Protocol Amendment 2

Study ID: 208982

Official Title of the Study: Durability of Antiretroviral Suppression and the Real World Clinical Profile of the Novel 2-Drug Regimen Juluca, a Onepill-Regimen Consisting of Dolutegravir and Rilpivirine, in Routine Clinical Care in Germany

NCT Number: NCT03518060

Date of Document: 30 June 2020 (This date was redacted on Page 5, as it is part of signature [Personal Information] in the document)

JUNGLE STUDY PROTOCOL

UNIQUE IDENTIFIER/ eTrack ID	208982
FULL TITLE	Durability of Antiretroviral Suppression and the Real World Clinical Profile of the Novel 2-Drug Regimen Juluca, a Onepill-Regimen Consisting of Dolutegravir and Rilpivirine, in Routine Clinical Care in Germany
ABBREVIATED TITLE	JUNGLE
FINAL PROTOCOL APPROVED	06 MAR 2018
SPONSORSHIP	ViiV Healthcare Germany sponsored non-interventional study
DIVISION	ViiV Healthcare
BUSINESS UNIT	Medical Affairs
DEPARTMENT	ViiV Healthcare GmbH, Germany
STUDY ACCOUNTABLE PERSON	PPD
CONTRIBUTING AUTHORS	Dr. PPD PPD
PRINCIPAL INVESTIGATOR	Dr. med. Dr. phil. Celia Jonsson-Oldenbüttel, MVZ Stachus, Germany

ASSET ID	GSK3365791 (Juluca)
ViiV ASSET	JULUCA

INDICATION	FINAL EU LABEL AVAILABLE AFTER CHMP OPINION AND WILL BE UPDATED, US LABEL BELOW: *"JULUCA, a two-drug combination of dolutegravir, a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, a HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of JULUCA."*

REVISION CHRONOLOGY:

Version Date	Document Type	Change(s) since last version
06 MAR 2018	Original	n/a
07 DEC 2018	Amendment 1	The following change was made: **3.2 Study Population (page 14, 3.2 paragraph 2)** All patients will be followed during routine clinical practice and will not be burdened with additional site visits or medical procedures, besides their routine treatment. Inclusion into the study is independent from prescription of Juluca. ~~**and is capped at a maximum of 5 patients per month and 30 patients per site in total.**~~ **Rationale** This limit was set to prevent too many patients being contributed from a limited number of sites, thus ensuring the multicenter character of the study. As 17 out of 26 possible sites have already enrolled patients, this is no longer an issue and removing this limit will both ensure a timely recruitment and allow the study to be a true account of the real world use of Juluca.
15.06.2020	Amendment 2	The following changes were made: Second sponsor signatory and study principal investigator Dr. Ravi Kumar Walli is no longer associated with the study. The role of study principal

		investigator is now being fulfilled by Dr. med. Dr. phil. Celia Jonsson-Oldenbüttel.

Description: JUNGLE
Unique Identifier /eTrack ID: 208982

SPONSOR SIGNATORY

PPD

Date

Annemiek de Ruiter
Head, Global Medical Sciences, ViiV Healthcare

STUDY PRINCIPAL INVESTIGATOR SIGNATORY

Date

Dr. med. Dr. phil. Celia Jonsson-Oldenbüttel
MVZ Stachus, Germany

Description: JUNGLE
Unique Identifier / eTrack ID: 208982

Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:
_____

_____ _____
Investigator Signature Date (DD-MMM-YYYY)

PROTOCOL SYNOPSIS

Unique Identifier/eTrack	208982
Abbreviated Title	JUNGLE
ViiV Product	Dolutegravir/Rilpivirine; JULUCA
Rationale	Gather real-world data on Juluca use in routine clinical care in Germany, to supplement clinical trial data to further improve / optimize patient care in PLHIV in Germany
Objectives (Primary, Secondary)	Primary objective: • Evaluate sustainability of antiretroviral suppression in suppressed patients using Juluca in routine clinical care in Germany to evaluate antiretroviral efficacy of the novel 2-Drug Regimen (2DR) of Juluca Secondary objectives: • Gain an understanding of the major relevant patient populations for Juluca in Germany, in terms of patient characteristics and history • Describe real-life efficacy profile of Juluca • Describe real-life tolerability profile of Juluca as measured by discontinuation rates due to adverse drug reactions (ADRs) and overall number of serious adverse events (SAE) • Analyze the development of viral resistance by evaluating available resistance data in case of virologic failure • Describe impact on lipid metabolism • Evaluate medical need for a substance and/or class sparing treatment regimen by assessing the reason for switching to Juluca • Describe patients' treatment satisfaction and symptom distress based on validated questionnaires • Evaluate number of monitoring measures and referrals to other specialists
Study Design	Prospective, non-interventional, single-arm, multi-center study of patients with a clinical indication for HIV-1 therapy in routine clinical care with an observational period of 3 years
Study Population and Sampling Methods	N=250 HIV-1 positive patients are aimed to be included into this study. Subjects must be on stable ART for at least 6 months prior to the inclusion into this study. Patients' eligibility is based on the local SmPC of Juluca. Any subject with contraindications for Juluca are ineligible for study participation.

	Inclusion criteria: • ≥ 18 years of age • Documented HIV-1 infection • Virologically suppressed (HIV-1 RNA < 50 c/mL for at least 6 months) • Prescription for Juluca was issued independently from entering this study • Ability to understand informed consent form and other relevant study documents Exclusion criteria: • Any contraindication according to Juluca SmPC • Documented viral load > 50 c/ml at any timepoint within 6 months prior to inclusion into this study • History of treatment failure • Known or suspected substitutions associated with resistance to any NNRTI or INSTI • Any antiretroviral therapy for the treatment of HIV-1 in addition to Juluca • HBV-coinfection • Current participation in the ongoing non-interventional study TRIUMPH (study number: 202033) or any interventional clinical trial irrespective of indication • Previous participation in clinical trials involving Juluca Investigators may enroll eligible subjects according to their availability and accessibility. The sample is deliberately non-stratified to reduce limitations on recruitment. This non-probabilistic convenience sampling may not ensure for the sample group to be a true representative of the population without sampling error.
Data Source	• Data collected during routine clinical care will be documented as study visits. This may include data from hospital records, clinical charts, electronic patient records or laboratory notes • Once a year and additionally at first follow-up visit, patients will be asked to complete the HIV Symptom Distress Module and the HIV treatment satisfaction questionnaire on a voluntary basis • At each visit, patients will be prompted to give an estimate of their level of adherence in a single-item question

Data Analysis Methods	Descriptive statistics will be used to analyze all primary and secondary objectives for both total patient population and for pre-defined subgroups. The used questionnaires will be analyzed according to their respective validated scoring instructions. Detailed methodology for summary and statistical analysis of data collected in this study as well as data sets will be specified in a Statistical Analysis Plan (SAP) prior to database lock.
Sample Size and Power	Sample size was calculated based on the assumption of an antiviral efficacy of 90% (defined as VL <50 c/ml) and a max. study dropout rate of 30% over a period of 3 years. To reach a level of confidence of 95% with a target width of 0.1 (10%), a minimum of N=158 subjects are needed at the end of the study. When max. drop-out rate is included, a minimum number of N=226 subjects are needed. Therefore, the recruitment goal is N=250.
Limitations	This is a non-interventional, single-arm study aimed at gathering real-world data on the use of Juluca in routine clinical care in Germany. As such there are a number of limitations. The sample is deliberately non-stratified to reduce limitations on recruitment. And with convenience sampling, the population may also be subject to selection bias. Thus, this approach may result in some characteristics being over or under-represented within in the sample and limited diversity in terms of demographics and introduction of confounding factors. However, real world data may provide valuable evidence for a patient population that is broader than that of controlled clinical trials, thus enhancing the generalizability and transferability of findings despite large random variations due to a heterogenic patient population.

TABLE OF CONTENTS

ABBREVIATIONS

2DR	2-Drug Regimen
ADR	Adverse Drug Reaction
AE	Adverse Event
ART	Antiretroviral Therapy
BfArM	Bundeinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CD	Cluster of Differentiation
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
DTG	Dolutegravir
DVD	Digital Versatile Disc
eCRF	Electronic-Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GKV-SV	National Association of Statutory Health Insurance Funds
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
INSTI	Integrase Strand Transfer Inhibitor
ml	Milliliter
NIS	Non-interventional study
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
ODM	Operational Data Model
PDF	Portable Document Format
PI	Protease Inhibitor
PLHIV	People Living With HIV
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TSQ	Treatment Satisfaction Questionnaire
VH	ViiV Healthcare
VL	Viral Load
XML	Extensible Markup Language

1 INTRODUCTION/BACKGROUND

2-Drug Regimens (2DR) have been investigated for a long time within the HIV community to address special needs of their patients with regard to resistance and / or tolerability issues of existing antiretrovirals [1]. These approaches have been driven by the need to find appropriate treatment regimens for patients with limited therapy options. However, several approaches have shown very promising results in naïve and in pre-treated patients [1, 2, 3].

The SWORD-1 & -2 studies are the first globally conducted registrational trials investigating antiretroviral treatment regimens consisting of 2 substances. The trial data has shown the high potential of the novel 2DR DTG+RPV in stably suppressed HIV-1 patients. The efficacy was non-inferior to the control arm in which patients continued their current ART until the measurement of the primary study endpoint at 48 weeks with 95% of patients below 50 HIV RNA copies/ml. The safety and tolerability profile was good, resulting in only 3% study discontinuations due to drug-related adverse events until week 48 in the DTG+RPV arm [1]. Patient related outcomes revealed a high rate of treatment satisfaction, which was, although very high at baseline in both arms, significantly increased in the DTG+RPV arm. A significant increase compared to the control arm, has been shown in the symptom distress scale, underlining the good tolerability of this regimen [2]. As of November, 21st 2017, Juluca, the first 2-Drug Regimen consisting of DTG and RPV, is licensed in the US for the maintenance treatment of HIV-1 infection in adults who are virologic suppressed (HIV-1 RNA <50 c/ml) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known or suspected substitutions associated with resistance to the individual components of Juluca [3].

In 2016, more than 88.000 patients in Germany were living with HIV, of which 75.700 were aware of their diagnosis and 64.900 were under ART [4]. Based on the current German-Austrian HIV Treatment Guidelines, HIV therapy should be initiated regardless of the CD4 cell count with either Integrase-Inhibitors (INSTI), the NNRTI Rilpivirine or Protease-Inhibitors (PI) (Darunavir or Atazanavir) in combination with a background regimen based on two NRTIs. Monotherapy is generally not recommended as initial therapy. Class- or substance-sparing combinations are mentioned, especially the combination of boosted Lopinavir with 3TC, however, it is not recommended as first-line therapy due to limited clinical experience. The recommendations for treatment switches rely on individual patient characteristics, such as resistance and intolerability, without providing clear guidance. [5]. However, based on the Positive Perspectives study, which is a survey with patients from 9 countries with over 1000 participants answering a questionnaire about psychological aspects of living with HIV, the dialogue between HCP and patients, and patients' treatment satisfaction, there are concerns about ART-related long-term toxicities in patients, favoring substance- or class-sparing treatment options [6]. This possibility to use class-/substance-sparing treatment strategies has been implemented very recently in the EACS guidelines, describing DTG+RPV as a treatment option in suppressed patients [7]. Furthermore,

the current DHHS guidelines mention DTG+RPV as a reasonable option when the use of NRTI is not desirable [8].
Regardless of the current treatment status of a patient, antiretroviral therapy must be taken lifelong to ensure suppression of viral replication, which is the overarching treatment goal and reduces the risk of HIV-associated complications, such as immunosuppression and the occurrence of opportunistic infections, as well as a chronic inflammation, which can result in a higher risk for cardiovascular events. Although antiviral therapies have been improved over the last decades in terms of efficacy and tolerability, most therapies require 3 or more drugs to achieve the overarching therapy goal of viral suppression. This is accompanied with the risk of drug-drug interactions, especially in the case when pharmacologic boosters are required to improve PK-profiles of distinct substances, such as protease-inhibitors and the integrase-inhibitor Elvitegravir [5]. Providing therapies with only two drugs, as in Juluca (DTG / RPV), addresses this obstacle in therapy, with a complete antiretroviral regimen with just 2 active substances. This might be beneficial in terms of pharmacology, especially taking into account that over 50% of all patients living with HIV in Germany are 45 years of age and older. Recent publications have shown, that about 20% of the general population, irrespective of their HIV status, have an intake of at least 2 non-ART drugs in that age category of 50 years or older [9]. Furthermore, it might be beneficial in terms of reducing the overall substance burden during a patients' life, when considered, that patients who have been infected and started their therapy between 2008 and 2010, have a life-expectancy of 78 years, meaning almost six decades of antiviral therapy [10].

Non-interventional studies (NIS) provide insights into the medication use in routine clinical care and generate real-world evidence for the used ART in terms of efficacy and tolerability, which can supplement data from randomized clinical trials.
ViiV Healthcare (VH) Germany is currently sponsoring two NIS, DOL-ART and TRIUMPH, observing patients taking either DTG or Triumeq in routine clinical care. Data generated in both studies are published regularly twice a year on national and international conferences to inform HCPs about the real-world profile of DTG when it is used in routine clinical care in Germany.
Likewise, a prospective multicenter NIS for Juluca will assess the drug profile of the first 2DR in a routine clinical setting in Germany.

2 OBJECTIVES

2.1 Primary

Evaluate sustainability of antiretroviral suppression in suppressed patients using Juluca in routine clinical care in Germany to evaluate antiretroviral efficacy of the novel 2-Drug Regimen (2DR) of Juluca

2.2 Secondary

- Gain an understanding of the major relevant patient populations for Juluca in Germany, in terms of patient characteristics and history
- Describe real-life efficacy profile of Juluca
- Describe real-life tolerability profile of Juluca as measured by discontinuation rates due to adverse drug reactions (ADRs) and overall number of serious adverse events (SAE)
- Analyze the development of viral resistance by evaluating available resistance data in case of virologic failure
- Describe impact on lipid metabolism
- Evaluate medical need for a substance and/or class sparing treatment regimen by assessing the reason for switching to Juluca
- Describe patients' treatment satisfaction and symptom distress based on validated questionnaires
- Evaluate number of monitoring measures and referrals to other specialists

3 RESEARCH METHODOLOGY

3.1 Study Design

This is a non-interventional, single-arm, prospective, multi-center study aimed at generating real-word data for the use of Juluca in HIV-1-postitive patients as indicated by the local SmPC in routine clinical care in Germany to supplement data obtained from controlled clinical trials.

Eligible subjects will be followed up for approximately 3 years collecting information that can be obtained in routine clinical care.

For a detailed schematic of study visits please refer to Appendix 1.

3.2 Study Population

Aim is the recruitment of 250 treatment-experienced and virologically suppressed patients as indicated by the local SmPC of Juluca at the discretion of the treating physician. Recruitment is expected to be concluded within an approximate timeframe of 6 months. If 250 patients cannot be recruited within this timeframe, recruitment period may be extended until a minimum number of 180 patients is reached.

All patients will be followed during routine clinical practice and will not be burdened with additional site visits or medical procedures, besides their routine treatment. Inclusion into the study is independent from prescription of Juluca.

3.2.1 Eligibility Criteria

3.2.1.1 Inclusion Criteria

- ≥ 18 years of age
- Documented HIV-1 infection
- Virologically suppressed (HIV-1 RNA < 50 c/mL for at least 6 months)
- Prescription for Juluca was issued independently from entering this study
- Ability to understand informed consent form and other relevant study documents

3.2.1.2 Exclusion Criteria

- Any contraindication according to Juluca SmPC
- Documented viral load > 50 c/ml at any timepoint within 6 months prior to inclusion into this study
- History of treatment failure

- Known or suspected substitutions associated with resistance to any NNRTI or INSTI
- Any antiretroviral therapy for the treatment of HIV-1 in addition to Juluca
- HBV-coinfection
- Current participation in the ongoing non-interventional study
- TRIUMPH (study number: 202033) or any interventional clinical trial irrespective of indication
- Previous participation in clinical trials involving Juluca

3.2.2 Sampling

HIV-1-positive patients on a stable antiretroviral regimen for whom DTG/RPV is indicated according to the local SmPC may be selected for inclusion. The decision for prescription of the treatment regimen must be completely independent from study inclusion. However, patients eligible for inclusion, should be included with start of the new therapy regimen. Eligible patients must meet all inclusion and none of the exclusion criteria and must be thoroughly informed about all aspects of the study. The written informed consent must be obtained from the patient before any patient data is documented into the eCRF.

Investigators may enroll eligible subjects according to their availability and accessibility. The sample is deliberately non-stratified to reduce limitations on recruitment. This non-probabilistic convenience sampling may not ensure for the sample group to be a true representative of the population without sampling error.
Thus, this approach may result in some characteristics not being represented within the sample and limited diversity in terms of demographics and introduction of confounding factors, which may be considered in subgroup analysis

But as there are few further restrictions introduced by inclusion / exclusion criteria other than what is permitted under the local label, this study may provide evidence for a patient population that is broader than that of controlled clinical trials.

3.3 Data Source / Data Collection

3.3.1 Data documented by study sites

Data will be collected from routine clinical care. Follow-up visits will not exceed those recommended by local guidelines, which suggest routine follow ups every 2-4 months. The frequency of follow-up visits is not defined by the study protocol due to the nature of a non-interventional study and is completely at the discretion of the treating physician. Every regular follow-up should be documented as a study visit. Additional patient contacts that merely involve blood sampling (e.g. viral load re-tests) without any further examination, will not need to be documented as study visits. However, the results of the viral load assessments should be documented. Data may be obtained from clinical records and findings, observations or other sources (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes).

3.3.2 Patient reported data sources (non-mandatory)

At baseline, first follow up and additionally at 12, 24 and 36 months, patients will be asked to complete the HIV Symptom Distress Module [11] (also called the HIV Symptom Index or Symptoms Impact Questionnaire) and the HIV treatment satisfaction questionnaire (TSQ) [12] on a voluntary basis.

The Symptom Distress Module is a 20-item self-reported measure that addresses the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment [11]

The HIV TSQ is a 10-item-self-reported scale that measures overall satisfaction with treatment and by specific domains e.g., convenience, flexibility [12].

At baseline and at each follow-up visit, patients will also be asked to give an estimation of their level of adherence to their ART.

3.3.3 Data collection

All country-specific, national and international legal requirements for data handling and data archiving will be met. Data will be collected using CVEDC, which is an electronic data capture (EDC) system compliant with Good Clinical Practice (GCP) and 21 code of federal regulations (CFR) part 11. CVEDC is technically based on an XML interexchange model called ODM (operational data model) which is implemented and validated by the clinical data interchange standards consortium (CDISC) data standards. All data safety regulations will be met by the system.

Medical data in this study will be recorded directly in the eCRF system without the use of study specific paper documents. The eCRF system will be available to all participating sites over the entire duration of the study. When the system is no longer available (at database closure), all participating sites will be provided with a DVD with PDFs of all site-specific data and metadata (e.g. audit trail, data queries).

3.4 Endpoints

All primary and secondary endpoints described under 3.4.1 and 3.4.2 are planned to be analyzed in respect of the total study population and in following subgroups:

- Gender
- Age
- Baseline CD4 cell count
- Baseline treatment status
- Prior therapy
- CDC status
- Baseline comorbidities

3.4.1 Primary Endpoint

Proportion of patients with sustained virologic suppression, defined as VL < 50 c/ml or if between 50-200 c/ml with a subsequent next available measurement* (within 120 days) < 50 c/ml at year 1, 2, and 3.

3.4.2 Secondary Endpoints [analyzed at year 1, 2, 3 unless otherwise stated]

- Proportion of patients with low level viremia, defined as a VL measurement >50 - <200 c/ml
- Proportion of patients with VL >50 c/ml with emergent resistance mutations (if available)
- Proportion of patients with virologic rebound, defined as two consecutive VL measurements ≥ 200 c/ml
- Proportion of patients with two consecutive measurements of ≥200 c/ml, or treatment switch due to VF or due to intolerability as determined at the discretion of the physician
- Proportion of patients VL <50 c/ml
- Number of monitoring measures [normalized to patient years]
- Number and frequency of serious adverse events (SAEs) [normalized to patient years]
- Number and frequency of adverse drug reactions (ADRs) [normalized to patient years]
- Adherence to therapy [refers to missed monthly doses]
- Change in lipid laboratory values

- Change in treatment satisfaction [HIV Treatment Satisfaction questionnaire]
- Change in symptom distress [HIV Symptom Distress Module questionnaire]
- Reason for switch to Juluca

[* Any subsequent measurement will be accepted as a consecutive measurement as long as measured no later than 120 days after the initial measurement. If no subsequent VL measurement is performed within 120 days this is scored as a confirmed VL.]

3.5 Sample Size / Power Calculations

Recruitment target is a total of N=250 patients. Based on both SWORD-1 & -2 protocol assumptions (87%) and actual efficacy rate (95%), we assumed an efficacy rate of 90%.
We further assumed a max. drop-out rate of 30% over the study period of 3 years, based on the two non-interventional studies TRIUMPH and DOL-ART.

With an anticipated antiviral efficacy of 90% and a level of confidence of 95% with a target width of 0,1 (10%), a total number of N=158 patients are needed after the observational period of 3 years. Calculating with a max. 30% drop-out rate, N=226 subjects have to be included into the study. Therefore, our goal is to recruit N=250 subjects.

Patient numbers were calculated using the PASS software.

3.6 Hypotheses

The study is not hypothesis testing, but rather of descriptive nature, with the aim of generating real-world evidence for the use of DTG/RPV in routine clinical care in Germany to supplement data obtained from controlled clinical trials. Thus, statistical analysis will be of descriptive nature only.

4 DATA ANALYSIS CONSIDERATIONS

Standard descriptive methods will be used to analyze all data. Continuous variables will be summarized using the number of observations, mean, median, standard deviation and interquartile range. Categorical variables will be summarized using the number of observations and percentages. To investigate the consistency of observations, analyses will be carried out for total study population as well as for subgroups; e.g.:

- Gender
- Age
- Baseline CD4 cell count
- Treatment status
- Prior therapy
- CDC status
- Baseline comorbidities

Questionnaires will be analyzed according to the validated scoring instructions of the respective questionnaires. When evaluating change from baseline only complete pairs will be analyzed.

Due to the descriptive nature of the analyses, missing data will not be substituted or recoded.

Detailed methodology for summary and statistical analysis of data collected in this study as well as data sets will be specified in a Statistical Analysis Plan (SAP) prior to database lock.

5 LIMITATIONS

This is a non-interventional single-arm study aimed at gathering real-word data for the use of Juluca in routine clinical care in Germany. And as such there are a number of limitations, such as data source and geographic limitations. The sample is deliberately non-stratified to reduce limitations on recruitment. And with convenience sampling, the population may also be subject to selection bias.
Thus, this approach may result in some characteristics under- or overrepresented within the sample and limited diversity in terms of demographics and introduction of confounding factors, which may be considered in subgroup analysis.

However, real world data may provide valuable evidence for a patient population that is broader than that of controlled clinical trials, thus enhancing the generalizability and transferability of findings despite large random variations due to a heterogenic patient population.

6 STUDY CONDUCT, MANAGEMENT & ETHICS

6.1 Ethics Committee/IRB Approval

Prior to the start of this study, the protocol, the proposed informed consent form and other information for subjects will be reviewed by a properly constituted Ethics Committee. A signed and dated statement that the protocol and informed consent have been approved by the Ethics committee must be obtained before study initiation. Any amendments to the protocol, other than administrative ones (for which the Ethics Committee will merely be informed), must be reviewed and approved by the Ethics Committee. Once a favorable opinion from the competent Ethics Committee has been granted, the study will be reported to the Federal Institute for Drugs and Medical Devices (BfArM). Furthermore, in accordance with the applicable regulations, the study and the participating investigators will be reported to the National Association of Statutory Health Insurance Funds (GKV-SV) and any and all payments made by VH will be made public.

6.2 Informed Consent

6.2.1 Written informed consent

The investigator will ensure that each study patient, or his legally acceptable representative, is fully informed about the nature and objectives of the study. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient’s legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

6.2.2 Withdrawal of consent

Patients may withdraw from the study at any time at their own request without giving reason for doing so without penalty of prejudice. There will be no consequences for subsequent medical treatment. In case a patient wishes to withdraw, the investigator may attempt to inquire about the reason for withdrawal and follow-up on unresolved adverse events. The patient may also withdraw permission for use of any data collected up until this point.

6.2.3 Withdrawal from the study by investigator or sponsor

Furthermore, patients may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. The investigator should withdraw any patient who is known to have had a period of non-adherence >28 days.

6.3 Data Protection

The study database is centrally stored on redundant servers in secured Data Center in Munich, Germany, provided by the eCRF system vendor. The Data Center is certificated and validated, physical access is monitored and only granted to a closed group of employees by the eCRF system vendor.
Electronical access to the system is granted via web application by an identity management service that provides a role and right system and ensures that only authorized users can access a requested resource.
Electronical access to the servers and the database directly is only granted from the local area network of the eCRF system vendor and controlled by the active directory service.
All regulations are noted in the Design Specification document for CVEDC computer system validation documentation.

6.4 Personal Identifiable Information (PII)

All study staff will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

All recorded data is pseudonymized for storage in the central database. Decoding information that would allow identification is only held by the investigator. After database closure, the data will be deleted from the vendor's servers and transferred to the sponsor where it will be stored for 10 years. Regarding to CDISC ODM standard the export format to archive the database is a XML file containing all data and metadata. Data safety, backup and recovery, export and archive are described in the respective SOP document within the CSV documentation by the eCRF vendor.

6.5 Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

All clinical safety data will be collected as outlined in the eCRF. Under ICH GCP and all applicable local regulations and legal requirements, the Sponsor, is responsible for, and undertakes to, assess all clinical safety information arising during the Study (including, but not limited to, that set out in the Definition 6.5.1 in order to generate all safety reports as required.

6.5.1 Definition of adverse events

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

An adverse drug reaction (ADR) is defined as a noxious and unintended response to a medicinal investigational product related to any dose where at least a reasonable possibility, i.e. the relationship cannot be ruled out.

A Serious Adverse Event (SAE) shall mean any adverse event which meets the following criteria:

- fatal
- life threatening
- disabling or incapacitating
- requires unplanned in-patient treatment or prolongs existing hospitalization
- is a congenital anomaly in the off-spring of the subject
- medically significant or which may require intervention to prevent the previously stated outcomes

For the purposes of this study, all ADRs and SAEs (whether related or not) will be captured in the eCRF and reported to the sponsor as defined in Section 6.5.5.

6.5.2 Data collected for adverse events

Main data being collected may include, but is not limited to:

- Study No
- Centre No

- Subject No
- Event No
- Sender
- Send date
- Event type/description
- Start date
- Outcome
- End date
- Severity/Maximum grade
- Action taken with regard to VH product
- Withdrawal from study as a result of an adverse event/adverse reaction
- Causal relationship to VH product
- Criterion for seriousness

6.5.3 Definition of seriousness

Criteria for seriousness are:

- fatal
- life threatening
- disabling or incapacitating
- requires unplanned in-patient treatment or prolongs existing hospitalization
- is a congenital anomaly in the off-spring of the subject
- medically significant or which may require intervention to prevent the previously stated outcomes

6.5.4 Definition of Outcome of AEs

SAE/ADR outcomes are:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequel
- Fatal
- Unknown

6.5.5 Reporting of AEs and timelines

The study investigator involved is obliged to collect and report from the time of informed consent to study termination, all ADRs and SAEs.

All ADRs and SAEs will be reported to GSK global safety case management (OAX37649@gsk.com) in the form of an electronic safety report within 24hrs of documentation via an automated process.

The safety-related information will be processed according to the legal requirements and country specific regulations to the competent authorities. The recording and reporting of safety data is in a pseudo anonymous format.

6.5.6 Reporting of pregnancy exposures

To ensure subject safety, each pregnancy must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the sponsor. Pregnancy complications and elective terminations for medical reasons must be reported.

Investigators will be provided with necessary “pregnancy exposure” and “pregnancy follow up” forms and supported by CRA and/or ViiV medical affairs in complying with pregnancy reporting procedures. Pregnancies will also be reported to the Antiretroviral Pregnancy Registry (APR) by GSK global safety. The investigator must not report to APR, to avoid duplication.

7 EXTERNAL INVOLVEMENT

7.1 Third Party Supplier

Datamanagement, Statistics and medical writing are carried out by:
MUC Research GmbH
Karlsplatz 8
80335 München

7.2 External Expert/Health Care Professionals (Consultants & Research PIs)

N.A.

8 References

1 Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet. 2018;

2 Oglesby et al. EACS 2017; Milan, Italy. Poster BPD1/2

3 Press Announcements - FDA approves first two-drug regimen for certain patients with HIV. (n.d.). Retrieved November 24, 2017, from https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm586305.htm

4 Retrieved November 24, 2017, from: http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2017/Ausgaben/47_17.pdf;jsessionid=26113C448538D51DAA1C7841D087BAFA.1_cid363?__blob=publicationFile

5 Retrieved November 24, 2017, from: http://www.daignet.de/site-content/hiv-therapie/leitlinien-1/Deutsch_Osterreichische%20Leitlinien%20zur%20antiretroviralen%20Therapie%20der%20HIV_Infektion.pdf

6 Marcotullio et al. EACS 2017; Milan, Italy. Poster PE25/9

7 Retrieved November 24, 2017, from: http://www.eacsociety.org/files/guidelines_9.0-english.pdf

8 Retrieved November 24, 2017, from: https://aidsinfo.nih.gov/guidelines

9 Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. J Antimicrob Chemother. 2011;66(9):2107-11.

10 Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. Lancet HIV. 2017;4(8):e349-e356.

11 Justice AC, Holmes W, Gifford AL, et al. Development and validation of a self-completed HIV symptom index. J Clin Epidemiol. 2001;54 Suppl 1:S77-90.

12 Woodcock A, Bradley C. Validation of the revised 10-item HIV Treatment Satisfaction Questionnaire status version and new change version. Value Health. 2006;9(5):320-33.

9 Appendix 1. Study schematic: