URBAN STUDY PROTOCOL AMENDMENT 3

UNIQUE IDENTIFIER /eTrack ID	208983
FULL TITLE	Description of Real World Antiviral Effectiveness and Sustainability of the 2-Drug Regimen Dolutegravir + Lamivudine in Untreated and Pre-treated Patients in Routine Clinical Care in Germany
ABBREVIATED TITLE	URBAN
FINAL PROTOCOL AMENDMENT 3 APPROVED	15 JUN 2020
SPONSORSHIP	ViiV Healthcare Germany sponsored non-interventional study
DIVISION	ViiV Healthcare
BUSINESS UNIT	Medical Affairs
DEPARTMENT	ViiV Healthcare GmbH, Germany
STUDY ACCOUNTABLE PERSON	[redacted]
PRINCIPLE INVESTIGATOR	[redacted]
CONTRIBUTING AUTHORS	[redacted] CCI

ASSET ID	GSK1349572 (Dolutegravir), GR109714 (Lamivudine), GSK3515864 (Dovato)
ViiV ASSET	Tivicay, Epivir, Dovato
INDICATION	HIV

REVISION CHRONOLOGY:

Version Date	Document Type	Change(s) since last version
06 MAR 2018	Original	n/a
03 JUL 2018	Amended Protocol	eTrack ID corrected
04 MAR 2019	Amendment 1	The following changes were made: **3.2 Study Population (page 15, 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 DTG + 3TC. ~~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 10 out of 24 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 DTG + 3TC.
21 JUL 2019	Amendment 2	The following changes were made: **3.2 Study population** Aim is the recruitment of 300 treatment-naïve and pre-treated HIV-1 infected subjects in total~~, as permitted per the locally approved label of Tivicay and Lamivudine~~. Recruitment target is to include 226 pre-treated and 74 naïve subjects. **3.2.1.1 Inclusion criteria** • ≥ 18 years of age • Documented HIV-1 infection • Prescription of Dovato or ~~DTG~~Tivicay + ~~3TC~~Lamivudine was issued independently from entering this study • Ability to understand informed consent form and other relevant regulatory documents

		3.2.1.2 Exclusion criteria • Any contraindication according to Dovato or Tivicay ~~or +~~ Lamivudine SmPCs • ~~VL >500.000 c/ml~~ • Known or suspected resistance to the integrase inhibitor class or lamivudine • Any antiretroviral therapy for the treatment of HIV-1 in addition to Dovato or ~~DTG~~Tivicay + ~~3TC~~Lamivudine • HBV-coinfection • Current participation in the ongoing non-interventional study TRIUMPH (study number: 202033) or in any interventional clinical trial irrespective of indication • Previous participation in clinical trials assessing ~~DTG~~Tivicay + ~~3TC~~Lamivudine **3.2.2 Sampling** Treatment-naïve and pre-treated HIV-1-positive patients for whom Dovato or ~~DTG~~Tivicay + ~~3TC~~Lamivudine is indicated according to local label may be selected for inclusion. **Synopsis – ViiV product** Dolutegravir (Tivicay), Lamivudine (Epivir), Dolutegravir/Lamivudine (Dovato) **Synopsis – Study population and sampling methods** N=300 HIV-1 positive, both treatment-naïve and pre-treated patients are aimed to be included into this study. Patients' eligibility is based in the local SMPCs of Dovato or Tivicay and Lamivudine. Inclusion criteria • ≥ 18 years of age • Documented HIV-1 infection • Prescription of Dovato or ~~DTG~~Tivicay + ~~3TC~~Lamivudine was issued independently from entering this study

		• Ability to understand informed consent form and other relevant regulatory documents Exclusion criteria • Any contraindication according to Dovato or Tivicay ~~or~~ and Lamivudine SmPCs • ~~VL >500.000 c/ml~~ • Known or suspected resistance to the integrase inhibitor class or lamivudine • Any antiretroviral therapy for the treatment of HIV-1 in addition to Dovato or ~~DTG~~Tivicay + ~~3TC~~Lamivudine • HBV-coinfection • Current participation in the ongoing non-interventional study TRIUMPH (study number: 202033) or in any interventional clinical trial irrespective of indication • Previous participation in clinical trials assessing ~~DTG~~Tivicay + ~~3TC~~Lamivudine **Administrative section and Synopsis were updated accordingly.** **Rationale** At start of recruitment, the inclusion/exclusion criteria reflected the current labels of Tivicay and lamivudine, as well as the anticipated label of Dovato. The final label of Dovato was not known at the time. As switch to Dovato is permitted within the study once it is available, inclusion/exclusion criteria were updated to reflect the final EU label of Dovato, thus ensuring patients enrolled in this study are strictly in label. All patients currently enrolled conform with the old and new inclusion/exclusion criteria. Standardized brand name use in inclusion/exclusion criteria was corrected where possible.
15.06.2020	Amendment 3	The following changes were made: Second sponsor signatory and study principal investigator [redacted] is no longer associated with the study. The role of study principal investigator is now being fulfilled by [redacted]

Description: URBAN
Unique Identifier /eTrack: 208983

SPONSOR SIGNATORY

[redacted]

[redacted]
Head, Global Medical Sciences, ViiV Healthcare

STUDY PRINCIPAL INVESTIGATOR SIGNATORY

[redacted]

[redacted]

Description: URBAN
Unique Identifier /eTrack: 208983

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:

_____

[redacted]

Investigator Signature

Date (DD-MMM-YYYY)

PROTOCOL SYNOPSIS

Unique Identifier /eTrack	208983
Abbreviated Title	URBAN
ViiV Product	Dolutegravir (Tivicay), Lamivudine (Epivir), Dolutegravir/Lamivudine (Dovato)
Rationale	This study will be conducted to supplement data gathered from several pilot studies and the pivotal randomized clinical trials GEMINI-1 and -2 with real-world evidence to evaluate the antiretroviral efficacy of DTG+3TC in suppressing and maintaining viral suppression in HIV-1 infected, untreated and pre-treated subjects in routine clinical care in Germany
Objectives (Primary, Secondary)	Primary objective: • Evaluate antiviral efficacy of DTG + 3TC for the initial suppression of HIV replication in HIV-1 infected, untreated, as well as maintaining viral suppression in pre-treated patients in routine clinical care in Germany Secondary objectives: • Gain an understanding of the major relevant patient populations for DTG + 3TC in Germany, in terms of patient characteristics and history • Describe real-life efficacy profile of DTG + 3TC • Describe real-life tolerability profile of DTG + 3TC as measured by discontinuation rates due to adverse drug reactions (ADRs) and overall number of serious adverse events (SAEs) • Analyze the development of viral resistance of 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 /prescription of DTG + 3TC • 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=300 HIV-1 positive, both treatment-naïve and pre-treated patients are aimed to be included into this study. Patients' eligibility is based in the local SMPCs of Dovato or Tivicay and Lamivudine. Inclusion criteria: • ≥ 18 years of age • Documented HIV-1 infection • Prescription of Dovato or Tivicay + Lamivudine was issued independently from entering this study • Ability to understand informed consent form and other relevant regulatory documents Exclusion criteria: • Any contraindication according to Dovato or Tivicay and Lamivudine SmPCs • Known or suspected resistance to the integrase inhibitor class or lamivudine • Any antiretroviral therapy for the treatment of HIV-1 in addition to Dovato or Tivicay + Lamivudine • HBV-coinfection • Current participation in the ongoing non-interventional study TRIUMPH (study number: 202033) or in any interventional clinical trial irrespective of indication • Previous participation in clinical trials assessing Tivicay + Lamivudine 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. drop-out rate of 30% over the observational period of 3 years. To reach a level of confidence of 95% with a target width of 0.1 (10%) a minimum number of N=158 subjects are needed at the end of the study. Calculating with max. 30% drop-outs, a minimum number of N=226 pre-treated subjects are needed (to assure comparability with the ongoing NIS JUNGLE). For treatment-naïve patients, the recruitment target is N=74. Therefore, the total number of subjects to be included into this study is N=300.
Limitations	This is a non-interventional, single-arm study aimed at gathering real-world data for the use of DTG + 3TC in routine clinical care in Germany. And 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 or 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
3TC	Lamivudine
ADR	Adverse Drug Reaction
AE	Adverse Event
ART	Antiretroviral Therapy
BfArM	Bundeinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
c/ml	Copies per Milliliter
CD	Cluster of Differentiation
CDC	Center of Disease Control
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CNS	Central Nervous System
DTG	Dolutegravir
DVD	Digital Versatile Disc
e-CRF	Electronic-Case Report Form
EDC	Electronic Data Capture
FDC	Fixed dose combination
G-BA	Gemeinsamer Bundesausschuß (Federal Joint Committee)
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
INSTI	Integrase Strand Transfer Inhibitor
NIS	Non-Interventional Study
NNRTI	Non-nucleoside Reverse Transcritptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
ODM	Operational Data Model
PDF	Portable Document Format
PI	Protease Inhibitor
RNA	Ribonucleid Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TDF/FTC	Tenofovir Disoproxilfumarate / Emtricitabine
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 pivotal, randomized, controlled clinical trials SWORD-1 and -2, investigated DTG + RPV in stable suppressed patients versus patients continuing their individual ART. The efficacy of DTG + RPV was non-inferior to the comparator arm, with 95% of patients remaining under 50 c/ml in both treatment arms. The safety and tolerability profile was good, resulting in only 3% study discontinuations due to drug-related adverse events until week 48 [4]. Patient related outcomes revealed a high rate of treatment satisfaction, which was, although very high at baseline in both arms, significantly improved in the DTG+RPV arm. A significant improvement compared to the control arm, has been shown in the symptom bother score, underlining the good tolerability of this regimen [5]. 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 and no known substitutions associated with resistance to the individual components of Juluca [6].

The substance combination of DTG and Lamivudine (3TC) has been investigated in several small studies in treatment naïve patients, e.g. the PADDLE [7] and the ACTG 5353 study [8], as well as in pre-treated patients, e.g. the LAMIDOL [9] and ASPIRE [10] studies.
In PADDLE, 20 treatment naïve subjects were allocated to receive DTG + 3TC as an initial antiretroviral therapy (ART). Although the protocol was designed to exclusively include patients with viral loads (VL) of <100.000 c/ml, n=4 patients had VL above this threshold at baseline and were treated with this investigational regimen. 100% of all study subjects were below 50 c/ml at week 8 and those who remained in the study (n=18) remained stably suppressed until week 96. 2 patients discontinued the study due to an adverse event and non-adherence to the study drug [7]. ACTG 5353 investigated DTG + 3TC in naïve patients and recruited N=120 subjects with viral loads below (n=83) and above (n=37) 100.000 c/ml. The overall efficacy was high with 90%, without significant differences between those patients with high or low viral loads [8]. The safety and tolerability profile was good in both studies, with very few discontinuations due to adverse events (AE). These two proof-of-concept studies have demonstrated high antiviral effectiveness of this 2DR, with a very good tolerability profile.

The GEMINI-1 and -2 studies [11, 12] are part of ViiV Healthcare's (VH) efforts to optimize ART by reducing the substance burden of a lifelong therapy. Both identical, international, randomized,

controlled, pivotal clinical trials recruited over 1.400 naïve HIV-1 infected patients to be treated either with DTG + 3TC or DTG + TDF/FTC. Patients are eligible to participate in these studies, if they have a viral load up to 500.000 c/ml. Results for the primary and secondary endpoints at weeks 24 and 48 will be available in the second half of 2018 for submission to regulatory authorities.

The LAMIDOL trial recruited 110 patients, who were stably suppressed prior to switching to DTG + 3TC. The rate of treatment success at week 48, defined as proportion of patients with a viral load <50 c/ml, was high with 97% achieving this goal. The overall safety and tolerability was good resulting in few patients discontinuing the study for adverse events or virologic failure [9]In the ASPIRE study, patients were eligible for study participation if they were HIV-1 infected and virologic suppressed on any 3-Drug Regimen without a history of treatment failure. A total number of 89 subjects were recruited to either receive DTG + 3TC or to continue with their current ART. The proportion of patients with a VL <50 c/ml in the 2DR-arm was 93.2% at week 24, and 90.9% at week 48. The safety and tolerability profile was good, with only 1 patient discontinuing DTG + 3TC due to a grade 2 constipation [10]. Besides numerous smaller studies and cohorts showing good efficacy and tolerability of a 2DR consisting of DTG + 3TC in maintaining viral suppression, VH is currently conducting a global RCT switch study (TANGO) for this patient population to further provide clinical trial data.

In 2016, more than 88.000 people in Germany were living with HIV [13], of which 75.700 were aware of their diagnosis and 64.900 treated. Based on the current German-Austrian HIV Treatment Guidelines (2016), 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. The recommendations for treatment switches rely on individual patient characteristics, such as resistance and intolerability, without providing clear guidance [14]. However, based on the positive perspectives survey, there are concerns about ART-related long-term toxicities in patients, favoring substance- or class-sparing treatment options [15]. 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 [16]. Furthermore, 2DR have been recently mentioned in the DHHS guidelines as reasonable option in some cases [17]. This shows the general acceptance of optimizing therapy in the treatment of HIV.

Regardless of the current treatment status of a patient, antiretroviral therapy has to be taken lifelong to ensure suppression of viral replication, which is the hallmark of therapy. Suppressing viral replication, as major goal of ART, reduces the risk of HIV-associated complications, such as immunosuppression and the abundance 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 [14]. Providing therapies with only two drugs, for example DTG + 3TC, 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 [18]. 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 can expect to see their 78th birthday, meaning almost six decades of antiviral therapy [19].

Non-interventional studies (NIS) provide insights into the medication use in routine clinical care and generate real-world evidence for the used drug in terms of efficacy and tolerability, which can supplement data from clinical and pivotal trials.
A prospective multicenter NIS for DTG + 3TC is capable to supplement clinical trial data in Germany, investigating and/or understanding the usability and durability of this novel treatment regimen outside randomized clinical trials Pivotal trials, investigating new drugs or drug formulations, are crucial for demonstrating the efficacy, safety and tolerability of these drugs. However, after approval of new drugs, real-world evidence is missing and therefore NIS are good tools to further assess the drug's profile in a routine clinical setting [14].

2 OBJECTIVES

2.1 Primary

Evaluate antiretroviral efficacy of DTG + 3TC for the initial suppression of HIV replication in treatment-naïve HIV-1 infected patients, as well as maintenance of viral suppression in pre-treated patients in routine clinical care in Germany.

2.2 Secondary

- Gain an understanding of the major relevant patient populations for DTG + 3TC in Germany, in terms of patient characteristics and history
- Describe real-life efficacy profile of DTG + 3TC
- Describe real-life tolerability profile of DTG + 3TC as measured by discontinuation rates due to adverse drug reactions (ADRs) and overall number of serious adverse events (SAEs)
- Analyze the development of viral resistance of 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 /prescription of DTG + 3TC
- 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 DTG + 3TC 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 36 months collecting information that can be obtained in routine clinical care. The substitution of the separate components (DTG + 3TC) by a fixed-dose combination of DTG/3TC (currently not available) is permitted within this study when available without further notice.

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

3.2 Study Population

Aim is the recruitment of 300 treatment-naïve and pre-treated HIV-1 infected subjects in total. Recruitment target is to include 226 pre-treated and 74 naïve subjects. Recruitment is expected to be concluded within an approximate timeframe of 6-9 months. However, hence recruitment of naïve subjects in Germany is inherently difficult, the recruitment period may be extended until a minimum number of 50 treatment-naïve patients is reached, while recruitment of pre-treated patients will also be continued.

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 DTG + 3TC.

3.2.1 Eligibility Criteria

3.2.1.1 Inclusion criteria:

- ≥ 18 years of age
- Documented HIV-1 infection
- Prescription of Dovato or Tivicay + Lamivudine was issued independently from entering this study
- Ability to understand informed consent form and other relevant regulatory documents

3.2.1.2 Exclusion Criteria

- Any contraindication according to Dovato or Tivicay and Lamivudine SmPCs
- Known or suspected resistance to the integrase inhibitor class or Lamivudine
- Any antiretroviral therapy for the treatment of HIV-1 in addition to Dovato or Tivicay + Lamivudine
- HBV-coinfection
- Current participation in the ongoing non-interventional study TRIUMPH (study number: 202033) or in any interventional clinical trial irrespective of indication
- Previous participation in clinical trials assessing Tivicay + Lamivudine

3.2.2 Sampling

Treatment-naïve and pre-treated HIV-1-positive patients for whom Dovato or DTG + 3TC is indicated according to local label 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 [18] (also called the HIV Symptom Index or Symptoms Impact Questionnaire) and the HIV treatment satisfaction questionnaire (TSQ) [19] 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 [18]

The HIV TSQ is a 10-item-self-reported scale that measures overall satisfaction with treatment and by specific domains e.g., convenience, flexibility [19].

At baseline (for pre-treated patients only) 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 e-CRF system without the use of study specific paper documents. The e-CRF 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 [for pre-treated patients]
- Proportion of patients with low level viremia, defined as a VL measurement >50 - <200 c/ml after initial suppression < 50 c/ml [for naïve patients]
- Proportion of virologic non-responders, defined as two consecutive measurements ≥200 after at least 24 weeks of treatment [for naïve patients only]
- Proportion of patients with virologic rebound, defined as two consecutive VL measurements ≥ 200 c/ml [for naïve patients: after suppression = one VL <50 c/ml]
- Proportion of patients VL <50 c/ml
- Proportion of patients with two consecutive VL 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 with VL >50 c/ml with emergent resistance mutations (if available) [Resistance analysis is performed at the physician's discretion and is not mandatory, due to the non-interventional nature of this study]

- Number of monitoring measures [normalized to patient years]
- Number and frequency of serious adverse events [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]
- Reasons for switching to /prescription of DTG + 3TC

[* 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 ≥ 200 c/ml.]

3.5 Sample Size / Power Calculations

Recruitment target is a total number of N=300 subjects. Assumption for sample size calculation was an antiretroviral efficacy of 90% and a max. drop-out rate of 30% over the whole observational period of 3 years.
To achieve a level of confidence of 95% with a target width of 0.1 (10%), a minimum of N=158 subjects after 3 years are needed. Calculating with a max. drop-out rate of 30%, N=226 patients are required.
Since recruitment of naïve patients is inherently challenging in Germany (according to local guidelines treatment of HIV should start immediately after diagnosis regardless of the CD4 cell count), recruitment goal is to include N=226 pre-treated (to assure comparability with the VH sponsored NIS JUNGLE) and N=74 treatment naïve HIV-1 infected patients.
If the total number of N=74 naïve patients is not reached during recruitment period, the minimum number of naïve patients is N=50. If the minimum recruitment target for naïve patients is not met, recruitment period will be extended to reach N=50 naïve patients.

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 + 3TC 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 statistical 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 DTG + 3TC 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 e-CRF system vendor. The Data Center is certificated and validated, physical access is monitored and only granted to a closed group of employees by the e-CRF 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 e-CRF 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 e-CRF 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 has 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
- Expectedness
- 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 Baril JG, Angel JB, Gill MJ, et al. Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients. PLoS ONE. 2016;11(2):e0148231.

2 Cahn P, Andrade-villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. Lancet Infect Dis. 2014;14(7):572-80.

3 Perez-molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. Lancet Infect Dis. 2015;15(7):775-84.

4 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;

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

6 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

7 PADDLE: Figueroa et al. IAS 2017; Paris, France. Poster MOPEB0287

8 Taiwo et al. IAS 2017; Paris, France. Slides MOAB0107LB).

9 Joly et al., EACS 2017, Poster PE9/11

10 Taiwo et al., EACS 2017, Poster PE8/5

11 An Efficacy, Safety, and Tolerability Study Comparing Dolutegravir Plus Lamivudine With Dolutegravir Plus Tenofovir/Emtricitabine in Treatment naïve HIV Infected Subjects (Gemini 1) - Full Text View. (n.d.). Retrieved November 24, 2017, from https://clinicaltrials.gov/ct2/show/NCT02831673?term=gemini%2Bdolutegravir&rank=1

12 An Efficacy, Safety, and Tolerability Study Comparing Dolutegravir (DTG) Plus Lamivudine (3TC) With Dolutegravir Plus Tenofovir/Emtricitabine in Treatment naïve HIV Infected Subjects (Gemini 2) - Full Text View. (n.d.). Retrieved November 24, 2017, from https://clinicaltrials.gov/ct2/show/NCT02831764?term=gemini%2Bdolutegravir&rank=2

13 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

14 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

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

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

17 Retrieved November 24, 2017, from: https://aidsinfo.nih.gov/guidelines on 11/24/2017

18 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.

19 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.

20 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.

21 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. Schematic of a Prospective Study: