NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY PROTOCOL

Study Title	Real-life study of single tablet regimen (STR) and multi tablet regimen (MTR) usage in Germany on persistency of initial therapy - STRingent
Protocol ID	GS-DE-236-1272
Protocol Version/Date:	Original: 24 March 2014
EU PAS Register No	ENCEPP/SDPP/6118
Clinical Trials.gov Identifier	Study not registered
Active substance	J05AR09 emtricitabine, tenofovir disoproxil, elvitegravir and Cobicistat J05AR08 emtricitabine, tenofovir disoproxil and rilpivirine and multi tablet regimens consisting of various approved HIV medications
Medicinal Product	STR: Stribild®, Eviplera® MTR: multi tablet regimens consisting of various approved HIV medications in various combinations consisting of at least 2 tablets/dosing forms
Product reference	EU/1/13/830/001 EU/1/13/830/002 EU/1/11/737/001 EU/1/11/737/002
Procedure number	Not applicable
Joint PASS	No
Research Question and Objectives	The primary objective of this study is as follows: • To evaluate persistency of initial HIV therapy in subjects starting with STR or MTR during the first year of therapy. The secondary objectives of this study are as follows: • To describe and evaluate real-life effectiveness of STR and MTR — by describing the characteristics of HIV-infected subjects with initial therapy in an HIV-specialized practice or outpatient setting — by describing the treatment motivation (early treatment according to guidelines, treatment as prevention (TasP)

or other) and the specific treatment regimen (STR or MTR) in Germany with respect to subject characteristics and factors driving treatment decision (such as side effect profile, co-morbidities/co-medications, resistance, anticipated subject adherence, and subject preference)

  - by describing STR/MTR efficacy using HIV-RNA and CD4 cell count changes

- To describe reasons for treatment discontinuation or change of therapy
- To describe adherence to ART medication
- To describe physical and mental health-related quality of life and health status using standardized questionnaires (Health Survey Short Form (SF-36) and HIV Symptom Index)
- To describe rates of severe and/or unexpected toxicities and drug-drug interactions derived from reported ADRs/SADRs

Country (-ies) of study	Germany
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CONFIDENTIALITY STATEMENT

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2. GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

(e)CRF	electronic case report form
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AMG	German drug act
AMNOG	Gesetz zur Neuordnung des Arzneimittelmarktes
ART	anti-retroviral therapy
AST	aspartate aminotransferase
CDC	Centers for Disease Control and Prevention
COPD	chronic obstructive pulmonary disease
CRO	clinical research organisation
CSR	clinical study report
EFV	efavirenz
EMA	European Medicines Agency
EU	European Union
FDA	(United States) Food and Drug Administration
FTC	emtricitabine
GPP	Good Pharmacoepidemiology Practices (guidelines for)
GVP	Good Pharmacovigilance Practices (guidelines for)
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IEC	independent ethics committee
IRB	institutional review board
LDL	low density lipoprotein
MTR	multi tablet regimen
PAS	post-Authorization Study
PASS	post-Authorization Safety Study
QPPV	qualified person responsible for pharmacovigilance
RCT	randomized clinical trial
SADR	serious adverse drug reaction
SAE	serious adverse event
SSR	special situation report
STR	single tablet regimen
SUSAR	serious unexpected suspected adverse reaction
TasP	treatment as prevention
TDF	tenofovir disoproxil fumarate
US, USA	United States, United States of America
Analytical dataset	The minimum set of data required to perform the statistical analyses leading to the

	results of the primary objective(s) of the study
Bias	Systemic error in the design, conduct or analysis of a study that results in a mistaken estimate
Cases	Group of individuals with the condition of interest
Cohort	Group of people characterized by a common experience (e.g., occurrence of a specified disease, exposure to a given medication)
Confounder	Extraneous factor that accounts for a difference in disease frequency between the exposure groups; associated factors serving as surrogates for these factors are also commonly called confounders
Confounding by indication	A patient characteristic that is related to the outcome of interest and which influences treatment choice (exposure)
Controls	Group of individuals without the condition of interest but are otherwise similar to cases, or unexposed to or not treated with the agent of interest
Date at which a study commences	Date of the start of data collection
Effect modifier	If the effect of an exposure on a given outcome varies within categories or levels of a variable, that variable is described as an effect- modifier of the relationship between the exposure and the outcome
End of data collection	The date from which the analytical dataset is completely available
Exposure	A variable whose effect is of interest and is being studied
External validity	Whether or not the results from the study can be generalized to other populations
Internal validity	Whether or not the study provides an unbiased estimate of what it claims to estimate
Odds	The ratio of the probability that an event will happen to the probability that it will not happen
Outcome	An event (such as disease occurrence or death) that is studied in relation to exposure
Prevalence	Proportion of persons with the exposure/outcome at a specific point in time
Rate	A measure of event occurrence, calculated by dividing the total number of events by the total amount of person-time within an exposure category
Relative Risk (RR)	A general term that can refer to the ratio of 2 risks or the ratio of 2 rates
Risk	The proportion of a fixed cohort in which an outcome occurs during a specified period of time
Start of data collection	Date from which information on the first study subject is first recorded in the study dataset

3. RESPONSIBLE PARTIES

Table 1. Table Responsible Parties

Responsibility	Name, Title, Qualifications, Affiliation, Address	Contact Information
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Leading Investigator	Prof. Dr. Hans-Jürgen Stellbrink Infektionsmedizinisches Centrum Hamburg ICH, Grindelallee 35, 20146 Hamburg, Germany	Phone: +49 40 41 32 420
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4. PROTOCOL SYNOPSIS/ABSTRACT

Gilead Sciences GmbH
Fraunhoferstr. 17
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Title:

Real-life study of single tablet regimen (STR) and multi tablet regimen (MTR) usage in Germany on persistency of initial therapy - STRingent
Version: Original
Date: 24 March 2014
Author: Armin Schuster, Gilead Sciences GmbH

Rationale and Background:

Background:

Since Jan 2011 the reimbursement & pricing process in Germany is defined by the AMNOG law. The AMNOG process consists of two steps: 1. the evidence-based assessment of the additional benefit of the new drug vs. a defined comparator and 2. the negotiation of a reimbursement price based on the achieved additional benefit.

A granted additional benefit is usually based on patient-relevant clinical endpoints regarding efficacy, safety and/or quality of life.

Within the AMNOG process data of highest evidence level (RCT) is preferred for the benefit assessment; however prospective, comparative cohort studies are also accepted if they enable conclusion within the German healthcare context.

The yet available STR data do not meet this requirement, which means that no additional benefit can be derived from the STR formulation. In order to close the data gap and describe STR benefits with clinical impact (direct or indirect via surrogates) respective real-life data on STR and MTR need to be collected. Whereas it would require longer study duration and/or higher patient numbers to measure clinical outcomes directly, both persistency and adherence to the complete regimen are valid surrogates for clinical outcomes which can be supported by patient-reported outcomes.

Rationale:

- No German real-life prospective data exists on persistency and adherence to complete regimen comparing STR versus MTR.
- No German real-life data exists on patient-reported outcomes comparing STR versus MTR.
- No German real-life data exists about treatment strategies such as rationale for treatment initiation and choice of therapy comparing STR versus MTR.

Research Question and Objectives:	The primary objective of this study is as follows: • To evaluate persistency of initial HIV therapy in subjects starting with STR or MTR during the first year of therapy. The secondary objectives of this study are as follows: • To describe and evaluate real-life effectiveness of STR and MTR — by describing the characteristics of HIV-infected subjects with initial therapy in an HIV-specialized practice or outpatient setting — by describing the treatment motivation (early treatment according to guidelines, treatment as prevention (TasP) or other) and the specific treatment regimen (STR or MTR) in Germany with respect to subject characteristics and factors driving treatment decision (such as side effect profile, co-morbidities/co-medications, resistance, anticipated subject adherence, and subject preference) — by describing STR/MTR efficacy using HIV-RNA and CD4 cell count changes • To describe reasons for treatment discontinuation or change of therapy • To describe adherence to ART medication • To describe physical and mental health-related quality of life and health status using standardized questionnaires (Health Survey Short Form (SF-36) and HIV Symptom Index) • To describe rates of severe and/or unexpected toxicities and drug-drug interactions derived from reported ADRs/SADRs
Study Design:	Prospective, non-interventional cohort study. Enrolled subjects will be documented in an eCRF by the participating sites, each enrolled subject will be followed for up to 12 months
Population:	The study will enroll adult HIV-1 infected subjects who initiate their first anti-retroviral therapy and have a CD4 count ≥200 cells/µL. Participating study sites (hospitals and private practitioners) are specialized on treating HIV patients. All study sites are located in Germany. Subjects who would initiate therapy on MTR but with an pre-planned switch to STR consisting of identical substance compounds are excluded from the study (eg. subjects starting on MTR with TDF and FTC and EFV to be switched after 3 months to Atripla® cannot be enrolled).

Variables:

At treatment initiation (baseline):

Gender, year of birth

Ethnicity and migration history

Employment status

Date of HIV diagnosis

Suspected mode of transmission

CDC stage, history of AIDS-defining events

Relevant co-morbidities (cardiovascular, asthmatic disease, COPD, hypertension, hyperlipidemia, neuropsychiatric disorder, osteopathic disorder, diabetes mellitus, nephropathy, chronic hepatitis B, chronic hepatitis C)

Laboratory parameters (as available from medical records): HIV RNA, CD4 cell count , AST, ALT, gamma-GT, triglycerides, total cholesterol, HDL, LDL, serum glucose, serum phosphate, serum creatinine, serum bilirubin, alkaline phosphatase, calculated creatinine clearance, serum uric acid, serum total protein, urine dipstick parameters (glucose, leukocytes, nitrite, protein, pH, ketone bodies)

Initial anti-retroviral therapy

Co-medications as available from medical records

Resistance status (if available)

Rationale for therapy start and regimen choice: e.g. subject wish for TasP, early treatment according to guidelines

HIV-Symptom Index

SF-36

During follow-up (approximately 3 months, 6 months , and 12 months after starting therapy):

Anti-retroviral therapy adherence – the patient will receive a questionnaire with the following questions "In the last 4 days, how many days have you missed any dose of your prescribed anti-HIV medication? Of these days how many days did you miss the whole daily dose(s), how many days did you miss parts of the daily dose(s)?" and "In the last 30 days, how many days have you missed any dose of your prescribed anti-HIV medication? Of these days how many days did you miss the whole daily dose(s), how many days did you miss parts of the daily dose(s)?"

Switch or discontinuation of ART (including reasons e.g. patient wish, adverse reaction, insufficient efficacy)

Co-medications as available from medical records

Laboratory parameters (as available from medical records): HIV RNA, CD4 cell count , AST, ALT, gamma-GT, triglycerides, total cholesterol, HDL, LDL, serum glucose, serum phosphate, serum creatinine, serum bilirubin, alkaline phosphatase, calculated creatinine clearance, serum uric acid, serum, total protein, urine dipstick parameters (glucose, leukocytes, nitrite, protein, pH, ketone bodies)

New AIDS-defining events (CDC class C, excluding CD4 cell count < 200 cells/μL)

Changes in co-morbidities/co-infections

Adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs)

Special situations reports as appropriate

HIV Symptom Index (only month 6 and month 12)

SF-36 (only month 6 and month 12)

In case of virologic failure: resistance status

Data Sources: Collection of routine visit data and questionnaires via eCRF

Study Size: 1000 enrolled subjects, 500 per arm:

- Arm A: Initiating STR regime, n=500
- Arm B: Initiating MTR regime, n=500

It is assumed that persistency of therapy, defined as the percentage of subjects still being on the initial therapy, is greater in the STR arm (Arm A) than in the MTR arm (Arm B). The difference is expected to be ≥10% over one year.

To detect a minimum 10% difference (e.g. 80% and 70% persistency in Arm A versus Arm B) with a double sided test, with 80% power and with an alpha of 0.05 will require 349 subjects per arm. To allow for a 20% drop-out rate of subjects (due to loss to follow up, sites or subjects cancelling their participation, etc.) it is necessary to enroll at least 420 subjects per arm. To increase the chances for useful subgroup analyses (e.g. different MTR and STR regimens) the study aims to enroll 500 subjects per arm.

Data Analysis: We will employ descriptive statistics and multivariable analyses adjusting for relevant confounders and appropriate statistical tests. These include:

Binary/categorical/ordinal variables: Frequency distributions using Chi-square tests and Fisher's exact tests.

Continuous variables: Comparison of means (+ 95% CI) using t-tests, and comparison of medians (+ IQR) using non-parametric tests.

	Rates of events by person-time of exposure to either MTR or STR will be computed using Poisson regression, adjusting for confounding variables.
Milestones:	Start of data collection : approx. April 2014
	End of Data collection: approx. December 2015
	Final Study report: approx. Q2 2016
	Publication: submission in Q4 2016

This study will be conducted in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs) and Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

5. AMENDMENTS AND UPDATES

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
none				

Protocol Modifications

Protocol modifications may only be made by Gilead Sciences. Approval must be obtained before changes can be implemented.

6. MILESTONES

Milestone	Planned Date
Start of data collection	Approx. April 2014
End of data collection	Approx. December 2015
Registration in the EU PAS register	Before start of data entry into the eCRF
Final report of study results	Approx. Q2 2016

7. RATIONALE AND BACKGROUND

7.1. Rationale for the Current Study

Background

Since Jan 2011 the reimbursement & pricing process in Germany has been defined by the AMNOG law. The AMNOG process consists of two steps: 1. the evidence-based assessment of the additional benefit of the new drug vs. a defined comparator and 2. the negotiation of a reimbursement price based on the achieved additional benefit.

There are six benefit levels from significant [highest level] to less additional benefit [lowest benefit level] based on the clinical benefit; in addition to the benefit level the strength of the presented evidence is classified into three categories, i.e. proof [highest evidence category, only to be achieved with RCTs], indication and hint [lowest evidence category] based on the presented data.

A granted additional benefit is usually based on patient-relevant clinical endpoints regarding efficacy, safety and/or quality of life; formulation benefits are only considered patient-relevant if they have a direct or indirect impact on a clinical outcome – convenience only is not considered patient-relevant if it doesn't translate into clinical benefits.

Regarding evidence, according to the AMNOG law, data of the highest evidence level (RCT) is preferred for the benefit assessment; however it is stated in chapter 4, §7 (4) that prospective, comparative cohort studies are also accepted if they allow for drawing direct conclusions to German healthcare context.

The available STR data do not meet this requirement, which means that no additional benefit can be derived from the STR formulation. In order to close the data gap and describe STR benefits with clinical impact (direct or indirect via surrogates) respective real-life data on STR and MTR (multi tablet regimen) needs to be collected. Whereas it would require longer study duration and/or higher patient numbers to measure clinical outcomes directly, both persistency and adherence to the complete regimen are valid surrogates for clinical outcomes which can be supported by patient-reported outcomes.

Rationale

- No German real-life prospective data exists on persistency and adherence to complete regimen comparing STR versus MTR.
- No German real-life data exists on patient-reported outcomes comparing STR versus MTR.
- No German real-life data exists about treatment strategies such as rationale for treatment initiation and choice of therapy comparing STR versus MTR.

8. RESEARCH QUESTIONS AND OBJECTIVES

The primary objective of this study is as follows:

- To evaluate persistency of initial HIV therapy in subjects starting with STR or MTR during the first year of therapy.

The secondary objectives of this study are as follows:

- To describe and evaluate real-life effectiveness of STR and MTR
  - — by describing the characteristics of HIV-infected subjects with initial therapy in an HIV-specialized practice or outpatient setting
  - — by describing the treatment motivation (early treatment according to guidelines, treatment as prevention (TasP) or other) and the specific treatment regimen (STR or MTR) in Germany with respect to subject characteristics and factors driving the treatment decision (such as side effect profile, co-morbidities/co-medications, resistance, anticipated subject adherence, and subject preference)
  - — by describing STR/MTR efficacy using HIV-RNA and CD4 cell count changes
- To describe reasons for treatment discontinuation or change of therapy
- To describe adherence to ART medication
- To describe physical and mental health-related quality of life and health status using standardized questionnaires (Health Survey Short Form (SF-36) and HIV Symptom Index)
- To describe rates of severe and/or unexpected toxicities and drug-drug interactions derived from reported ADRs/SADRs

Specification of persistency for this study

Persistency of STR vs. MTR initial HIV therapy up to one year after starting initial HIV therapy, measured as percentage of subjects not having changed or discontinued initial therapy. A subject switching from one STR to another STR will also be considered switching therapies, i.e. non-persistency.

In the MTR arm a change in the daily dosage of one or all of the used substances or the replacement of any (or all) of the used substances or the addition of a new substance will be considered switching therapies (i.e. non-persistency).

A change from two substances e.g. TDF and FTC as single substances in the MTR arm to TDF+FTC as fixed-dose combination of the same substances will be considered switching therapies (i.e. non-persistency).

8.1. Population

Adult HIV-1 infected subjects who start their first anti-retroviral therapy with a baseline CD4 count ≥200 cells/μL can be enrolled into STRingent.

Subjects who initiate therapy on MTR but with a pre-planned switch to an STR consisting of the identical substance compounds as the MTR regimen are excluded from the study (eg. subjects starting on MTR with TDF and FTC and EFV to be switched after 3 months to Atripla® cannot be enrolled).

Enrollment will be stratified to allow enrollment of 500 STR subjects and 500 MTR subjects.

9. RESEARCH METHODS

9.1. Study Design

This study is a non-interventional cohort study designed to document a substantial portion of anti-retroviral treatment-naïve HIV-1 infected subjects starting their first anti-retroviral therapy in Germany in accordance with the German Drug Act (§4 Abs 23 Satz 3 AMG, and §4 Abs 34 AMG, §63 (f) AMG). We plan to involve specialized HIV practitioners throughout Germany to document the real-life use of initial STR and MTR. 1000 subjects shall be enrolled in this study, 500 per arm (STR and MTR).

9.2. Setting

STRingent is a non-interventional study in adult, HIV-1 infected subjects who start their first anti-retroviral therapy either with a STR or MTR. Participating study sites are specialized on treating HIV patients. It is the discretion of the respective physician if a specific subject will be treated and what regimen will be used. Only after these decisions have been made can the subject be consented to be included in STRingent.

9.3. Variables

In this non-interventional, post authorization study the time the subject has taken STR or MTR is the exposure of interest. Descriptive and outcome variables are the collected clinical and laboratory parameters as available.

At treatment initiation (baseline)

- Gender, year of birth
- Ethnicity and migration history
- Employment status
- Date of HIV diagnosis
- Suspected mode of transmission
- CDC stage, history of AIDS-defining events
- Relevant co-morbidities (cardiovascular, asthmatic disease, COPD, hypertension, hyperlipidemia, neuropsychiatric disorder, osteopathic disorder, diabetes mellitus, nephropathy, chronic hepatitis B, chronic hepatitis C)
- Laboratory parameters (as available from medical records): HIV RNA, CD4 cell count, AST, ALT, gamma-GT, triglycerides, total cholesterol, HDL, LDL, serum glucose, serum phosphate, serum creatinine, serum bilirubin, alkaline phosphatase, calculated creatinine

clearance, serum uric acid, serum total protein, urine dipstick parameters (glucose, leukocytes, nitrite, protein, pH, ketone bodies)

- Initial anti-retroviral therapy
- Co-medications as available from medical records
- Resistance status (if available)
- Rationale for therapy start and regimen choice: e.g. subject wish for TasP, early treatment according to guidelines
- HIV-Symptom Index
- SF-36

During follow-up (approximately 3 months, 6 months, and 12 months after starting therapy)

- Anti-retroviral therapy adherence – the patient will receive a questionnaire with the following questions "In the last 4 days, how many days have you missed any dose of your prescribed anti-HIV medication? Of these days how many days did you miss the whole daily dose(s), how many days did you miss parts of the daily dose(s)?" and "In the last 30 days, how many days have you missed any dose of your prescribed anti-HIV medication? Of these days how many days did you miss the whole daily dose(s), how many days did you miss parts of the daily dose(s)?"
- Switch or discontinuation of ART (including reasons e.g. patient wish, adverse reaction, insufficient efficacy)
- Co-medications as available from medical records
- Laboratory parameters (as available from medical records): HIV RNA, CD4 cell count, AST, ALT, gamma-GT, triglycerides, total cholesterol, HDL, LDL, serum glucose, serum phosphate, serum creatinine, serum bilirubin, alkaline phosphatase, calculated creatinine clearance, serum uric acid, serum, total protein, urine dipstick parameters (glucose, leukocytes, nitrite, protein, pH, ketone bodies)
- New AIDS-defining events (CDC class C, excluding CD4 cell count < 200 cells/µL)
- Changes in co-morbidities/co-infections
- Adverse drug reactions (ADRs) and serious adverse drug reactions (SADRs)
- Special situations reports as appropriate
- HIV Symptom Index (only month 6 and month 12)

- SF-36 (only month 6 and month 12)

- In case of virologic failure: resistance status

9.4. Data Sources

The conduct of a non-interventional study (NIS) requires, according to definition of a ”non-interventional study“ in terms of Guideline on Good Pharmacovigilance Practices (GVP) – Module VIII (Rev 1), that the protocol does not stipulate or dictate on the diagnosis, therapeutic decisions and follow-up of the individual subject. This study only observes and collects the use of drugs (STR or MTR) and the corresponding descriptive and clinical outcome by the treating physician in the specific indication.

Clinical data is collected from the physician’s documentation of the subject’s visit in subject medical records that are closest to the prespecified follow up time points (approximately month 3, 6 and 12), each +/- 6 weeks. Primary data sources are electronic medical records, where available or paper records at the participating sites. Questionnaires on anti-retroviral therapy adherence, SF-36 and HIV Symptom Index will be filled in by the subjects in paper form and collected by site staff. Data from medical records and from the collected questionnaires will be manually transcribed by the investigator or site staff into electronic case record forms (eCRF).

9.5. Study Size

1000 enrolled subjects, 500 per arm:

- Arm A: Initiating STR regime, n=500

- Arm B: Initiating MTR regime, n=500

It is assumed that persistency of therapy defined as the percentage of subjects still being on the initial therapy is greater in the STR arm (Arm A) than in the MTR arm (Arm B). The difference is expected to be ≥10% over one year.

To detect a minimum 10% difference (e.g. 80% and 70% persistency in Arm A versus Arm B) with a double sided test, with 80% power and with an alpha of 0.05 will require 349 subjects per arm.

To allow for a 20% drop-out rate of subjects (due to loss to follow up, sites or subjects cancelling their participation, etc.) it is necessary to enroll at least 420 subjects per arm. To increase the chances for useful subgroup analyses (eg. different MTR and STR regimens) the study aims to enroll 500 subjects per arm.

9.6. Data Management

The study will use an electronic data entry system (eCRF), all users will receive specific access codes to enable them to enter their data. The electronic data entry system will contain automatic checks for data completeness and to identify inconsistent data.

9.7. Data Analysis

Descriptive analysis

Binary, categorical and ordinal variables will be described by counts and frequencies of each modality (over the total number of responses), and comparisons between groups will be tested using chi square tests and/or Fisher's exact tests.

Continuous variables will be described by means, standard errors, 95% confidence intervals, medians, minima, and maxima. Differences in means and medians between groups will be tested using t-tests and non-parametric tests, respectively.

When deemed necessary, sub-group comparisons and/or between time point comparisons may be implemented.

Multivariable analysis

As part of the secondary objectives of this study, rates of events per person-time of exposure will be computed using Poisson regression, after adjusting for potential confounding factors. These events include medication switching, medication discontinuation, co-medication use, ADRs and SADRs.

9.8. Quality Control

The electronic data entry system will contain automatic checks for data completeness and to identify inconsistent data and respective queries will be generated when necessary. Data and queries will be remotely monitored for consistency and completeness.

9.9. Limitations of the Research Methods

In a non-interventional study all decisions on the management of the subject are made solely by the treating physician. As such, patients may be channeled to one MTR or STR on the basis of clinical or other factors. This also includes the frequency of the evaluation of lab values and other collected variables. Documentation of study variables not obligatory, missing data of unpredictable extent can occur.

9.10. Other Aspects

It is planned to involve around 60 participating sites in Germany. The sites will be distributed throughout Germany, reflecting the distribution of HIV patients in the country. With around 60 participating sites it should be possible to cover approximately 50% of the HIV infected population starting their initial therapy (4000-5000 patients annually). The subjects enrolled into the study should therefore be a good representation of this population in Germany.

9.10.1. Joint Investigator/Sponsor Responsibilities

9.10.1.1. Access to Information for Monitoring

The involved CRO is responsible for routine online review of the eCRFs at regular intervals throughout the study to check the completeness, consistency, and accuracy of the data being entered on the forms. The investigator agrees to cooperate with the CRO to ensure that any problems detected in the course of this monitoring are resolved.

9.10.1.2. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies, IRBs, and IECs as necessary. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Good Pharmacoepidemiology and Pharmacovigilance Practices

The investigator will ensure that this study is conducted in accordance with the laws and regulations of the country in which the research is conducted.

The investigator will conduct this study in accordance with the guidelines of Good Pharmacoepidemiology Practices (GPPs), Heads of Medicines Agencies (HMA) Good Pharmacovigilance Practices (GVP) including archiving of essential documents.

10.2. Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Review

The sponsor will submit this protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, subject questionnaires, or descriptions of the study used to obtain informed consent) to an IEC. The investigator will not begin any study subject activities until approval from the IEC has been documented and provided to the investigator.

Any subsequent modifications made to the protocol or any accompanying material to be provided to the subject after initial IEC approval will also be submitted for IEC approval prior to use, with the exception of those necessary to reduce immediate risk to study subjects.

10.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, and objectives of the study prior to study participation and before performing any study-related activities.
The investigator must utilize the most current IEC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IEC or local requirements.

10.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only month and year of birth and a unique study subject number should be recorded on any study-related document.

The investigator agrees that all information received from Gilead, including but not limited to this protocol, CRFs, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

11.1. Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed. These are considered to be preexisting conditions and should be documented on the medical history CRF (if applicable).

11.1.1. Adverse Drug Reactions

An **adverse drug reaction** (ADR) is defined as an untoward medical occurrence (unintended or noxious responses) considered causally related to an investigational or approved medicinal product at any dose administered. Adverse reactions may arise from medication errors, uses outside what is foreseen in the protocol or prescribing information (off-label use), misuse and abuse of the product, overdose, or occupational exposure.

11.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-subject hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. Therefore, if death occurred, the event that led to death needs to be reported as an SAE.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, is life-threatening, or meets any of the other definitions of an SAE, then it is an SAE.

- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis (and not the individual signs/symptoms) should be documented as the AE and/or SAE.

A distinction should be drawn between seriousness and severity of AEs. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed for severity. An AE is defined as "serious" when it meets one of the predefined outcomes described above.

11.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as ADRs or SADRs. However, causally related laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation must be recorded as an ADR, as well as an SADR, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an ADR or SADR if they meet the definition of an ADR or SADR as described in Section 11.1**.** If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 11.3.

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing ADRs and SADRs for causality and for final review and confirmation of accuracy of event information and assessments.

11.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is a reasonable possibility that the event may have been caused by the medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of ADR/SADR reporting.

11.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Not applicable

11.4. Special Situations Reports

11.4.1. Definitions of Special Situations

Special situation reports (SSRs) include reports of pregnancy; medication error, abuse, misuse, or overdose; lack of effect; adverse reactions in infants following exposure from breastfeeding; and adverse reactions associated with product complaints and occupational exposure.

A pregnancy report is used to report any pregnancy of a study participant that occurs during the study.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in

question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Lack of effect is defined as the failure of the expected or intended pharmacologic action or therapeutic effect as described in the pharmacology and/or indications section of the current product labeling.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

11.4.2. Instructions for Reporting Special Situations

11.4.2.1. Instructions for Reporting Pregnancies

All pregnancies that occur while exposed to the study drugs and the outcome of the pregnancy are to be reported to the CRO Safety Department- Cromsource (for contact information refer to section 11.5) using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours.

The outcome should be reported to the CRO Safety Department using the pregnancy outcome report form.

11.5. Gilead Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all ADRs and serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs) as determined by country-specific legislation or regulations where the study is conducted. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for ADRs and SADRs will be determined by Gilead using the respective EU SmPC for Gilead products.

The procedure for reporting all ADRs is as follows:

- Record the ADR/SADR on the AE eCRF and complete the "Non-Interventional Study AE/SAE Report Form" form.

- Email or fax the "Non-Interventional Study AE/SAE Report Form" form to the attention of the CRO-Cromsource within 24 hours of the Investigator's knowledge of the event. Contact information is as follows:

CRO Safety Department: **Cromsource - Fax: 0241 / 7500755**

alternatively:
Gilead Sciences
DSPH: Phone: 1-800-GILEAD-5 (1-800-445-3235)
E-mail: Safety_fc@gilead.com
Fax: (650) 522-5477

11.6. Investigator Requirements and Instructions for Reporting Drug Reactions and Serious Adverse Drug Reactions to CRO

All serious and non-serious ADRs that occur after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study must be reported to CRO Safety department as instructed.

All ADRs and SADRs will be recorded on the Non-Interventional Study AE/SAE Report Form and forwarded to the designated CRO within 24 hours of the investigator's knowledge of the event.

Special Situations Reporting Process

All SSRs will be recorded on the Non-interventional Study Special Situations Report Form and submitted by faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of the designated CRO (for contact information refer to section 11.5).

11.7. Investigator and Sponsor Reporting Requirements

Gilead is responsible for reporting and analyzing reports of all ADRs and serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs), and special situation reports (SSRs) as determined by country-specific legislation or regulations where the study is conducted and other applicable countries. Gilead may be required to report to other regulatory agencies.

Assessment of expectedness for ADRs, SADRs and SSRs will be determined by Gilead using the respective EU SmPC for Gilead products.

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of ADRs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the applicable regulatory agencies. Gilead will ensure that the report meets the standards set out in the Guideline on Good Pharmacovigilance Practices (GVP) Module VIII and/or respective EMA guidance (EMA/48663/2013) "Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies". The final CSR will be submitted within 12 months of study completion.

The investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

Gilead shall communicate to the EMA and the competent authorities of the Member States in which the product is authorized the final manuscript within two weeks after first acceptance for publication.

13. REFERENCES

None.

14. APPENDICES

Appendix 1. Signature Page

GILEAD SCIENCES GMBH
FRAUNHOFERSTR 17, 82152 MARTINSRIED, GERMANY

Real-life study of single tablet regimen (STR) and multi tablet regimen (MTR) usage in Germany on persistency of initial therapy - STRingent

Original, 24 March 2014

This protocol has been approved by Gilead Sciences. The following signatures document this approval.

Armin Schuster
Gilead Study Director (Printed)
Author

Signature

25.03.2014
Date

Karen Pattenden
Gilead EU QPPV (Printed)

Signature

25 March 2014
Date