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TITLE:
Retrospective evaluation of treatment durability among treatment-naive HIV-infected individuals initiated first-line ART in Russia

Summary of changes

Protocol Section	Change
Protocol Summary	"between February 01 and April 30, 2017" replaced with "February 01 and June 30, 2017"
3 METHODOLOGY 3.1 Summary of Study Design	"The study is to be conducted in 6 investigational sites across Russia with up to 200 patients recruited per site." replaced with "The study is to be conducted in up to 8 investigational sites across Russia with up to 200 patients recruited per site." "All patients must have initiated ART between February 01 and April 30, 2017" replaced with "All patients must have initiated ART between February 01 and June 30, 2017"
3 METHODOLOGY 3.3 Inclusion Criteria	" • Initiated their first-line ART between February 01 and April June 30, 2017" replaced with " • Initiated their first-line ART between February 01 and June 30, 2017"
5 STUDY PROCEDURES OF DATA COLLECTION 5.3. Retrospective Data Collection	"Data will be retrospectively collected from 6 investigational sites with up to 200 patients recruited per site." replaced with "Data will be retrospectively collected from up to 8 investigational sites with up to 200 patients recruited per site."
11 Attachments	Updated External Adverse Event and Product Quality Complaint Form

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List of Abbreviations

AE	Adverse event
SAE	Serious adverse event
IRB	Independent Review Board
IEC	Independent Ethics Committee
WHO	World Health Organization
MoH	Ministry of Health
HIV	Human Immunodeficiency Syndrome
AIDS	Acquired Immunodeficiency Syndrome
PLWH	People living with HIV
MSM	Men having sex with men
ART	Antiretroviral therapy
cART	Combined antiretroviral therapy
PI	Protease inhibitors
bPI	Boosted protease inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitor
EFV	Efavirenze
ZDV	Zidavudine
TDF	Tenofovir
3TC	Lamivudine
FTC	Emtricitabine
ABC	Abacavir
CV	Cardiovascular
CK	Chronic kidney (disease)
CNS	Central nervous system
CD	Cluster of differentiation
SAR	Serious adverse reaction
NSAR	Non-serious adverse reaction
HOI	Health outcomes of specific interest
MAH	Market authorization holder
PQCs	Product quality complaint
CD	Calendar day
EDC	Electronic data capture
eCRF	Electronic clinical reporting form
CI	Confidentiality interval
SOP	Standard Operating Procedure

PROTOCOL SUMMARY

Title	Retrospective evaluation of treatment durability among treatment-naive HIV-infected individuals initiated first-line ART in Russia
Supplier	Atlant Clinical Ltd
Rationale	Treatment durability is an important factor in HIV disease management since HIV infected individuals need to take ART life-long. To date, there is limited data on treatment durability in HIV infected individuals initiating ART in Russia. Understanding the durability of treatment is essential for improving medical care of patient living with HIV.
Primary Objective	To evaluate the 48 weeks treatment durability among treatment naive HIV-infected individuals determined as a percentage of patients remained on initial therapy
Study Design	A non-interventional retrospective study.
Study Population	Treatment-naive at the time of initiation of ART with NNRTI plus two NRTIs or PI boosted by ritonavir with 2 NRTIs per usual standard of care of the investigator in AIDS clinics of Russia.
Study Duration	Up to 24 months will be dedicated to retrospective data collection and analysis from treatment-naïve HIV-infected patients who initiated their first-line ART between February 01 and June 30, 2017
Exposure and Outcome	Initial ART per usual standard of care in AIDS clinics of Russia: NNRTI plus 2 NRTIs or PI boosted by ritonavir with 2 NRTIs. Treatment durability determined as a percentage of patients continuing their first-line for 48 and 96 weeks without changes (switch or withdrawal) evaluated retrospectively
Statistical Methods	Data will be presented descriptively as follows: the number of observations, mean and standard deviation, median, first and third quartiles, minimum and maximum for continuous variables, and the absolute frequencies and percentage of patients presenting the given feature for qualitative variables. The results on the study endpoints (proportion of patients who remain on first-line ART at 48 and 96 weeks) will be presented with two-sided 95% confidence intervals. Univariate and multivariate logistic regression will be used to study the association between patients' baseline demographic and clinical characteristics and treatment discontinuation status.
Sample Size and Power Calculations	1000 patients. The assumed 1-year (approximately 48 weeks) discontinuation rate, based on published research, is 30% [20] therefore the assumed proportion of patients who remain on the first line ART regimen at 48 weeks is 70%. Inclusion of 1000 patients will allow the estimation of this proportion with 95% CI: Lower bound - 67.2%, Upper bound – 72.8%, Actual width (precision) - 5.7% (±2.8%).
Limitations	In this a retrospective study the quality of the data is important. And the potential issue of missing data is a limitation of the study. Therefore, it is important for the sponsor or designee to monitor data completion and perform quality checks during the study. To minimize missing data, a set of core variables is required to be available at enrollment as part of inclusion criteria.

1 Background and Rationale

1.1 Background

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions which interfere with increasing the risk of developing common infections such as tuberculosis, as well as other opportunistic infections, and tumors that rarely affect people who have working immune systems.[1] These late symptoms of infection are referred to as acquired immunodeficiency syndrome (AIDS).[2] From the time AIDS was identified in the early 1980s to 2017, the disease has caused an estimated 35 million deaths worldwide.[3] In 2016, about 36.7 million people were living with HIV and it resulted in 1 million deaths.[4] Unlike most countries, Russia's HIV epidemic is growing, with the rate of new infections rising by between 10 and 15% each year. It is estimated that over 250 people become infected with HIV every day. [5, 6] By mid-2017, 1.16 million people had been diagnosed with HIV in Russia. However, this does not equate to the number of people currently living with HIV as it does not account for AIDS-related deaths or people who have HIV but are undiagnosed. Although Russia has collected extensive data on HIV since 1987, official estimates for these measures remain under reported and inconsistent. A 2017 data analysis suggests the numbers of AIDS-related deaths are rising. From January to June 2017, 14,630 AIDS-related deaths were recorded, a 13.5% increase over the previous six-month period. HIV is one of the top 10 causes of premature death in Russia. [7, 8]

Life expectancy of people living with HIV (PLWH) increased substantially with the introduction of combined active antiretroviral therapy (cART) [9]. Consequently, assessing long-term treatment outcomes and regimen durability has become increasingly relevant. Patients still experience treatment modifications and interruptions for reasons that may include virological failure, adverse events, or poor adherence [10, 11]; and treatment modifications or interruptions may be associated with increased costs or adverse clinical outcomes. Efavirenz (EFV) and other NNRTIs are the preferred options for the third component in first antiretroviral regimens (first-line ART) to treat HIV infection, according to the World Health Organization Consolidated Guidelines (WHO) [12] and Russian National cART guidelines [13].

In most clinical trials, before the introduction of integrase strand transfer inhibitors (INSTIs), NNRTIs showed better efficacy or non-inferiority in suppressing HIV replication when compared with other regimens [14–16]. Randomized clinical trials, however, are typically conducted over 48- to 96-week periods and evaluate primarily rates of virological suppression in populations selected with stringent criteria [17]. A recent meta-analysis using pooled data of 29 clinical trials evaluated the risk of death [17], AIDS progression, and treatment discontinuation in ART-naive patients comparing non-nucleoside reverse transcriptase inhibitors (NNRTIs), including EFV-based regimens, with boosted protease inhibitor (bPI)–based regimens, and it showed no statistically significant differences between regimens in any of the individual and combined outcomes.

1.2 Rationale

The Russian MoH has recently initiated a national program aimed to increase the proportion of HIV diagnosis and linkage to care of HIV infected individuals. Treatment durability is an important factor in HIV disease management since HIV infected individuals need to take ART for many years. [5] To date, there is limited data on treatment durability in HIV infected individuals initiating ART in Russia. Understanding the durability of treatment is essential for improving patient management in order to achieve the goals set by the Russian MoH and the HIV elimination goals set by the WHO.

According to the robust clinical studies data, there was significant increase of CNS AEs in groups of patients treated with EFV [14]. As with other NNRTIs, drug interactions and a low resistance barrier have to be considered. Novel NNRTis such as etravirine and rilpivirine were implemented in routine clinical practice in Russia recently and have higher cost which may influence access and therefore durability to this third drug medications.

Observational studies, in contrast to clinical trials, have the potential to offer valuable additional information with respect to real-life settings, such as durability of the regimen over longer periods of time. Cohort studies have evaluated the reasons for change of first-line regimen in the short term [10, 18] and long term [19] and the prevalence of use of different NNRTIs and PIs in first-line [12]. Nevertheless, durability of first-line ART and prognostic factors (either positive or negative) measured in current study, such as the probability of requiring ART switch, may have significant economic and public health relevance. Also durability can be highly influenced by local circumstances. Therefore, in this study, the durability of initial ART will be evaluated according to the third component in a cohort from Russia and association of baseline patient characteristics with treatment durability over a long period of time will be explored.

2 Objectives and Hypotheses

2.1 Primary Objective

- To evaluate the 48 weeks treatment durability among treatment naive HIV-infected individuals initiated ART (NNRTI, PI) determined as a percentage of patients remained on initial therapy without change of the NNRTI or PI agent

2.2 Secondary Objectives

- To evaluate the estimated time on therapy without change of the NNRTI or PI agent at 48 weeks among treatment naive HIV-infected individuals initiated ART (NNRTI, PI)
- To describe baseline clinical and demographic characteristics of treatment naive HIV-infected individuals initiated ART (NNRTI, PI)
- To assess association between clinical and demographic characteristics of patients and treatment durability at 48 weeks

- To evaluate the 96 weeks treatment durability among treatment naive HIV-infected individuals initiated ART (NNRTI, PI) determined as a percentage of patients remained on initial therapy without change of the NNRTI or PI agent
- To evaluate the estimated time on therapy without change of the NNRTI or PI agent at 96 weeks among treatment naive HIV-infected individuals initiated ART (NNRTI, PI)
- To assess association between clinical and demographic characteristics of patients and treatment durability at 96 weeks

3 METHODOLOGY

3.1 Summary of Study Design

This study is a non-interventional retrospective study. Data from patients who signed informed consent form will be collected through retrospective chart or medical records review. Patients have been receiving treatment and diagnostic procedures according to daily clinical practice conducted by his/her physician. There are no procedures that are required as part of this study.

The study is to be conducted in up to 8 investigational sites across Russia with up to 200 patients recruited per site. Each investigational site will be a dedicated HIV clinic or an HIV department in clinic of infectious diseases. It is planned that the first half of the study population (500 patients) will be enrolled during the first 6-9 months and the second half of the study population (500 patients) during the second 6-9 months of the study.

HIV-infected patients with no experience of therapy at time of initiation of ART with NNRTI plus two NRTIs or PI boosted by ritonavir with 2 NRTIs will be enrolled and followed retrospectively for up to 96 weeks with data collection at the approximate time points of baseline (pre-treatment) and at 48 and 96 weeks after start of treatment.

The following ARV drugs are considered according to the standards of care:

- NNRTIs: efavirenz (EFV), nevirapine (NVP), rilpivirine (RPV), ETR (etravirine) etc.
- PIs: LPV (lopinavir), DRV (darunavir), ATV (atazanavir), FPV (fosamprenavir) etc.

All patients must have initiated ART between February 01 and June 30, 2017. A time window for the retrospective visits at baseline, 48 and 96 weeks is envisaged as approximately ± 8 weeks.

Patients will be retrospectively screened and selected according to inclusion and exclusion criteria prior to enrollment in each investigational site starting the day of its initiation. The study sites will maintain a list of all screened patients. All patients eligible according to the inclusion/exclusion criteria and after signing the informed consent form are to be consequently enrolled for their demographic and clinical data collection through retrospective chart or medical records review. The enrollment will continue until the recruitment goal is reached.

Baseline and follow-up data will be extracted through retrospective chart or medical records review, if available at each investigational site. No additional interventional tests or medical procedures such as additional blood samples, X-ray or other technical investigations will be performed as a part of this study. If any data element is not available, it will be reported as missing.

At baseline, demographic and clinical data on age, gender, employment status, marital status, substance abuse, HIV diagnosis duration, route of infection, AIDS stage, viral load, CD4 count, concomitant medication, comorbidities (noted diagnosis by physician) are to be collected through retrospective chart or medical records review.

At 48 and 96 weeks of retrospective follow-up, the investigators will assess through the medical records whether the patient was still on treatment with initiated ART (NNRTI, PI) and evaluate the estimated time on therapy without change of the NNRTI or PI agent within the class or without change of the NNRTI or PI agent to a different class.

3.2 Study Population

All patients enrolled must be treatment naive at the time of initiation of ART with NNRTI plus two NRTIs or PI boosted by ritonavir with 2 NRTIs per the usual standard of care of the investigator in AIDS clinics of Russia.

3.3 Inclusion Criteria

- Adult patients (>18 years of age) with definite HIV-1 infection based on positive lab test and judgement of treating physician according to standards of care
- Naive to antiretroviral treatment at the time of initiation
- Viral load of >1000 copies/ml at the time of initiation of ART
- Initiated their first-line ART between February 01 and June 30, 2017
- Patients are included, if the third component of their first line ART was either NNRTI or boosted PI plus 2 NRTIs
- Completed follow-up from baseline for at least 96 weeks
- Signed informed consent

3.4 Exclusion Criteria

- HIV-2 infection

3.5 Subgroups of study population

The study population will be divided to several subgroups based on the baseline demographic and clinical characteristic which are the following:

1) Age: < 40, 40-60, > 60 years;
2) Gender: male, female, transgender;

3) Employment status: employed, unemployed, student, pensioner, incarcerated;
4) Marital status: married, single, divorced;
5) Substance abuse: no, alcohol, drugs;
6) HIV diagnosis duration at baseline: 0-0.5, 0.5-1, 1-2, 2-3, 3-5, >5 years;
7) Route of infection: IV drug use, homosexual (MSM), heterosexual, other;
8) HIV stage (if applicable): I-V;
9) Baseline viral load: <50 000, 50 000-100 000, >100 000 copies/ml;
10) Baseline CD4 cells count: <50, 50-100, 101-200, 201-350 and >350 cells/µl;
11) Concomitant medications at baseline: 0, 1-2, 3-5, >5;
12) Comorbidities at baseline: No, Yes CV disease, diabetes mellitus, CK disease, liver disease, viral hepatitis, pulmonary disease, tuberculosis, CNS disease, psychiatric disorder;
13) ART therapy: NNRTI plus two NRTIs; PI boosted by ritonavir with 2 NRTIs.

4 Variables and Outcomes

4.1 Patient Demographics

The following demographic parameters will be retrospectively recorded at baseline:

- Age (years);
- Gender: male, female, transgender;
- Employment status: employed, unemployed, student, pensioner, incarcerated;
- Marital status: married, single;
- Substance abuse: no, alcohol, drugs.

4.2 Clinical Variables

The following clinical parameters will be retrospectively recorded at baseline:

1) HIV diagnosis duration at baseline (years);
2) Route of infection: IV drug use, homosexual (MSM), heterosexual, other;
3) HIV stage (if applicable): I-V;
4) Baseline viral load (copies/ml);
5) Baseline CD4 cells count (cells/µl);
6) Concomitant medications at baseline;
    a. Data will be retrospectively captured on medication given for the treatment for any disorder/disease but HIV/AIDS at baseline

7) Comorbidities at baseline: No, Yes – CV disease, diabetes mellitus, CK disease, liver disease, viral hepatitis, pulmonary disease, tuberculosis, CNS disease, psychiatric disorder;
8) ART therapy: NNRTI plus two NRTIs; PI boosted by ritonavir with 2 NRTIs.

It should be noted that demographic and clinical variables collected in this non-interventional retrospective study are recommended for daily-practice clinical record keeping for the management of HIV-infection in Russia. Thus, these variables are available for the majority of the HIV-infected patients in regular clinical practice and can be collected within locally applicable legal and ethical framework for non-interventional research.

4.3 Outcomes

4.3.1. Treatment Durability

Treatment durability is determined as a percentage of patients continuing their first-line ART with NNRTI plus 2 NRTIs or PI boosted by ritonavir with 2 NRTIs for 48 and 96 weeks without change of the NNRTI or PI agent ("anchor" or "third agent") within the class or without change of the NNRTI or PI agent to a different class.

According to the Primary objective, the treatment durability is to be retrospectively evaluated at 48 weeks from the time of initiation.

According to the Exploratory objective, the treatment durability is to be retrospectively evaluated at 96 weeks from the time of initiation.

4.3.1. Time on therapy

According to the Secondary objective, the estimated time on therapy (weeks) without change of the NNRTI or PI agent ("anchor" or "third agent") is to be retrospectively evaluated at week 48 from the time initiation.

According to the Exploratory objective, the estimated time on therapy (weeks) without change of the NNRTI or PI agent ("anchor" or "third agent") is to be retrospectively evaluated at week 48 from the time initiation.

4.3.2. Association between of patients characteristics and treatment durability

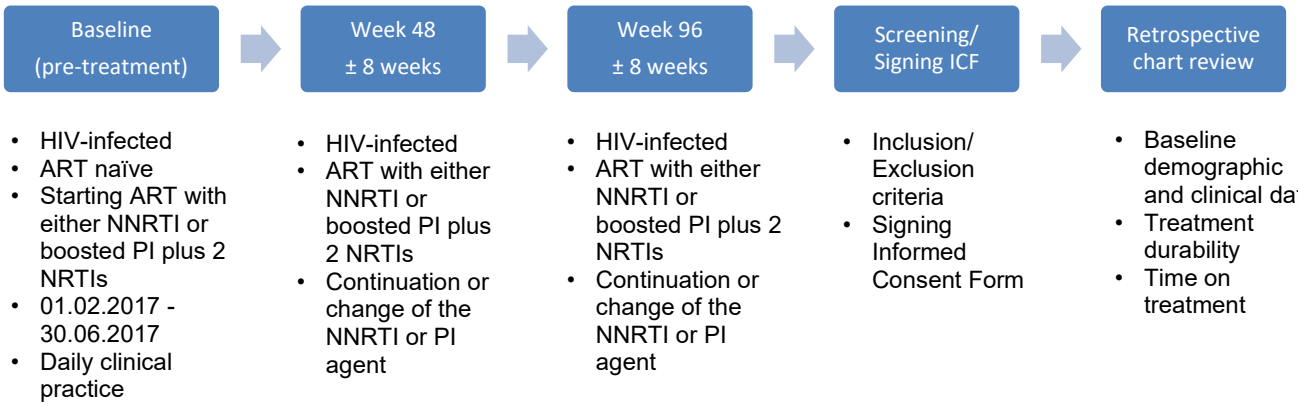
According to the Secondary objective, association between clinical and demographic characteristics of patients and treatment durability at 48 weeks will be retrospectively evaluated.

According to the Exploratory objective, association between clinical and demographic characteristics of patients and treatment durability at 96 weeks will be retrospectively evaluated.

5 STUDY PROCEDURES OF DATA COLLECTION

The Study Flow Chart and Study Procedures Table summarize the procedures of data collection to be performed retrospectively. Individual study procedures of retrospective data collection are described in detail below.

Study Flow Chart



Study Procedures

Study period	Screening	Retrospective clinical data extraction through chart or medical records review
Visit Number	**0**	**1**
Screening and chart review	X	
Informed consent	X	
Inclusion/Exclusion criteria	X	
Age at baseline		X
Gender at baseline		X
Employment status at baseline		X
Marital status at baseline		X
Substance abuse		X
HIV diagnosis duration at baseline		X
Route of infection at baseline		X
HIV stage at baseline		X
Viral load at baseline		X
CD4 at baseline		X
Concomitant medications at baseline		X
Comorbidities at baseline		X
Initial ART at baseline		X
Treatment durability: NNRTI or PI continuation at Week 48/96		X
Estimated time on treatment with NNRTI or PI at Week 48/96		X
Adverse events at baseline and at Week 48/96		X

5.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before the demographic and clinical data are extracted through retrospective chart or medical records review.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

5.2 Withdrawal/Discontinuation

The patient may withdraw his/her consent to participate in the study at any time for any reason. This decision will not have any consequences for his/her future medical care. The sponsor may stop the study at any time. In such case, all investigators will be informed in advance.

5.3 Retrospective Data Collection (Clinical Assessments)

This retrospective study will only involve Secondary Data Collection by reviewing medical chart generated in routine clinical cares.

Data will be retrospectively collected from up to 8 investigational sites with up to 200 patients recruited per site. It is planned that the first half of the study population (500 patients) will be enrolled during the first 6-9 months and the second half of the study population (500 patients) during the second 6-9 months of the study.

Based on the protocol, an electronic data capture (EDC) or electronic clinical reporting form (eCRF) will be developed for data collection. Each local center will be asked to enter the data into the EDC. All the data collected will be entered into a single database stored centrally and analyzed.

If any reportable safety events are identified during retrospective chart review, it is to be ensured they are reported as per section 6 of the protocol.

5.4 Interim Statistical Analysis

Interim Statistical Analysis will be performed when data retrospectively collected from at least 500 patients during the first 6-9 months of the study.

6 Safety Reporting and Related Procedures

Adverse Event Reporting Language for Non-Interventional Study Protocols

Introduction

This is a non-interventional study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

6.1 Adverse Event and Product Quality Complaint Reporting

6.1.1 INVESTIGATOR RESPONSIBILITY:

Although adverse events (AEs) and product quality complaints (PQCs) are not actively solicited in this study, there are certain circumstances in which individual AEs and/or PQCs will be reported. For example, during review of medical records or physician notes (paper or electronic), to collect data as required by the protocol, if a notation of an AE* or PQC to any Merck product is identified, the AE/PQC must be reported according to Table 1.

*For the purposes of this protocol, the term "AE" collectively refers to the following reportable events (refer to section 6.2 for definitions):

- Serious adverse reactions (SARs), including death
- Non-serious adverse reactions (NSARs)
- Special situations
- Study-specific Health Outcomes of Interest (HOIs) that meet criteria for SAR/NSAR or special situation

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to Table 1.

Table 1: AE and PQC Reporting Timeframes and Process for Investigators

AEs AND PQCs	INVESTIGATOR TIMEFRAMES Investigator to MSD [1]
SAR (including study-specific HOIs that meet criteria for SAR Serious Special Situation, regardless of causality	24 hours from receipt
NSAR (including study-specific HOIs that meet criteria for NSAR) Non-serious Special Situation, regardless of causality	10 CD from receipt
PQC with or without an AE (SAR/NSAR/Special situation)	24 hours from receipt
Spontaneously reported AEs/PQCs for Merck products-submit using above timeframes	
Follow-up to any AE/PQC-submit using above timeframes	
BD-Business Day; CD-Calendar Day	

If the investigator elects to submit AEs/PQCs for **non-MSD products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.
[1] Investigator to MSD: AEs and PQCs for MSD products are submitted to MSD for reporting to worldwide regulatory agencies as appropriate.
Submitting AEs and PQCs to Local Designated Point of Contact (DPOC): All AEs and PQCs must be submitted to Local DPOC Mailbox FAX +7 495 228 32 39 in English using the AE/PQC reporting form.

6.2 DEFINITIONS

6.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

6.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

6.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

6.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 6.2.3.

6.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent

- Unexpected Therapeutic Benefit/Effect

6.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnoses, treatments or procedures. Examples of HOIs include syncope, disease progression, or hypoglycaemia collected as study endpoints. HOIs may meet the criteria of an SAE/SAR, NSAR or special situation, and if so, must be collected as such, in addition to being collected as an HOI. Specifically, collected HOI data must be assessed for the criteria described herein and reported accordingly.

6.2.7 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

6.2.8 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

6.2.9 Sponsor's Product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

6.2.10 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form for each reported event in relationship to a Sponsor's product.

Secondary Data Collection

Only AEs with an explicit and definitive notation (by a healthcare provider) of a causal relationship with a product in the medical records or other secondary data being reviewed should be reported as NSAR/SARs. During review of secondary data, causality should never be assigned retrospectively.

7 Statistical Analysis Plan

7.1 Statistical Methods

Data will be presented descriptively as follows: the number of observations, mean and standard deviation, median, first and third quartiles, minimum and maximum for continuous variables, and the absolute frequencies and percentage of patients presenting the given feature for qualitative variables. The results on the study endpoints (proportion of patients who remain on first-line ART at 48 and 96 weeks) will be presented with two-

sided 95% confidence intervals. Univariate and multivariate logistic regression will be used to study the association between patients' baseline demographic and clinical characteristics and treatment discontinuation status.

7.1.1 Primary Objective:

- Percentage of HIV-infected patients remained on first-line ART at 48 weeks after the start of treatment will be presented descriptively with 95% confidence interval by initial ART regimen (NNRTI or boosted PI plus 2 NRTIs) and overall

7.1.2 Secondary Objectives:

- Time on therapy (weeks) without change of the NNRTI or PI agent at week 48 from the ART initiation will be presented in Kaplan-Meier plots
- Demographic and clinical characteristics at baseline will be presented descriptively by initial ART regimen (NNRTI or boosted PI plus 2 NRTIs) and overall
- Association between characteristics of patients and treatment durability at 48 weeks will be investigated via:
    - Subgroup analysis: number and percent of patients continuing treatment at 48 weeks will be presented descriptively by demographic and clinical characteristics categorized according to 8.1.4
    - Multivariate logistic regression analysis to identify potential risk factors for discontinuation of initial ART at 48 weeks. Demographic and clinical characteristics categorized according to 8.1.4 will be included into multivariate analysis only if they are found significant in univariate logistic regression analysis. Unadjusted (univariate model) and adjusted (multivariate model) odds ratios will be presented with 95% confidence intervals for the parameters included in each of the analyses.
- Percentage of HIV-infected patients remained on first-line ART at 96 weeks after the start of treatment will be presented descriptively with 95% confidence interval by initial ART regimen (NNRTI or boosted PI plus 2 NRTIs) and overall
- Time on therapy (weeks) without change of the NNRTI or PI agent at week 96 from the ART initiation will be presented in Kaplan-Meier plots
- Association between characteristics of patients and treatment durability at 96 weeks will be investigated via:
    - Subgroup analysis: number and percent of patients continuing treatment at 96 weeks will be presented by demographic and clinical characteristics categorized according to 8.1.4

- Multivariate logistic regression analysis to identify potential risk factors for discontinuation of initial ART at 96 weeks. Demographic and clinical characteristics categorized according to 8.1.3 will be included into multivariate analysis only if they are found significant in univariate logistic regression analysis ($p<0.1$). Unadjusted (univariate model) and adjusted (multivariate model) odds ratios will be presented with 95% confidence intervals for the parameters included in each of the analyses.

7.1.3 Subgroup analysis

The study population will be divided to several subgroups based on the baseline demographic and clinical characteristics. The following categories will be used for the subgroup analysis:

1) Age: < 40, 40-60, > 60 years;
2) Gender: male, female, transgender;
3) Employment status: employed, unemployed, student, pensioner, incarcerated;
4) Marital status: married, single, divorced;
5) Substance abuse: no, alcohol, drugs;
6) HIV diagnosis duration at baseline: 0-0.5, 0.5-1, 1-2, 2-3, 3-5, >5 years;
7) Route of infection: IV drug use, homosexual (MSM), heterosexual, other;
8) HIV stage (if applicable): I-V;
9) Baseline viral load: <50 000, 50 000-100 000, >100 000 copies/ml;
10) Baseline CD4 cells count: <50, 50-100, 101-200, 201-350 and >350 cells/µl;
11) Concomitant medications at baseline: 0, 1-2, 3-5, >5;
12) Comorbidities at baseline: No, Yes CV disease, diabetes mellitus, CK disease, liver disease, viral hepatitis, pulmonary disease, tuberculosis, CNS disease, psychiatric disorder;
13) ART therapy: NNRTI plus two NRTIs; PI boosted by ritonavir with 2 NRTIs.

7.1.4 Interim Statistical Analysis

Interim Statistical Analysis will be performed when data retrospectively collected from at least 500 patients during the first 6-9 months of the study. Since this observational study is not aimed at testing any hypothesis, no adjustment on significance level will be applied.

7.2 Bias

Potential sources of bias are errors in recruitment.

7.2.1 Methods to Minimize Bias

Bias from errors in recruitment of patients can be reduced with rigorous adherence to inclusion/ exclusion criteria when recruiting patients for the study.

7.2.3 Limitations

In this a retrospective study the quality of the data is important. And the potential issue of missing data is a limitation of the study.

Therefore, it is important for the sponsor or designee to monitor data completion and perform quality checks during the study. To minimize missing data, a set of core variables is required to be available at enrollment as part of inclusion criteria.

There is a risk that patients who had already been receiving ART might be enrolled due to unavailable medical records from his/her previously clinic which is not a part of the study.

7.3 Sample Size and Power Calculations

There is no formal hypothesis testing the current study. Sample size justification is based on desired precision for the estimation of the primary variable – proportion of patients who continue the first line ART regimen at 48 weeks without changes.
The assumed 1-year discontinuation rate, based on published research, is 30% [20], therefore the assumed proportion of patients who remain on the first line ART regimen at 48 weeks is 70%. Precision (half-width of the 95% Wald confidence interval for the proportion) and 95% confidence intervals (CIs) for the proportion resulting from a range of sample sizes are presented in the table below:

Assumed Proportion	Patients enrolled	Patients with known status	95% CI Lower bound	95% CI Upper bound	95% CI Actual width (precision)
70.0%	250	250	64.3%	75.7%	11.4% (±5.7%)
70.0%	500	500	66.0%	74.0%	8.0% (±4.0%)
70.0%	750	750	66.7%	73.3%	6.6% (±3.3%)
70.0%	**1000**	**1000**	**67.2%**	**72.8%**	**5.7% (±2.8%)**
70.0%	1250	1250	67.5%	72.5%	5.1% (±2.5%)
70.0%	1500	1500	67.7%	72.3%	4.6% (±2.3%)

8 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 Confidentiality

8.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the

investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

8.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

8.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

8.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

8.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes

later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

8.5 Quality Management System

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

8.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

For an outsourced study the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

9 Publications

The Risk Management Subteam (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any interim report. The safety and conclusion sections of the final study report or interim report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

The study results will be submitted as abstract submission to relevant international and local HIV congresses. A manuscript will be drafted and submitted for publication in local/international scientific/professional journal.

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11 Attachments

External Adverse Event and Product Quality Complaint Form

MSD **External Adverse Event and Product Quality Complaint Form**

Case Details

Date Received	Country of Incidence	Program/Study ID#	Program/Study Name
	Russia	NIS 8370	Retrospective evaluation of treatment durability

Sender Details (Business Partner (BP), Investigator, Vendor, Supplier)

Name/Initials: Email Address:	BP/Vendor ID#

Patient Details (complete in accordance with local privacy laws)

Name/Initials: Address:	Patient/Subject ID#

Anonymized ☐ Unknown ☐	DOB:	Age:	Age Group:
Sex: Male ☐ Female ☐ Unknown ☐	Pregnant: Yes ☐ No ☐ NA ☐	If yes, date of last menstrual period?	

Reporter Details (complete in accordance with local privacy laws)

Name/Initials:	Address:		
Anonymized ☐ Unknown ☐	Phone:	Fax:	Email:
Physician ☐ Pharmacist ☐ Other Health Prof ☐ Consumer ☐ Lawyer ☐	Is the Reporter/HCP willing to be contacted? Yes ☐ No ☐ Unknown ☐		

Product(s) Details

Product Name Suspect (S) Concomitant (C)	Formulation Dose/Frequency	Indication	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Action Taken	Lot/Batch/Serial #/ Model#/Catalog#/UDI#

Adverse Event/Product Quality Complaints

Event	Onset Date	Outcome
		Fatal ☐ Not recovered ☐ Recovered ☐ Recovering ☐ Sequelae ☐ Unknown ☐
		Fatal ☐ Not recovered ☐ Recovered ☐ Recovering ☐ Sequelae ☐ Unknown ☐

Was the event considered Serious? Yes ☐ No ☐ Unknown ☐
If yes, select all that apply (see cover page for details): Hospitalization ☐ Life Threatening ☐ Death ☐ Disability ☐ Medically Significant ☐
Congenital Anomaly ☐ Required Intervention to Prevent Permanent Impairment or Damage (Devices) ☐ Other (provide details in narrative) ☐

Was the Adverse Event(s) related to the product? Yes ☐ No ☐ Unknown ☐	This is a non-interventional study/program with no HCP assessment of seriousness or causality ☐

Is this a Product Quality Complaint? Yes ☐ No ☐ Is the product available for return, if requested? ☐ Yes, provide contact details ☐ No, specify reason (if known)	Medical Devices Only:	
	Date Implanted	Date Explanted
	Initial Use ☐ Repeated Use ☐	Operator of Device: HCP ☐ Non-HCP ☐ Other ☐

Description of Adverse Event(s) and/or Product Quality Complaint: *Information not captured in the fields (other products taken by the patient, current medical conditions, relevant medical history, laboratory tests etc.)*

Merck Study Lead's name and contact details: Vladimir Achikyan, Medical Affairs Manager
vladimir.achikyan@merck.com

General Guidance for completing External Adverse Event and Product Quality Complaint Form

MSD General Guidance for completing External Adverse Event and Product Quality Complaint Form

- **Complete all sections** that apply
- **Dates** should be entered as DD-MMM-YYYY. If exact dates are unknown, provide the best estimate. Partial dates are acceptable.
- **Date Received**: Earliest date initial and/or follow up adverse event information is received by company employee or person/agent acting on the company's behalf. For Non-Interventional Studies (NIS), where there is both an Investigator and Vendor, this field should be completed by the Vendor if the Vendor is managing AE reporting from the Investigator to MSD.
- **Patient/Reporter Details**: Name or initials
  - Anonymized: Patient/reporter details need to be withheld for privacy
  - Unknown: Patient/reporter details are not known
- **Product:** Trade/brand name(preferred) Generic Name (acceptable)
- **Action Taken:** Dose (decreased, increased, interrupted, or not changed), Withdrawn, Unknown, NA
- **Lot/Batch/Serial #/ Model#/Catalog#/UDI#**: provide all numbers exactly as they appear on the device or device labeling (including spaces, hyphens, etc.) or pharmaceutical product (lot/batch), as applicable.
- **Seriousness:** Adverse event resulted in:
  - **Hospitalization:** prolonged hospital stay, or an emergency room visit results in hospital admission
  - **Life-threatening**: Substantial risk of dying or continued product use may have resulted in death
  - **Death:** Death (include the date, cause of death, if known)
  - **Disability:** significant, persistent or permanent impairment or diminished quality of life
  - **Medically Significant**: could have jeopardized the patient or required medical or surgical intervention (treatment) to prevent serious outcome
  - **Congenital Anomaly/Birth Defects:** Outcome in a child from exposure to a medical product prior to conception or during pregnancy
  - **Required Intervention to Prevent Permanent Impairment or Damage:** Medical or surgical intervention was necessary to preclude permanent impairment of a body function or permanent damage to a body structure
- **Was the Adverse Event related to the product?** For multiple events, detail in narrative
- **Narrative:** Summary of all relevant medical information (clinical course, treatment) office visit notes, hospital discharge summary (if applicable)

12 SIGNATURES

12.1 Sponsor's Representative

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

12.2 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 6 – Safety and Product Quality Complaint Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

12.3 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 6 – Safety and Product Quality Complaint Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	