV-containing regimens

Secondary objectives:

- To describe the demographic characteristics, comorbidities, and medical condition of patients initiating RPV or EFV treatment

- To describe antiretroviral (ARV) treatment status (naïve/experienced) of patients prior to initiating RPV or EFV treatment
- To describe prior use of ARV treatment, if any, of patients initiating RPV- or EFV-containing regimens
- To describe the frequency of pre-treatment RAMs for RPV and EFV among patients subsequently initiating RPV or EFV treatment respectively
- To describe viral load at start of RPV or EFV treatment
- To describe viral load over the course of RPV or EFV treatment
- To describe HIV-treatment regimens of patients initiating RPV- or EFV-containing regimens and changes over the course of RPV or EFV treatment
- To describe concomitant medications (only those contraindicated for RPV as per the SmPC) of patients initiating RPV-containing regimens and changes over the course of RPV treatment
- To describe reasons for switch of ARV treatment
- To describe adverse events over the course of RPV or EFV treatment

A DUS of HIV-1 positive patients captured in the EuroSIDA cohort initiating RPV –containing regimens will be used to meet the study objectives. HIV cohorts, such as EuroSIDA, provide detailed longitudinal information on patient demographics, HIV treatment regimens, treatment status (naïve/experienced), duration of therapy, clinical events, reason for discontinuation of HIV treatment, and adverse events.

Additionally, a comparator cohort of EFV-treated patients will be included to provide contemporary context to utilization and outcomes observed within the RPV-treated group. The EFV treatment group will further elucidate which patient characteristics are more likely to influence health-care providers to channel patients to EFV- or RPV- containing regimens. Additionally, the EFV treatment group will provide a better understanding of the observed rates of virologic failure, resistance patterns, and prescribing factors observed within the RPV-treatment group.

The DUS will identify a minimum of 800 patients newly initiating RPV-containing regimens and 800 patients newly initiating EFV-containing regimens and captured in the EuroSIDA cohort. Exposure to RPV-containing regimens will be identified by treatment records for the single tablet regimen of FTC/RPV/TDF (Eviplera®) or the single agent tablets of RPV (Edurant®) among the patient data. Exposure to EFV will be identified by the treatment records for the available formulations of EFV in patient data. The sample size targets will produce an error rate of no more than 5% for the proportions estimated. A minimum of 800 RPV-treated patients will be included in the DUS to assess the proportion of appropriate use of RPV-containing regimens. The study period will start at the date of market availability of RPV-containing products in the first of the participating countries and will end when in total 800 patients from each treatment group have been included in the study and followed up for 12 months, until virologic failure, loss to follow-up or death, whichever occurs first.

An evaluation of appropriate use will be conducted through an analysis describing and summarizing the treatment patterns and use of RPV-containing regimens. Treatment with RPV- or EFV-containing regimens will be summarized by patient demographics and clinical characteristics. In addition, the details of RPV-containing regimens use patterns will be described, including duration of use, persistence of therapy, and usage of other HIV treatments. This analysis will describe and summarize the utilization patterns of RPV-containing regimens with respect to viral load, CD4 counts, pre-treatment resistance testing, HIV treatment status (naïve/experienced), prior HIV treatment regimens, concomitant medications, and comorbidities. The analysis will ascertain the number of patients initiating treatment with RPV-containing regimens and the proportion of patients treated in accordance with the SmPCs of RPV-containing regimens. Treatment use will be summarized by patient demographics and potential confounders.

Incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance will be calculated for the RPV and EFV-treated patients, separately. The three primary event rates of interest (incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance) will be analyzed in 3 separate sets of analyses. Additional descriptive analyses will include incidence rates for each drug product calculated by dividing the number of events by the total person-exposure time and expressed as the number of events per person-year, and 95% confidence intervals. Relative risks comparing the RPV-containing regimens with EFV-containing regimens and 95% confidence intervals will be calculated and appropriate stratified analyses will be conducted for virologic failure and emergence of treatment resistance. Adjustments for imbalances between the treatment groups before receiving the first dose of RPV or EFV-containing regimens will be applied using accepted methods based on sample size availability and the observed overlap of key patient characteristics based on propensity score construction.

Risk factors associated with virologic failure among those treated with RPV-containing regimens will be assessed using a multivariable Poisson regression model. This analysis will include all patients treated with RPV and adjust for confounding factors by including patient demographics, clinical characteristics and length of time enrolled in EuroSIDA as covariates in the model. This provides maximal statistical power while also being able to assess the risk of virologic failure according to all factors included in the model by comparing the incidence of virologic failure in each subgroup.

ABBREVIATIONS

AACTG	Adult AIDS Clinical Trials Group
ARCA	Antiretroviral Resistance Cohort Analysis database
ART	Antiretroviral therapy
ARV	antiretroviral
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CHIC	Collaborative HIV cohort
CHMP	The Committee for Medicinal Products for Human Use
CI	confidence interval
CoRIS	Cohort of Spanish AIDS Research Network
DUS	Drug Utilization Study
EC	Ethics Committee
EFV	efavirenz
EU	European Union
FHDH	French Hospital Database on HIV
FTC	emtricitabine
GPP	Good Pharmacoepidemiology Practice
HA	Health Authority
HAART	highly active antiretroviral therapy
HIV-1	human immunodeficiency virus type 1
IRB	Institutional Review Board
JRD	Janssen Research and Development LLC.
MAR	missing at random
MCAR	missing completely at random
MNAR	missing not at random
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OR	Odds ratio
PI	protease inhibitor
PBRER	Periodic Benefit Risk Evaluation Report
PSUR	Periodic Safety Update Report
RAM	resistance associated mutation
RMP	Risk Management Plan
RNA	ribonucleic acid
RPV	rilpivirine
SD	standard deviation
SERAD	Self-Reported Adherence
SHCS	Swiss HIV Cohort Study
SHCS-AQ	Swiss HIV Cohort Study Adherence Questionnaire
SMAQ	simplified medication adherence questionnaire
SmPC	Summary of Product Characteristics
STR	Single tablet regimen
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
TDF	tenofovir disoproxil fumarate
TDR	transmitted drug resistance
VAS	visual analog scale

1. INTRODUCTION

1.1. Background

Rilpivirine (RPV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of HIV-1 infection in antiretroviral treatment-naïve adult patients with a baseline viral load ≤100,000 HIV-1 ribonucleic acid (RNA) copies/mL in the European Union (EU). RPV is available as two formulations on the European market: a single agent tablet, marketed by Janssen-Cilag International NV (Edurant®), and a single tablet regimen (STR) containing emtricitabine (FTC)/RPV/tenofovir disoproxil fumarate (TDF), marketed by Gilead Sciences International Ltd (Eviplera®). The Committee for Medicinal Products for Human Use (CHMP) has requested further assessment of the development of resistance with RPV-containing regimens and whether RPV-containing regimens are used in accordance with their approved Summaries of Product Characteristics (SmPCs). The development of resistance with RPV-containing regimens and the utilization of RPV-containing regimens according to their SmPCs will be assessed through a drug utilization study (DUS) conducted in the EuroSIDA cohort. Additionally, the DUS will provide context to the observed rates of virologic failure and development of resistance for patients initiating RPV treatment by describing the treatment outcomes in a control group of patients initiating efavirenz (EFV). The relative risk of virologic failure and emergence of resistance-associated mutations (RAMs) after initiating RPV-containing regimens will be estimated separately by comparing the incidence rates of virologic failure and RAMs among RPV-treated patients to the incidence of virologic failure and RAMs among EFV-treated patients.

Several factors have been shown to be associated with virological response to antiretrovirals (ARV) for the treatment of HIV-1, including the degree of immunodeficiency and level of plasma HIV RNA when therapy is initiated, antiretroviral experience, drug resistance, and type of and adherence to the therapeutic regimen (Hull, 2009).

Virological response to highly active antiretroviral therapy (HAART) regimens has been evaluated among patients enrolled in large, observational HIV cohorts. These studies have included evaluations of NNRTI and protease inhibitor (PI)-

containing regimens (Paredes, 2000; Cozzi-Lepri, 2002) as well as short term and long term virological response when treated with NNRTI or PI-based HAART regimens (Mocroft, 2006). A few cohort studies have specifically examined virological failure among patients initiating nevirapine (NVP)-containing regimens or EFV-containing regimens. Phillips and colleagues conducted a study among 2203 patients in EuroSIDA who began a regimen with nevirapine or efavirenz after July 1997 (Phillips, 2001). A total of 1325 patients initiated NVP and 878 EFV. During a median of 8 months follow-up, 669 patients experienced virological failure giving an overall rate of 0.48 per year (0.83 per year if excluding those in first 6 months of follow-up who had baseline viral load >500 copies/ml). A total of 505 people on a NVP regimen experienced virological failure compared with 164 people on an EFV regimen, giving incidence rates of 0.55 per person-year and 0.35, respectively. A more recent EuroSIDA analysis examined virological outcome and drug resistance in 759 patients starting NNRTI-containing regimens (Bannister, 2008). A total of 287 (78.3%) of the 389 NVP patients and 168 (45.4%) of the 370 EFV patients experienced virological failure. NNRTI-resistant HIV was detected in 3% of patients at baseline. Out of the 131 patients still on an NNRTI and with resistance test results available at time of virological failure, NNRTI resistance was detected in 86% of patients and was similar between groups. The high levels of NNRTI resistance suggest that these drugs fostered selection pressure, and that patients had actually adhered to their regimens.

Several large HIV cohort databases have investigated the prevalence of transmitted drug resistance (TDR). Among 525 chronically infected treatment-naïve patients in the EuroSIDA cohort, the overall prevalence of TDR was 11.4% from 1996-2004 (Bannister, 2008). In the German HIV-1 Seroconverter cohort of 1276 patients, the overall prevalence of TDR was 12.4% from 1997 through 2007. Nucleoside reverse transcriptase inhibitor (NRTI) associated resistance was identified most frequently (6.3%), followed by NNRTI resistance (2.4%) and PI resistance (2.1%) (Bartmeyer, 2010). In the Swiss HIV cohort of 822 newly infected patients identified from 1996-2005, the overall prevalence of TDR was 7.7% for any ARV drug, 5.5% for NRTIs, 1.9% for NNRTIs, and 2.7% for PIs (Yerly, 2007). A recent investigation by the UK Collaborative Group in HIV drug resistance reported a decline in the rate of

TDR in treatment-naïve recently and chronically infected patients from around 14% in 2001-2002 to around 8% by the end of 2004 (Dunn, 2007).

The level of adherence to antiretroviral therapy (ART) is one of the critical factors in achieving viral suppression, avoiding viral rebound, increasing CD4 cell counts, and minimizing the risk of development of AIDS-defined illnesses that may result in death among HIV-infected patients on ART (Cambiano, 2010). Patient self-reports via questionnaires or interviews are the most frequently used measure of treatment adherence to HAART. More quantitative measures exists, such as electronic monitoring devices, pill counts, and pharmacy prescription refill monitoring; however use of these methods is limited by high cost, labor intensity, and other issues (Nieuwkerk and Oort, 2005). Self-report questionnaires that have been used in the clinical setting and validated include the simplified medication adherence questionnaire (SMAQ), the visual analog scale (VAS), the Adult AIDS Clinical Trials Group (AACTG) questionnaire, and the Self-Reported Adherence (SERAD) (Deschamps, 2008). While self-reports offer significant correlation with viral load, this measurement method tends to underestimate nonadherence. An adherence questionnaire (SHCS-AQ) was introduced into follow-up of the Swiss HIV Cohort Study (SHCS) in July 2003 to assess overall doses missed and drug holidays over the past 4 weeks. The SHCS-AQ has been validated in a small study that compared the European HIV treatment questionnaire, a visual analog scale, and electronic monitoring. Using virological failure as the gold standard, the SHCS adherence questionnaire in the validation study performed slightly better than either electronic monitoring or a combination of the SHCS-AQ and a VAS with a sensitivity of 88% and a specificity of 79% (Deschamps, 2008). Despite its importance, there are no readily available measures of treatment adherence beyond notes of issues with treatment adherence given as the reason for treatment failure ordinarily used in routine clinical practice, nor are there methods available for comparison of adherence levels across large patient populations captured in the multiple HIV cohorts.

In summary, a DUS using data from the EuroSIDA cohort will be conducted in order to address the CHMP concerns on the potential for development of virologic resistance and potential for improper prescribing or use (according to

the SmPC). HIV cohorts, such as EuroSIDA, have a demonstrated history of assessing virologic failure, RAMs, and associated risk factors. This DUS will provide significant real-world data on (amongst other parameters) ARV drug resistance, frequency of resistance testing, viral load at the start of treatment, prior use of ARV treatment, reasons for switch of ARV treatment, adverse events, concomitant medications (only those medications contraindicated for RPV as per the SmPC), and comorbidities. Additionally, risk factors associated with virologic failure among those treated with RPV-containing regimens will be assessed.

1.2. Overall Rationale for the Study

The CHMP has requested an assessment of the use of RPV-containing regimens by prescribers in accordance with their SmPCs. The development of resistance with RPV-containing regimens and the utilization of RPV-containing regimens according to their SmPCs will be assessed through a DUS conducted in the EuroSIDA cohort.

1.3. Study Objectives

1.3.1. Primary Objectives:

The primary objectives were specifically chosen to meet the CHMP request to assess appropriate use of RPV-containing regimens. For all primary objectives, frequency and rates will be reported separately for the RPV and EFV-treated groups.

- To describe the proportion of patients treated with RPV-containing regimens in accordance with their SmPCs. The proportion of patients treated with RPV-containing regimens in accordance with their SmPCs will be described by estimating a proportion separately for each recommendation of patient treatment. The denominator for each proportion will consist of the number of all patients initiating RPV-containing regimens included in the study. Proportions will be estimated separately using the following numerators:
    - The number of patients naïve to HIV treatment regimens
    - The number of patients with documented pre-treatment screening for ARV RAMs

- The number of patients initiating RPV-containing regimens with a baseline viral load ≤ 100,000 HIV-1 RNA copies/mL

- To describe treatment emergent RAMs in patients treated with RPV or EFV-containing regimens

- To describe virologic failure in patients treated with RPV or EFV-containing regimens

1.3.2. Secondary Objectives:

The secondary objectives were specifically chosen to assist in meeting the CHMP request to assess appropriate treatment of patients with RPV-containing regimens in accordance with their SmPCs or to provide context to events observed within the RPV treatment group. For all secondary objectives, frequency and rates will be reported separately for the RPV and EFV-treated groups, as well as for RPV relative to EFV.

- To describe the demographic characteristics, comorbidities, and medical condition of patients initiating RPV or EFV treatment

- To describe ARV treatment status (naïve/experienced) of patients prior to initiating RPV or EFV treatment

- To describe prior use of ARV treatment, if any, of patients initiating RPV- or EFV-containing regimens

- To describe the frequency of pre-treatment RAMs for RPV and EFV among patients subsequently initiating RPV or EFV treatment respectively

- To describe viral load at start of RPV or EFV treatment

- To describe viral load over the course of RPV or EFV treatment

- To describe HIV-treatment regimens of patients initiating RPV- or EFV-containing regimens and changes over the course of RPV or EFV treatment

- To describe concomitant medications (only those medications contraindicated for RPV as per the SmPC) of patients initiating RPV-containing regimens and changes over the course of RPV treatment
- To describe reasons for switch of ARV treatment
- To describe adverse events over the course of RPV or EFV treatment

2. OVERVIEW OF STUDY DESIGN

2.1. Study Design

This DUS will be implemented using longitudinal data collected by the EuroSIDA study group. A minimum of eight hundred patients will be entered into the study based on the prescribing of RPV-containing regimens, either as a single agent tablet or as an STR. An additional minimal number of 800 patients will be entered into the study based on the prescribing of EFV-containing regimens. Retrospective data available from the EuroSIDA cohort will be used to describe patient clinical characteristics prior to receipt of RPV- or EFV-containing regimens.

Data will be collected in an observational manner such that the management of the patient is determined by the patient and the caregiver and not influenced by the DUS protocol. The DUS will evaluate care as it is provided. It will capture data on a heterogeneous population treated with RPV- or EFV-containing regimens in a comprehensive manner without exclusions to assure representativeness of the populations treated with RPV- or EFV-containing regimens.

All patients initiating RPV treatment will be eligible for inclusion in the DUS. Patients initiating EFV treatment will also be eligible for inclusion in the comparator group based on the date of EFV treatment initiation. Relevant Institutional Review Board (IRB)/Ethics Committee (EC) and Health Authority (HA) approvals will be secured prior to initiating the study.

2.2. Study Design Rationale

A DUS design using existing HIV cohort(s) was chosen to assess proper prescribing and effectiveness of RPV-containing regimens in routine clinical

practice in Europe and to provide the greatest access to HIV prescribers. HIV cohorts operating in Europe and using electronic medical record-based databases have proven to be an important resource for post-marketing observational studies in HIV. These studies are generally not subject to additional informed consent and may be completed expeditiously.

An important strength of HIV cohorts, such as EuroSIDA, relevant to the proposed DUS is their ability to evaluate conditions under which HIV drugs are prescribed in large numbers of patients. Data from these cohorts are useful in evaluating treatment patterns and appropriateness of treatment. The design was also chosen due to the robust patient numbers available within the HIV cohorts in Europe that capture the experience of patients with HIV. Multiple HIV cohorts were evaluated for inclusion in the DUS. The EuroSIDA cohort was selected to meet the study objectives and sample size requirement of 800 patients exposed to RPV-containing regimens and 800 patients exposed to EFV-containing regimens.

EuroSIDA and other HIV cohorts have been established in Europe specifically to facilitate research in HIV infected patients. Data salient to meeting the CHMP request are available within the EuroSIDA cohort and do not require additional data collection or interaction with physicians or patients. It is important to note that one of the reasons these cohorts were established was because traditional resources for patient identification were insufficient in identifying HIV infected patients due to HIV infected patients seeking treatment outside of payer systems and from health care providers other than general practitioners.

HIV cohorts, such as EuroSIDA, capture care as given and are generalizable to the population likely to be exposed to RPV-containing regimens. The proposed design does not interfere with the physician's decision regarding what to prescribe for the individual patient. Patients receive the drug in everyday practice and are not a highly selected group of patients who may not be representative of the 'real-world' population. The major strength of using HIV cohorts, such as EuroSIDA, for a DUS is that the protocols for data collection have been specifically designed for HIV research (www.hicdep.com). Data are systematically collected on all clinical aspects salient to HIV care. These data

include laboratory variables for HIV viral load, CD4 counts, drug resistance information, concomitant medications, adverse events, and detailed information on HIV treatment. Additionally, patients are followed in the cohort until death or loss to follow-up from the cohort. Data are collected independent of the proposed DUS and are not subject to physician recall or potential biases involving self-reported drug prescribing or patient management. These data are collected longitudinally and in a time-dependent manner so that variation in time-dependent variables can be assessed. This is particularly important when considering the outcome of virologic failure and potential factors contributing to loss of virologic control. Finally, these data are collected electronically and do not place additional burden on the treating physician or patient.

Additionally, a comparator group of EFV-treated patients will be included in this study to provide contemporary context to utilization and outcomes observed within the RPV-treated group. The EFV-treated group will provide insight into patient characteristics likely to influence health-care providers to channel patients to EFV-containing regimens or to RPV-containing regimens. Additionally, the EFV treatment group will provide a better understanding of the observed rates of virologic failure and prescribing factors observed within the RPV-treated group.

3. STUDY POPULATION

3.1. Patient Selection

The study population will be drawn from the population of patients enrolled in the EuroSIDA cohort. Eligible patients must be new users of RPV-containing regimens at the initiation of therapy (inception cohort). Patients eligible for the comparator cohort must be new users of EFV-containing regimens. Data will be included for analysis based on the availability of RPV-containing regimens in each country. Patients in the EFV-treated group will be eligible for selection if they initiate an EFV-containing regimen after the availability of a RPV-containing regimen is observed within the cohort. The study period will start at the date of market availability of RPV-containing regimens in the first of the participating countries and will end when in total a minimum of 800 patients from each treatment group (RPV and EFV) have been included in the study and

followed for 12 months, until virologic failure, loss to follow-up, or death, whichever occurs first.

3.1.1. Inclusion Criteria

Patients who initiate therapy with RPV- or EFV-containing regimens during the study period will be identified. Initiation of therapy is defined as first initiation of RPV- or EFV-containing regimens documented in the EuroSIDA cohort. Patients will be included in the study if they meet all of the following criteria:

- Have documented enrollment in the EuroSIDA cohort database prior to the start of RPV or EFV-treatment regimens;
- Have documented initiation of RPV- or EFV-containing regimens

3.1.2. Exclusion Criteria

No exclusion criteria will be applied in this study other than those specific to the EuroSIDA cohort.

3.1.3. Data Source(s)

The DUS will be implemented using data collected by the EuroSIDA study group. The EuroSIDA study is a prospective, observational cohort of 18,722 HIV-1 infected patients in 108 centers across 33 European countries, Israel and Argentina. The patients included are enrolled to be representative of the patients followed in the various clinical centers that participate in the cohort. Only those countries in the EuroSIDA cohort which are member states of the EU/European Economic Area will be included in the DUS. EuroSIDA is one of the largest pan-European cohorts and has collected data since 1993. Information is collected on a standardized data collection form every 6 months, including CD4 counts and viral loads measured since the last follow-up, starting and stopping dates of all antiretroviral drugs, and concomitant medications. Dates of diagnoses of all AIDS-defining illnesses are also recorded, including those made subsequent to the initial diagnosis, using the 1993 clinical definition of AIDS from the Centers for Disease Control and Prevention (CDC). EuroSIDA has resistance testing data from two sources stored centrally. Some clinical centers submit resistance data directly by electronic data transfer or paper forms from testing performed locally during normal clinical care, although the

quantity of this data is relatively limited and varies greatly by geographic region. Other resistance data have been collected from samples in the central plasma repository when study specific research questions required it. Antiretroviral treatment adherence data in EuroSIDA are collected qualitatively. Patients that have data have their adherence in the period prior to the latest follow-up graded as "Poor: <70%", "Excellent: >95%", or "Anything in between". This data is available only for a subset of patients and data quality and quantity varies by geographic region.

4. STATISTICAL METHODS

4.1. Sample Size and Study Precision

The sample size targets will produce an error rate of no more than 5%. A minimum of 800 patients exposed to RPV-containing regimens will be included in the DUS to assess the proportion of appropriate use of RPV formulations. The error rate under these assumptions and an observed proportion of appropriate use of 95% is estimated at +/- 0.02.

Proportion of appropriate use (%)	95% CI error (+/-) with 800 patients
70	0.03
75	0.03
80	0.03
85	0.02
90	0.02
95	0.02

4.2. Measurement

4.2.1. Exposure Definition and Measures

Exposure to RPV will be determined by the presence of treatment records for the STR of FTC/RPV/TDF or single agent of RPV among patient data. The baseline date for exposure follow-up (index date) for a patient within a given treatment group will be defined by first initiation of RPV- or EFV-containing regimens as captured in the patient data. Duration of exposure will be based on start and stop dates for each drug. Switches from one drug to another will be captured and time on drug will be defined by the exposure periods. The total length of exposure to a given drug will be the time between start and stop periods of exposure to the same drug.

4.2.2. Outcome Definition and Measures

Outcome definitions for the DUS will include:

- HIV viral load prior to initiating RPV- or EFV-containing regimens as well as over the course of therapy
- Virological failure time point to be defined as the latter of 2 consecutive HIV viral load measurements > 50 copies/ml ≥6 months after starting therapy. As defined by the European AIDS Clinical Society (http://www.europeanaidsclinicalsociety.org/)
- HIV treatment status (naïve/experienced) at RPV or EFV treatment initiation
- Prior use of ARV treatment, if any
- NNRTI and NRTI drug resistance at RPV or EFV treatment initiation as well as over the course of therapy
- Proportion of patients who have resistance testing prior to initiating RPV or EFV therapy as well as over the course of therapy
- Concomitant medications (only those medications contraindicated for RPV as per the SmPC) prior to initiating RPV as well as over the course of therapy

- Comorbidities prior to initiating RPV or EFV therapy
- Reason for discontinuation of RPV- or EFV-containing regimens
- Reason for switch of ARV treatment
- Adverse events over the course of RPV or EFV therapy

4.2.3. Potential Confounders and Effect Modifiers

Potential confounders and effect modifiers will be collected from the databases and assessed to determine their association with the outcomes of interest. These covariates will be used to perform adjusted analyses and to describe the treatment groups. Patient factors to be considered will include, but are not limited to, demographics, comorbidities and concomitant medications that might influence appropriate use.

- Age
- Sex
- Ethnicity
- Geographic region
- Weight or BMI
- CD4 count at treatment initiation and at treatment failure
- Viral load at treatment initiation
- Route of HIV infection
- Co-infection with hepatitis B/C
- Prior AIDS and non-AIDS diagnoses
- Hypertension
- Diabetes
- Chronic kidney disease
- Smoking
- Length of time enrolled in EuroSIDA

- Antiretroviral treatment adherence, if available. Data is collected qualitatively in EuroSIDA and graded as "Poor: <70%", "Excellent: >95%" or "Anything in between: 70%-95%".

4.2.4. Length of Follow-up

Each patient will be followed for 12 months from the initiation of RPV- or EFV-containing regimens, or until death, loss to follow-up within the cohort, or virologic failure, whichever occurs first. Time varying variables will be recorded at each patient visit.

4.3. Analyses

4.3.1. Descriptive Analysis

This DUS is descriptive in nature and frequency and rates of virologic failure, baseline resistance, and treatment emergent resistance will be reported separately for the RPV and EFV-treated groups.

4.3.2. Specific Comparisons

Specific comparisons will be made with respect to patient clinical characteristics, rates of virologic failure, baseline resistance, and treatment emergent resistance between the RPV- and EFV-containing regimen treatment groups.

4.4. Missing Data Handling

An evaluation of missing data will be conducted to assess the assumptions under which inference is valid. Missing data will be categorized into: missing completely at random (MCAR) in which there is no difference in subjects with missing data and those with complete data; missing at random (MAR) in which missing data are based on known or observed values of the collected variables, but not unmeasured data; and missing not at random (MNAR) where missing data is dependent on variables not measured. The evaluation will consist of comparing the distribution of the observed variables for patients with complete data with the distribution of observed variables for patients with missing data. Strategies for managing missing data may include limiting the analysis to patients with complete data or missing data imputation to estimate the value of the missing data.

4.5. Statistical Analysis Plan

4.5.1. Analysis of Baseline Characteristics

Baseline characteristics including demographics, medical history and use of medications at cohort entry will be described separately for the RPV and EFV-treated groups. The analysis will report the frequency distribution (number and percentage of patients) for categorical variables and descriptive statistics (median, mean, standard deviation [SD]) for continuous variables. Descriptive statistics will be used to evaluate and compare the baseline characteristics of the treatment groups and analyze the prescribing patterns of RPV- or EFV-containing regimens. Characteristics to be analyzed will be covariates and all potential confounding factors listed in Section 4.2.3, if data are available.

4.5.2. Analysis of Appropriate Use

This analysis will describe and summarize the use of RPV- or EFV-containing regimens. The analysis will ascertain the number of patients exposed to each regimen. Treatment with RPV- or EFV-containing regimens will be summarized by patient demographics (age, sex, geography) and clinical characteristics (viral load, CD4 counts, pre-treatment resistance testing, adverse events, HIV treatment status [naïve/experienced], prior HIV treatment regimens, concomitant medications [only those contraindicated for RPV as per the SmPC], comorbidities, and route of infection). In addition, the details of RPV and EFV-containing regimens use patterns will be described including duration of use, persistence of therapy, and usage of other HIV treatments.

The analysis will ascertain the number of patients initiating RPV-containing regimens and the proportion of patients treated in accordance with RPV products' SmPC. Proportions will be estimated separately for each recommendation of patient treatment. The denominator for each proportion will consist of the number of all patients initiating RPV-containing regimens included in the study. Proportions will be estimated separately using the following numerators:

- The number of patients naïve to HIV treatment regimens
- The number of patients with documented pre-treatment screening for ARV RAMs

- The number of patients initiating RPV-containing regimens with a baseline viral load ≤ 100,000 HIV-1 RNA copies/mL

Proper use will be summarized by patient demographics and potential confounders.

4.5.3. Additional analysis on virologic failure and emergence of resistance

Additional analyses will be conducted to evaluate outcomes within twelve months of initiating RPV or EFV-containing regimens. Specific analyses to be conducted are as follows:

- The proportion of patients with virologic failure within twelve months of initiation of RPV- or EFV-containing regimens
- The proportion of patients with treatment emergent NNRTI or NRTI RAMs within 12 months of initiation of RPV- or EFV-containing regimens

The decision to prescribe RPV-containing regimens or EFV-containing regimens will be influenced by the treatment recommendations, patient characteristics, the prescriber assessment of the health status and risk profile, and the local policies and formularies. Thus, when planning to compare rates of virologic failure and emergence of resistance, it will be important to first determine whether the populations are comparable. The parameters available in EuroSIDA will be used to investigate the relative importance of patient demographic and clinical characteristics that may be used to identify which patients are selected to receive RPV-containing regimens compared with EFV-containing regimens. The evaluation of appropriateness of a comparison of RPV-exposed patients with EFV- exposed patients will be based on the consistency of the clinical experience of the two treatment groups. This assessment will be conducted based on distribution of propensity scores for receipt of RPV-containing regimens or EFV-containing regimens. Patient characteristics associated with initiating RPV versus EFV-containing regimen will be assessed using logistic regression. Factors that are significant in the univariable models ($p<0.01$) will be incorporated into a multivariable model.

Incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance will be calculated for the RPV and EFV-exposed patients. The three primary event rates of interest (incidence rates of virologic failure, pre-treatment resistance, and treatment-emergent resistance) will be analyzed in 3 separate sets of analyses. Additional descriptive analyses will include incidence rates for each drug calculated by dividing the number of events by the total person-exposure time and expressed as the number of events per person-year, and 95% confidence intervals. Analyses of virologic failure will be stratified by HIV treatment status (naïve/experienced) at treatment initiation. Relative risks comparing the RPV-containing regimens with EFV-containing regimens and 95% confidence intervals will be calculated and appropriate stratified analyses will be conducted for virologic failure and emergence of treatment resistance. Adjustments for imbalances between the treatment groups before receiving the first dose of RPV or EFV-containing regimens will be applied using accepted methods based on sample size availability and the observed overlap of key patient characteristics based on propensity score construction.

Risk factors associated with virologic failure among those treated with RPV-containing regimen will be assessed using a multivariable Poisson regression model. This analysis will include all patients treated with RPV and adjust for confounding by including the patient demographic and clinical characteristics [age, sex, ethnicity, geography, weight, CD4 cell count, HIV viral load, route of HIV transmission, coinfection with hepatitis B/C, prior AIDS diagnoses, prior non-AIDS diagnoses (including myocardial infarction, stroke, angina pectoris, endarterectomy, coronary bypass, end stage renal disease, and pancreatitis), hypertension, diabetes, chronic kidney disease, smoking, and length of time enrolled in EuroSIDA] as covariates in the model. This provides maximal statistical power while also being able to assess the risk of virologic failure according to all factors included in the model by comparing the incidence of virologic failure in each subgroup. In addition, the effect of ARV treatment adherence on virologic failure among patients treated with RPV-containing regimens will be evaluated if sufficient data are available in EuroSIDA.

4.6. Data Quality Assurance

A summary of the data holder's internal data quality procedures will be requested and reviewed. The data holder is responsible for implementing and maintaining quality assurance and control systems to ensure that this DUS is conducted and data are generated, documented, and reported in compliance with applicable regulations and guidelines.

4.6.1. Validation Procedures

A literature review will be conducted to identify external validation studies performed in the database.

5. STUDY LIMITATIONS

The proposed study is based on analysis of medical records from the EuroSIDA cohort. The following limitations should be considered:

There is potential misclassification of the diagnosis or the outcomes of interest.

Attribution of loss of virologic control to failure to follow RPV-containing products' SmPCs may not be feasible given the multiple factors and dynamics salient to virologic control.

Data analysis cannot be performed for Eviplera® alone independent of Edurant® due to the way data is collected in EuroSIDA. .

Reasons for switch of ARV treatment may be captured inconsistently across EuroSIDA cohort centres.

Adverse events during the course of RPV or EFV treatment will be described in aggregate; it is not possible or appropriate to assess the causality of individual cases.

Measurement of adherence to treatment regimens is difficult to assess with reliability beyond prescription refills, which are not available in the EuroSIDA cohort. ARV treatment adherence is part of the EuroSIDA data collection form, but is incompletely captured and available for only a subset of patients.

DUS include bias related to the observational nature of the data and potential lack of data due to loss to follow-up or essential data not collected as routine fields. These studies are also subject to real-world prescribing practices that may not provide sufficient patient numbers to meet study goals of ascertainment within a reasonable timeframe.

Allocation of treatment is not subject to randomization. Patients will likely be channeled to treatment based on several measured and unmeasured characteristics and based on treatment guidelines. For example, treatment guidelines for the STR of EFV (EFV/FTC/TDF, Atripla) are likely to channel ARV-treatment experienced patients into the STR as opposed to the single agent formulation of EFV. This potentially introduces associations between exposures and outcomes that are confounded and may result in imbalances in the exposure groups when comparing EFV- and RPV-containing regimens.

All comparative analyses will be conducted under the assumption that unmeasured or missing effect modifiers, risk factors, or confounders are distributed equally across the RPV and EFV treatment groups and that the effects of these unmeasured or missing variables are non-differential with respect to treatment.

6. ETHICAL ASPECTS

6.1. Privacy of Personal Data

Confidentiality of patient records will be maintained at all times. All analyses of data will be performed using appropriately de-identified data without access to personal identifying information. All study reports will contain aggregate data only and will not identify individual patients or physicians. Medical record abstraction, if available, will only be performed after receiving a waiver of authorization from the relevant data holder's privacy board and approval from an Ethics Committee (EC). At no time during the study will the sponsor receive patient identifying information.

7. ADMINISTRATIVE REQUIREMENTS

7.1. Adverse Event Reporting

This study is designed to assess the appropriate use of RPV-containing regimens based on aggregate analyses. The sponsor will report aggregate

findings as study reports, not as individual spontaneous reports. In this study, it is not possible or appropriate to assess the causality of individual cases. Instances where individual patient data review identifies adverse events or serious adverse events, which may be attributable to RPV, e.g., if a chart indicates a physician or other health care professional considered the event possibly related to the regimen, the events will be entered to the Sponsor's Safety database and serious adverse events will be reported as individual case safety reports under expedited timelines as appropriate per company standard operating procedures.

7.2. Study Completion/Termination

7.2.1. Study Completion

The study will be completed once a minimum of 800 patients have entered each of the RPV and EFV treatment groups and have been followed individually for 12 months from RPV or EFV-containing regimen initiation, death, virologic failure, or loss to follow-up to the HIV cohort, whichever comes first. Interim analyses will be conducted to check the number of RPV-treated patients captured in the DUS and to review the estimated timeframe that will be needed to obtain the required sample size. Updates on patient accrual and timelines for study completion will be provided as part of Periodic Safety Update Reports (PSURs)/Periodic Benefit Risk Evaluation Reports (PBRERs) and Risk Management Plan (RMP) updates.

7.2.2. Study Termination

Study termination will be determined based on the projected ability of the study to meet sample size requirements using the health care database.

7.2.3. Dissemination and Communication of Study Results

Study results will be disseminated and communicated through the final study report. Study progress will be provided in the PSURs/PBRERs and RMPs for RPV-containing products. Additionally, findings of potential scientific or public health importance will be disseminated through conference presentations or journal articles as appropriate.

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