Title Page

Title	Pro**S**pective, Mult**I**-Center, Observational Progra**M** to Assess the Effectiveness of Dual Thera**P**y (**L**opinavir/ritonavir + Lamivudin**E**) in Treatment-Experienced HIV Infected Patients in the Routine Clinical Settings of the Russian Federation (**SIMPLE**)
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Procedure Number	Not applicable
Marketing Authorisation Holder(s)	AbbVie Deutschland GmbH & Co. KG, Knollstrasse 67061 Ludwigshafen, Germany
Joint PASS	Not applicable
Research Question and Objectives	To assess the virologic effectiveness of dual therapy (lopinavir/ ritonavir (LPV/r) + lamivudine (3TC)) in population of treatment-experienced HIV-1 infected patients with an undetectable plasma HIV-1 RNA level (for at least 6 months) at the 48 week timepoint of treatment in the routine clinical settings of the Russian Federation.
Country(-ies) of Study	Russian Federation
Author	[redacted]

This study will be conducted in compliance with this protocol.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	AbbVie Deutschland GmbH & Co. KG, Knollstrasse 67061 Ludwigshafen, Germany
MAH Contact Person	Not applicable

1.0 Table of Contents

2.0 Abbreviations

3TC	Lamivudine
AIDS	acquired immune deficiency syndrome
AE	Adverse event
ART	Antiretroviral Therapy
CI	Confidential Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
CVD	Cardiovascular Disease
eCRF	Electronic Case report form
EDC	Electronic Data Capture
GPV	Global Pharmacovigilance
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
LPV/r	Lopinavir/ ritonavir
MAH	Marketing Application Holder
MedDRA	Medical Dictionary for Regulatory Activities
NC=F	Non-completer=Failure algorithm
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PI	Protease Inhibitor
PMOS	Post-Marketing Observational Study
RNA	Ribonucleic acid
SAE	Serious adverse event

3.0 Responsible Parties

AbbVie

[redacted]

Contract Research Organization (CRO)

[redacted]

4.0 Abstract

Title: Prospective, Multi-Center, Observational Program to Assess the Effectiveness of Dual Therapy (Lopinavir/ritonavir + Lamivudine) in Treatment-Experienced HIV-1 Infected Patients in the Routine Clinical Settings of the Russian Federation

Rationale and Background: Standard of care treatment of HIV-1-infected patients is usually associated with the use of a triple antiretroviral therapy (ART) with regimens including two nucleos(t)ide analogues (NRTIs) (4). NRTIs are not always well tolerated (short and long term). For example, some NRTIs can cause anemia (zidovudine), neurotoxicity and lipodystrophy (stavudine and didanosine) and kidney dysfunction (tenofovir). Cardiovascular disease (CVD) is also associated with abacavir in some cohort studies (5 - 7). Lamivudine (3TC) is an effective NRTI with good safety profile that has been widely used as a first line drug for the treatment of HIV infected adults and children. The antiviral potency of LPV/r (lopinavir/ritonavir) has been clearly demonstrated in a wide spectrum of patients in a number of different clinical trials, for periods of up to seven years (13-14).

LPV/r+3TC dual therapy has been studied in HIV-1-naïve and HIV-1 experienced patients in the GARDEL and OLE studies respectively (1-3). Over 48 weeks, LPV/r + 3TC demonstrated non-inferior efficacy and comparable safety to LPV/r + 2 NRTIs, as first line regimen in GARDEL study and as maintenance therapy in virologically suppressed patients in OLE study (1-3).

Efficacy data for LPV/r+3TC dual therapy data from treatment-experienced HIV-1 populations are overwhelmingly from OLE study (1) whereas no data exists on that effectiveness of LPV/r + 3TC in treatment-experienced HIV-1 infected patients in routine clinical settings of the Russian Federation.

Research Question and Objectives:

Primary Objective

To assess the virologic effectiveness of dual therapy (lopinavir/ ritonavir (LPV/r) + lamivudine (3TC)) in population of treatment-experienced HIV-1 infected patients with an undetectable plasma HIV-1 RNA level (for at least 6 months) at the 48 week timepoint of treatment in the routine clinical settings of the Russian Federation.

Secondary Objectives

1. To evaluate virologic effectiveness of dual therapy at week 24.
2. To evaluate immune reconstitution on the dual therapy at weeks 24 and 48.
3. To assess the development level of drug resistance over 48 weeks of treatment.
4. To evaluate metabolic and anthropometric parameters change over 48 weeks of treatment.
5. To evaluate the safety and tolerability of dual therapy (LPV/r + 3TC)

Study Design: This is a non-interventional, product-focused, longitudinal and multi-center study with no control group.

Population: HIV-1 infected patients aged 18 years and older on any triple HAART with undetectable plasma HIV-1 RNA level for at least 6 months (two consequently plasma HIV-1 RNA levels) transferred as medically appropriate to LPV/r + 3TC in the routine clinical settings.

Endpoints

Primary endpoint

1. Proportion of patients on dual therapy (LPV/r + 3TC) with undetectable plasma HIV-1 RNA level at week 48 of the observational period.

Secondary endpoints

1. Proportion of patients on dual therapy (LPV/r + 3TC) with undetectable HIV-1- RNA level at week 24 of the observational period.
2. Absolute values of HIV-1- RNA viral loader at weeks 24 and 48 and the change as compared to the baseline (untransformed and base-10 logarithm transformed data).
3. Absolute values of CD4+ T-cell counts at weeks 24 and 48 and the change as compared to the baseline.
4. Proportion of patients who develop resistance to each drug in the study regimen.
5. Absolute values at weeks 24 and 48 and changes of anthropometric measurements (arm, hip and waist circumference in cm) as compared to the baseline.

6. Absolute values at weeks 24 and 48 and changes of metabolic parameters (glucose, insulin, total cholesterol, LDL- and HDL-cholesterol, trigclycerides, creatinine) as compared to the baseline.
7. Proportion of patients with AEs (non-serious AEs spontaneously reported [including AE causing treatment discontinuations], SAEs, [including SAEs that cause deaths]) over the study period.

Data Sources: Data for the study will be collected from clinical interview with the parent and from source documents at the center. Source documents will be original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, etc.

Study Size: The OLE study (1) reported that 87.8% of pre-suppressed treatment-experienced HIV-1 infected patients remained suppressed (undetectable plasma HIV-1 RNA level) on the LPV/r plus 3TC arm at 48 weeks, with non-inferiority to the LPV/r plus 2 NRTi control arm. Therefore, for this observational program, it is estimated that a similar percentage of the patients among study sample will have undetectable plasma HIV-1 RNA level at week 48. When the sample size without a consideration of dropout is 196, a Simple Asymptotic two-sided 95% confidence interval for a single proportion using normal distribution will extend 5% (i.e. half width of the 95% confidence interval) from the observed proportion for an expected proportion of 85%. Considering an approximate dropout rate about 10%, number of enrolled patients will constitute 216.

Data Analysis: Since this is an open-label, non-randomized trial, the analyses will primarily involve the generation of descriptive summary statistics. Quantitative variables will be summarized with number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum values. Qualitative variables will be summarized with the number and proportion of patients in each category. In addition, two-sided 95% confidence intervals will be generated for parameter estimates. Graphs may be generated for visual interpretation of the results, as appropriate.

Milestones:

Start of Data Collection:	16 October 2015
End of Data Collection:	14 April 2017
Interim Report:	15 November 2016
Final Report of Study Results:	10 December 2017

5.0 Amendments and Updates

Not applicable by now.

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection:	16 October 2015
End of Data Collection:	14 April 2017
Study Progress Report:	N/A
Interim Report:	15 November 2016
Registration in the EU PAS register	N/A
Final Report of Study Results:	10 December 2017

7.0 Rationale and Background

7.1 Background

Standard of care treatment of HIV-1 infected patients is usually associated with the use of a triple antiretroviral therapy (ART) with regimens including two nucleos(t)ide analogues (NRTIs) (4). NRTIs are not always well tolerated (short and long term). For example, some NRTIs can cause anemia (zidovudine), neurotoxicity and lipodystrophy (stavudine and didanosine) and kidney dysfunction (tenofovir), cardiovascular diseases is also associated with abacavir in some cohort studies (5 - 7).

In addition, the selection of drugs in the regimens of ART should take into account interactions with drugs for the treatment of comorbidities diseases such as tuberculosis and hepatitis C. Excluding these interactions as treatment for HIV and related diseases may be ineffective. And finally, the drugs included in the standard triple ART regimens, and in some cases may not be available for use for different reasons.

NRTI-sparing studies have historically focused on monotherapy with a protease inhibitor (PI) boosted with ritonavir (lopinavir or darunavir) (8, 9). However, although there are studies reporting non-inferiority of this strategy when used following HAART-led viral suppression, the proportion of patients showing one or more episodes of detectable viral load is usually higher in the groups treated with boosted PI monotherapy (10). Maintaining or adding lamivudine (or 3TC) to this strategy could help overcome this limitation. 3TC is an effective drug with good safety profile that has been widely used as a first line drug for the treatment of HIV-1 infected adults and children. This drug is susceptible to a single point mutation in the HIV-1 genome (M184V mutation) which renders lamivudine inactive but also impacts the viral replicative capacity (11). The antiviral potency of LPV/r (lopinavir/ritonavir) has been clearly demonstrated in a wide spectrum of patients in a number of different clinical trials, for periods of up to seven years (13-14).

LPV/r+3TC dual therapy was studied in HIV-1-naïve and HIV-1 experience patients in the GARDEL and OLE studies respectively (1-3). Over 48 weeks, LPV/r + 3TC demonstrated non-inferior efficacy and comparable safety to LPV/r + 2 NRTIs, as first line regimen in GARDEL study and as maintenance therapy in virologically suppressed patients in OLE study (1-3).

The cost of antiretroviral therapy and its cost implications are also increasingly important for the health systems (12). As an added value, simplifying triple therapy to LPV/r plus 3TC may significantly reduce the cost of treatment, especially as 3TC is an established generic ARV.

7.2 Rationale

Efficacy data for LPV/r+3TC dual therapy data from treatment-experienced HIV-1 populations are overwhelmingly from OLE study (1) whereas no data exists on that real world effectiveness of LPV/r + 3TC in treatment-experienced HIV-1 infected patients in the routine clinical settings of the Russian Federation.

Experience of using the dual therapy (LPV/r+3TC) regimen in the Russian routine clinical settings could lead to its addition to the National guidelines and provide the advantage of the additional and less expensive regimen of choice for stakeholders.

8.0 Research Question and Objectives

8.1 Primary Objective

To assess the virologic effectiveness of dual therapy (lopinavir/ ritonavir (LPV/r) + lamivudine (3TC)) in population of treatment-experienced HIV-1 infected patients with an undetectable plasma HIV-1 RNA level (for at least 6 months) at the 48 week timepoint of treatment in the routine clinical settings of the Russian Federation.

8.2 Secondary Objectives

1. To evaluate the virologic effectiveness of dual therapy at week 24.
2. To evaluate the immune reconstitution on the dual therapy at weeks 24 and 48.
3. To assess the development level of drug resistance over 48 weeks of treatment.
4. To evaluate the metabolic and anthropometric parameters change over 48 weeks of treatment.
5. To evaluate the safety and tolerability of dual therapy (LPV/r + 3TC)

9.0 Research Methods

9.1 Study Design

This is a non-interventional, product-focused, longitudinal and multi-center study with no control group.

This study design will be used to access the effectiveness of the dual therapy (LPV/r + 3TC) in population of treatment-experienced HIV-1 infected patients with an undetectable plasma HIV-1 RNA level (for at least 6 months) at the 48 week time point of treatment in the routine clinical settings of the Russian Federation.

9.2 Product Supply

As this is a post-marketing observational study, AbbVie is NOT involved in the product supply since the drug is being used according to the approved market label and is to be prescribed by the physician under usual and customary practice of physician prescription.

9.3 Setting

For purpose of this program participants will be recruited and observed in approximately 15 national and regional AIDS centers.

9.4 Program Duration

Enrollment will start from 16 October 2015 and continue approximately 6-8 months LPV/r + 3TC will be administrated according to physician's prescription and the local label to all enrolled subjects. All enrolled patients will be followed by a personal or telephone contact at 30 days after their last dose in the study. All visits of the program will be organized according to routine clinical practice (approximately every 3 months).

9.5 Investigator selection criteria

In order to assure credibility of the final results the below listed criteria will be considered during the recruitment process of physician/investigators:

- Physician licensed in infection diseases;
- Physician is working at a national or regional AIDS center;
- Availability of patient population fulfilling the inclusion/exclusion criteria;
- Ability to appropriately conduct the observational program.

9.6 Inclusion Criteria

ART therapy will be prescribed by physician according to the routine clinical practice. Patient can be included in the study, if he/she will be switched on the dual therapy (LPV/r + 3TC) due to any reason such as documented toxicity, management of potential drug interactions, side effects, prevention of long-term toxicity (pre-emptive switch), patient wish to simplify regimen, actual regimen no longer recommended, etc, and will be satisfy the following criteria:

1. Age 18 years and older (male and female).

2. HIV-1 infected patients on any triple HAART with plasma HIV-1 RNA level <50 copies/mL for at least 6 months (two consequently plasma HIV-1 RNA levels) transferred as medically appropriate to LPV/r + 3TC as decided by the physician in the routine clinical settings. OR HIV-1 infected patients who were switched on the dual therapy (LPV/r + 3TC) no more than 60 days ago.

3. Cumulative HAART experience at least 6 months.

4. Authorization (Consent) for Use/Disclosure of Data signed by the patient.

9.7 Exclusion Criteria

A patient will not be eligible for this PMOS if he/she fulfils the following criterion:

1. Has contraindications for the treatment with lopinavir/ritonavir and lamivudine (please see the latest versions of the locally approved labels).

2. Previous participation in this program.

9.8 Description of Activities

The patient visits will be scheduled based on routine clinical practice and prescription of consulting physician. However, it would be 5 observational visits (approx. every 3 months) when dual therapy (LPV/r + 3TC) will be administrated to the patient and one follow-up visit/termination contact. Failure to observe these 3-month usual practice intervals of patient visits will not constitute a breach or violation of the protocol.

Table 2. Program Activities

Activity	Visit 1[1] Enrollment	Visit 2	Visit 3	Visit 4[3]	Visit 5[4]	Follow-up Visit/ Termination or Early Termination Contact[3]
ApproximateTimelines[2]	Day 0[2]	Week 12[2]	Week 24[2]	Week 36[2]	Week 48[2]	After 30 day of Last Dose in the Study
Signature on authorization to use and/or disclose personal and/or health data	X					
Inclusion/Exclusion Criteria	X					
HIV-1 RNA test result	X	X	X	X	X	
CD4+ T-cell counts test result	X	X	X	X	X	
Relevant Medical History	X					
Result of resistance test[4]	X	X	X	X	X	
Registration of prescribed medications	X	X	X	X	X	
Anthropometric parameters[5]	X		X		X	
Laboratory tests results[6]	X		X		X	
SAE monitoring	X	X	X	X	X	X
Completion form						X

[1]Visit of enrollment can fall after first dose of dual therapy administration, if the patient was switched on before the enrollment. See criterion of inclusion #2.

[2]Number of weeks estimated from the switching to the dual therapy.

[3]Personal or telephone contact.

[4]Should be measured and collected if HIV-1 RNA > 50 copies/ml.

[5]Arm, hip and waist circumference (in cm).

[6]Glucose (mmol/L), insulin (µEq/ml), total cholesterol (mmol/L), LDL- and HDL-cholesterol (mmol/L), trigclycerides (mmol/L), creatinine (µmol/L), ALT (u/l), AST (u/l).

Collected data and planned activities within the observational program:

Observational Visit 1 – Enrollment

- Signing of the Authorization (Consent) for Use/Disclosure of Data form by patient

- Assignment of patient's identification number (two-digit center number + three-digit patient individual enrollment number)
- Inclusion/exclusion criteria verification
- Last available CD4+ T-cell count test result
- Last available HIV-1- RNA test result
- Collection of relevant medical history
- Last available resistance test result for LPV/r and 3TC, if any
- Registration of start date and doses of prescribed LPV/r and 3TC
- Collection of anthropometric parameters measurement (arm, hip and waist circumference in cm).
- Collection of laboratory tests results (glucose (mmol/L), insulin (µEq/ml), total cholesterol (mmol/L), LDL- and HDL-cholesterol (mmol/L), trigclycerides (mmol/L), creatinine(µmol/L), ALT (u/l), AST (u/l)).
- SAEs monitoring

Observational visits 2 and 4

- Last available CD4+ T-cell count test result
- Last available HIV-1- RNA test result. If last test result was detectable and re-test was done or planned both test and re-test results will be collected
- Last available resistance test result for LPV/r and 3TC (if plasma HIV-1 RNA level is detectable at a given visit and at the previous visit the plasma HIV-1 RNA was undetectable, data of confirmatory plasma HIV-1 RNA test will be collected after 1 month. If the confirmatory plasma HIV-1 RNA is >400 copies/mL, data of HIV-1 drug resistance genotyping test will be collected, if the consulting physician designated these tests and the such information is available)
- Registration of prescribed medications

Monitoring of AEs (non-serious AEs spontaneously reported) [including AE causing treatment discontinuations], SAEs, [including SAEs that cause deaths]

Observational visits 3 and 5

- Last available CD4+ T-cell count test result
- Last available HIV-1- RNA test result. If last test result was detectable and re-test was done or planned both test and re-test results will be collected
- Last available resistance test result for LPV/r and 3TC
- Registration of prescribed medications
- Collection of anthropometric parameters measurement (arm, hip and waist circumference in cm)
- Collection of laboratory tests results (glucose (mmol/L), insulin (µEq/ml), otal cholesterol (mmol/L), LDL- and HDL-cholesterol (mmol/L), trigclycerides (mmol/L), creatinine(µmol/L), ALT (u/l), AST (u/l))
- Monitoring of AEs (non-serious AEs spontaneously reported) [including AE causing treatment discontinuations], SAEs, [including SAEs that cause deaths]

Follow-up Visit/Termination or Early Termination Contact - Personal or telephone contact

- Monitoring of AEs (non-serious AEs spontaneously reported) [including AE causing treatment discontinuations], SAEs, [including SAEs that cause deaths] Completion form of eCRF has to be completed at the end of the study and also if a patient prematurely discontinued the study. Reason for premature discontinuation will be collected

9.9 Termination of the Program

Decision regarding the discontinuation of the dual therapy (LPV/r + 3TC) for each participant will be ultimately based on the treating physician's judgment. The reason for treatment discontinuation will be collected and summarized in the study report.

AbbVie may stop the program in case there is evidence of harm that is done or could be done to participants if they continue to participate.

9.10 Endpoints

9.10.1 Primary Endpoint

1. Proportion of patients on dual therapy (LPV/r + 3TC) with undetectable HIV-1-RNA level at week 48 of the observational period.

9.10.2 Secondary Endpoints

1. Proportion of patients on dual therapy (LPV/r + 3TC) with undetectable HIV1-RNA level at week 24 of the observational period.
2. Absolute values of HIV-1- RNA viral loader at the weeks 24 and 48 and the change as compared to the baseline (untransformed and base-10 logarithm transformed data).
3. Absolute values of CD4+ T-cell counts at the weeks 24 and 48 and the change as compared to the baseline.
4. Proportion of patients who develop resistance to each class of drugs in the study regimen.
5. Absolute values at the weeks 24 and 48 and changes of anthropometric measurements (arm, hip and waist circumference in cm) as compared to the baseline.
6. Absolute values at the weeks 24 and 48 and changes of metabolic parameters (glucose, insulin, total cholesterol, LDL- and HDL-cholesterol, triglycerides, creatinine, ALT, AST) as compared to the baseline.
7. Proportion of patients with AEs (non-serious AEs spontaneously reported) [including AE causing treatment discontinuations], SAEs, [including SAEs that

cause deaths], with AEs organized according to System Organ Classification (SOCs) and by frequency

9.11 Data Sources

Data for the study will be collected within clinical interview with the patient and source document at the center. Source documents will be original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, etc.

9.12 Study Size

The OLE study (1) reported that 87.8% of pre-suppressed treatment-experienced HIV-1 infected patients remained suppressed (undetectable plasma HIV-1 RNA level)) on the LPV/r plus 3TC arm at 48 weeks, with non-inferiority to the LPV/r plus 2 NRTi control arm. Therefore, for this observational program, it is estimated that a similar percentage of the patients among study sample will have undetectable plasma HIV-1 RNA at week 48.

When the sample size without a consideration of dropout is 196, a Simple Asymptotic two-sided 95% confidence interval for a single proportion using normal distribution will extend 5% (i.e. half width of the 95% confidence interval) from the observed proportion for an expected proportion of 85%. Considering an approximate dropout rate about 10%, number of enrolled patients will constitute 216.

9.13 Data Management

For this program electronic Case report forms (eCRF) will be used. Prior to set-up of eCRF data management plan and data validation specification will be developed by CRO and reviewed/approved by AbbVie representative(s). eCRF will be completed for each subject enrolled in this program. These forms will be used to transmit and collect the program data for AbbVie (or a CRO for data management) and regulatory authorities, as

applicable. Electronic CRFs will be set by CRO designee as web based site. In eCRF data must be entered by trained and authorized person only. eCRF training will be performed for site staff during site initiation. eCRF tracks all changes to the entered data automatically. Data discrepancies detected by eCRF will be addressed to investigator. All information entered in the eCRFs must also be reflected in the patient source documents.

The investigator will store subject data in his/her source documents in accordance to his/her routine practice. These subject files will serve as source data for the program. The principal investigator will review the eCRFs for completeness and accuracy and sign each subject's set of eCRFs by electronic signature where indicated. The eCRFs will be reviewed periodically for completeness, legibility and acceptability by AbbVie/CRO.

9.14 Data Analysis

The principal features of the statistical analysis of the data are described in this section. Since this is an open-label, non-randomized trial, the analyses will primarily involve the generation of descriptive summary statistics. Quantitative variables will be summarized with number of patients, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum values, and 95% CI for mean or median (as appropriate). Qualitative variables will be summarized with the number and proportion of patients in each category. Graphs may be generated for visual interpretation of the results, as appropriate.

Data Analysis Set

The following analysis populations will be defined:

All Enrolled Set will include all patients who signed Authorization (Consent) for Use/Disclosure of Data form to participate in the study and have any collected data. All Enrolled Set be used for all study analyses.

The primary and secondary effectiveness analyses will be performed on the observed data. No imputations for missing data will be performed.

Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics will be summarized with descriptive statistics mentioned above.

Analysis of primary endpoint

Number and proportion of patients on dual therapy (LPV/r + 3TC) with undetectable HIV-1- RNA level at week 48 of the observational period will be presented. A simple asymptotic two-sided 95% confidence interval for a single proportion will be generated.

Analysis of secondary endpoints

1. Number and proportion of patients on dual therapy (LPV/r + 3TC) with undetectable HIV-1- RNA level at week 24 of the observational period will be presented. A simple asymptotic two-sided 95% confidence interval for a single proportion will be generated.

2. Absolute values of HIV-1- RNA viral load at baseline, at weeks 24 and 48 and the change as compared to the baseline (untransformed and base-10 logarithm transformed data) will be summarized with described above statistics. 95% CI for mean will be generated for transformed data and 95% CI for median will be generated for untransformed data.

3. Absolute values of CD4+ T-cell counts at the baseline, at weeks 24 and 48 and the change as compared to the baseline will be summarized with described with abovementioned statistics. 95% CIs for means will be generated.
4. Number and proportion of patients who develop resistance to each drug will be presented separately. The two proportions will be presented: (1) number of patient who develops the resistance divided on number of patients who had the resistance test; (2) number of patient who develops the resistance divided on number of patients who were enrolled in the study. An exact two-sided 95% confidence interval for a single proportion will be generated.

5. Absolute values at weeks 24 and 48 and changes of anthropometric measurements (arm, hip and waist circumference in cm) as compared to the baseline will be summarized with described with abovementioned statistics. 95% CIs for means will be generated.

6. Absolute values at weeks 24 and 48 and changes of metabolic parameters (glucose (mmol/L), insulin (µEq/ml), total cholesterol (mmol/L), LDL- and HDL-cholesterol (mmol/L), trigclycerides (mmol/L), creatinine(µmol/L), ALT (u/l), AST (u/l)) as co pared to the baseline will be summarized with described with abovementioned statistics. 95% CIs for means will be generated.

7. Number and proportion of patients with all AEs (non-serious AEs spontaneously reported) [including AE causing treatment discontinuations], SAEs, [including SAEs that cause deaths]will be presented. An exact two-sided 95% confidence interval for a single proportion will be generated. The common table with all AEs as well as separated tables with non-serious AEs, SAEs, SAE including SAEs that cause deaths, and AEs causing treatment discontinuations will be presented. The tables of AEs will be generated with coded by Preferred Terms (PTs) consistent with the latest version of MedDRA (Medical

Dictionary for Regulatory Activities) . Tables will present information about SAEs (including deaths), non-serious AEs, and AEs causing treatment discontinuation organized according to PT frequencies and by SOC, Severity and Causality. Summary tables of the common AEs, SAEs, and AEs causing treatment discontinuation will be generated and included in the body of the report. A complete tabulated list of these AEs and their frequencies may be appended to the report.

9.15 Quality Control

The AbbVie representatives are responsible for ensuring that a quality control and quality assurance system is in place to ensure that the program is conducted and data generated, documented, and reported in compliance with the protocol, accepted standards and any applicable local laws and regulations.

Study protocol is developed by AbbVie Study Team in accordance with internal templates and guidelines.

The AbbVie representative can monitor the electronic case report forms in EDC. Any discrepancies will be communicated to site for clarification. Any necessary corrections will be made to the database per applicable EDC procedures.

Data Management Plan and Data Validation Specification will be developed by CRO and approved by AbbVie representative before eCRF launch. These documents will describe data process within the study and responsible personal.

Study report will be developed by CRO and reviewed/approved by AbbVie Study Team in accordance with internal templates and guidelines.

9.16 Limitations of the Research Methods

The study is planned as a non-interventional, product-focused, longitudinal and multi-centers study with no control group. The study is aimed to access the effectiveness of the dual therapy (LPV/r + 3TC) in population of treatment-experienced HIV-1 infected patients with an undetectable plasma HIV-1 RNA level (for at least 6 months) over 48 weeks in the routine clinical settings of the Russian Federation.

Therefore, the limitations of the study based on its observational and non-comparative nature and results of the study are valid only for understanding of effectiveness of the dual therapy (LPV/r + 3TC) in routine clinical settings in Russia.

9.17 Other Aspects

Not applicable.

10.0 Protection of Human Subjects

This observational program will be conducted in accordance with Declaration of Helsinki (15) and with Federal Law of 27 July 2006 N 152-FZ “On personal data” (18).

Written authorization to use and/or disclose personal and/or health data must be obtained prior to enrolling each patient in the program and parents not willing to provide such written authorization will not be included in the program. However, all reasonable efforts will be made in order to avoid subject identifying information (such as name, address, etc). All data will be captured and handled in such a way so as to not reveal identity of individual patients and hence patient confidentiality will be maintained at all times.

The protocol and relevant program documents will be submitted for review and approval of Central and/or local (if applicable) Independent Ethics Committee(s) (IEC) and patient enrollment will start only after obtaining written approval from the IEC.

11.0 Management and Reporting of Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 11.2.2). For adverse events, please refer to Sections 11.1.1 through 11.1.6. For product complaints, please refer to Section 11.2.

11.1 Medical Complaints

11.1.1 Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event an result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.1.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

11.1.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event.

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

11.1.4 Serious Adverse Event Collection Period

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days following the intake of the last dose of physician-prescribed treatment.

11.1.5 Serious Adverse Event Reporting

In the event of a serious adverse event, the physician will:

- For events from patients using and AbbVie product - notify the AbbVie contact person identified below within 24 hours of the physician becoming aware of the event.

Contact for SAEs reporting:

[redacted]

Back-up contact for SAEs reporting:

[redacted]

11.1.6 Pregnancy Reporting

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie contact person identified in Section 11.1.5 within 24 hours of the physician becoming aware of the pregnancy.

11.2 Product Complaint

11.2.1 Definition

A Product Complaint is any Complaint (see Section 11.0 for the definition) related to the drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

11.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints involving a non-Sponsor investigational product should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

Primary contact for Product Complaint reporting:

Back-up contact for Product Complaint reporting:

12.0 Plans for Disseminating and Communicating Study Results

At the end of the study, a study report will be written in collaboration with CRO study report author. This report will contain a description of the objectives of the PMOS, the methodology of the study and its results and conclusions. The completed case report forms and the study report must be treated as the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie.

The study will be registered at www.ClinicalTrials.gov and results of the study will be published at this web-based resource after internal approval. Also the results of this PMOS will be published by AbbVie and/or by any one of the participating investigators after prior written agreement from AbbVie in scientific journals and presented at the scientific conferences.

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