TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	A Comprehensive Assessment of Adverse Events and Overall Safety Profile in HIV Positive Patients Treated with Dolutegravir as Compared to Other Integrase Strand Transfer Inhibitors or Darunavir.

Compound Number: GSK1349572, GSK2619619

Development Phase IV

Effective Date: xx-xxx-2017

Subject: integrase strand transfer inhibitors, adverse events

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1. LIST OF ABBREVIATIONS

3TC	lamivudine
/c	cobicistat
/r	ritonavir
ABC	abacavir
ADAP	AIDS drug assistance programs
ADE	AIDS defining event
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ART	antiretroviral therapy
BAA	Business Associate Agreement
BID	twice daily
CDC	Centers for Disease Control & Prevention
CVD	cardiovascular disease
DHHS	Department of Health and Human Services
DTG	dolutegravir
EFV	efavirenz
ELISA	enzyme-linked immunosorbent assay
EMR	electronic medical record
EVG	elvitegravir
FDA	Federal Drug Administration
FTC	emtricitabine
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health Act
HIV	human immunodeficiency virus
INSTI	integrase strand transfer inhibitor
IQR	interquartile range
mL	millilitre
NRTI	nucleoside analogue reverse-transcriptase inhibitor
OPERA	Observational Pharmaco-Epidemiology Research & Analysis
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
QA	quality assurance
RAL	raltegravir
STR	single tablet regimen
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate
US	United States
VACS	Veterans Aging Cohort Study
VL	viral load

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2. **RESPONSIBLE PARTIES:** SPONSOR INFORMATION PAGE

MARKETING AUTHORISATION HOLDER

ViiV Healthcare UK Limited

Sponsor Legal Registered Address:

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SPONSOR SIGNATORY:

Vani Vannappagari Primary Author/ Project officer	**Date**
Harmony Garges VP, Global Medical Sciences	**Date**
Nassrin Payvandi VP, Safety and Pharmacovigilance	**Date**

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: PPD

Investigator Signature Date

Investigator Name: PPD

Investigator Signature Date

3. ABSTRACT

Introduction:

Toxicity concerns with multi-agent regimens, and pharmacokinetic interactions with medications for co-morbidities suggest the need for a comprehensive safety evaluation of the newest class of antiretroviral therapies, integrase strand transfer inhibitors, in a real-world setting. As the use of this newest class increases in various demographic populations and clinical situations, an understanding of the overall safety profile of the members of the class will provide additional information for clinicians as treatment strategies are designed.

Objectives:

Primary:

1) To describe the baseline demographic and clinical characteristics of HIV+ patients initiating dolutegravir (DTG), elvitegravir (EVG),raltegravir (RAL), or Darunavir (DRV) as part of an ART regimen.
2) To quantify and compare the prevalence and incidence of select on-label potential and identified risks included in the DTG Risk Management Plan in HIV+ patients who initiated DTG, EVG, RAL or DRV as part of an ART regimen.

Study Design:

An observational clinical cohort analysis utilizing prospectively collected electronic medical record (EMR) data obtained from the OPERA® Observational Database will be used to address the study objectives.

Period of subject inclusion:

- August 01, 2013 (DTG-approval)
- December 31, 2016 (allows for a minimum of one-year of follow-up)

Period of observation:

- August 01, 2013 (DTG-approval)
- December 31, 2017

Population:

- HIV+
- Male or Female
- ART naïve or experienced
- Exposed to DTG (Tivicay® or Triumeq®)-containing regimen or
- Exposed to RAL (Isentress®)-containing regimen or
- Exposed to EVG (Stribild® or Genvoya®)-containing regimen or
- Exposed to DRV containing regimen

Endpoints & Outcomes:

Descriptive statistics will be used to summarize baseline demographics, clinical characteristics and adverse event history of HIV+ patients initiating an INSTI-based regimen.

All individual adverse events diagnosed (prevalence) and new individual adverse events diagnosed (incidence), according to the risk management plan, will be described as frequencies (counts and proportions). Adverse events will be classified by the system-organ-class (SOC) hierarchical categorization deemed most appropriate for incidence rate (IR) calculations. P-values will be calculated to evaluate differences between groups.

Risks/adverse events of interest detailed in the risk management plan and product label:

1. Hypersensitivity reactions (HSR)*
2. Hepatobiliary disorders [drug Induced liver injury (DILI) and transaminase elevations] *
3. Drug interaction with dofetilide*
4. Serious rash (DAIDS Grade 3 or 4) **
5. Renal disorders**
6. Gastrointestinal intolerance and erosions**
7. Pancreatitis and Lipase elevations (Grade 3 to 4) **
8. Rhabdomyolysis and Musculoskeletal Events/ Elevated Creatinine Phosphokinase (CPK)**
9. Immune Reconstitution Inflammatory Syndrome (IRIS)**
10. Redistribution/accumulation of body fat^

**identified risks in RMP, **potential risks in RMP, ^risk in product label*

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<Date>	<Text>	<Text>	<Text>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	Planned date
Start of data analysis	08-JAN-2018
End of data analysis	30-MAR-2018
Preliminary tables	30-APR-2018
Final report of study results	30-JUN-2018
Draft abstract	30-JUN-2018

6. BACKGROUND AND RATIONALE

6.1. Background

Highly active antiretroviral therapy (ART) has changed human immunodeficiency virus (HIV) infection from a fatal illness to a chronic disease. Since the mid-1990's, regimens containing multiple antiretroviral drugs from at least two classes have been the standard of care in HIV treatment [1]. Combination therapy presents multiple barriers to viral replication and reduces the development of drug-resistant mutations as well as regain suppression due to previous treatment-emergent resistance [2,3,4].

Integrase strand transfer inhibitors (INSTI) are the newest tool for prolonging survival and improving quality of life for HIV patients. This class of medications appears to cause a more rapid decline in viral load and a greater increase in CD4 counts when compared to protease inhibitors (PI) or EFV based regimens. Raltegravir (RAL) was the first such agent approved for clinical use by the FDA in 2007. Multiple trials demonstrated it to be a very effective agent in both naïve and treatment-experienced patients when used with either TDF/FTC or abacavir (ABC)/lamivudine (3TC) [2,3]. Elvitegravir (EVG) followed in 2012, achieving non-inferiority to both boosted PI and EFV containing regimens along with improved lipid profiles in several studies [4].

Dolutegravir (DTG), the newest INSTI, was approved in 2013. Unlike RAL, it does not require BID dosing. Unlike EVG, it does not require a pharmacokinetic boosting agent to be co-prescribed. In naïve patients, the combination of DTG/ABC/3TC was found to be non-inferior and superior to TDF/FTC/EFV with no INSTI or NRTI mutations found in the DTG arm [5]. The SPRING-2 study compared DTG to RAL in naïve subjects and demonstrated that DTG was non-inferior to RAL [6,7]. A third study comparing DTG to darunavir showed non-inferiority and superiority with a better lipid response in the DTG arm [8]. In all three of these naïve studies, no INSTI resistance mutations emerged at virologic failure which has led many to state that DTG is a drug with a higher barrier to resistance [9,10]. As a result of these pivotal studies, the most recent US DHHS antiretroviral treatment guidelines has DTG with ABC/3TC or TDF/FTC on the recommended list along with the other INSTIs for treatment-naïve patients.

DTG has been shown to have a favourable safety profile and overall is well tolerated with minimal adverse effects [11]. Single and repeat dose safety studies found DTG to be well tolerated with no serious adverse events. The most common adverse effect after single and repeat doses was headache [12]. In proof of concept (POC) rising dose studies in HIV-1 infected patients (2, 10, 50 mg) or placebo, DTG was well tolerated with no serious adverse events. Mild-to-moderate diarrhoea was most commonly reported, which did not lead to any treatment discontinuations [13]. In the SPRING-1 trial, three different doses of DTG were compared with efavirenz (EFV) with no dose-related trend in adverse effects seen, but more nausea and headache did occur with all three DTG doses, however, more drug discontinuations did not result [14]. Overall, there were fewer discontinuations in the DTG arm (3%) compared to the EFV arm (10%). The SINGLE study [15] showed a slightly different pattern with the most frequent treatment-related adverse effects reported at 48 weeks being insomnia (3%) and headache (2%) with both being reported at

lower rates (<1%) in the SPRING-2 study [6] and both studies demonstrating low rates of treatment discontinuation (2%). The SINGLE study did report a higher overall rate of insomnia compared, however, this study supplied a targeted questionnaire on insomnia [15].

Most adverse events seen were grade 1–2 (mild-to-moderate in severity); however, DTG treatment-related adverse effects (determined by the investigator) were less frequent (1–3%) than comparator. DTG can increase serum creatinine by inhibition of the organic cation transporter 2 (OCT2) and multi-drug and toxin extrusion transporter (MATE) 1, which are responsible for the tubular secretion of creatinine, however, this increase is not associated with any change to the actual glomerular filtration rate (GFR). In the SPRING-1 study, the mean increase in serum creatinine observed at week 1 remained stable through week 24 and then declined at week 48 [14]. The SINGLE study showed a similar pattern with respect to serum creatinine with a mean increase of 0.12–0.15 mg/dl, which appeared by week 2, and was stable through week 48 [15]. The pattern appears to be an early increase followed by stabilization.

6.2. Rationale

As of this writing, a comprehensive safety evaluation of DTG and INSTI's has not been performed in a real-world setting. As the use of INSTI's increases in various demographic populations and clinical situations, an understanding of the overall safety profile of the members of the class will provide additional information for clinicians as treatment strategies are designed.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Primary:

1) To describe the baseline demographic and clinical characteristics of HIV+ patients initiating DTG, EVG, RAL, or DRV as part of an ART regimen.
2) To quantify and compare the prevalence and incidence of on-label potential and identified risks included in the DTG Risk Management Plan in HIV+ patients who initiated DTG, EVG,RAL, or DRV as part of an ART regimen.

8. RESEARCH METHODS

8.1. Study Design

Study objectives will be evaluated through an observational analysis of a clinical cohort utilizing prospectively-collected EMR data obtained from the OPERA Observational Database. Study participants will be identified from the most recent database build available and updated on most recent data available prior to dissemination. The observation period will begin on August 01, 2013 and proceed until December 31, 2017. Study participants can only be included into the analysis population until December 31,

2017. Participants in the descriptive population will be included until December 31, 2017.

Index date: The index date for an eligible patient is defined as the first date of the first regimen of interest ever prescribed to a patient between August 01, 2013 and December 2016.

Baseline period: The 12-month baseline period preceding the index date will be used to assess patient demographic and clinical characteristics.

Observation period: Patients will be observed from their index date until the first of the following censoring events:

a) Core agent discontinuation (defined as a gap of 45 days or more)
b) cessation of continuous clinical activity^^
c) death or
d) study end.

^^*Continuous clinical activity is defined as at least one clinic visit within a 12-month period. Patients failing to meet the continuous clinical activity requirement will be censored 12 months after their last contact.*

8.2. Study Population and Setting

The analysis population will be identified from the OPERA Observational Database according to the inclusion criteria defined below.

Patients initiating any INSTI or DRV between August 01, 2013 and December 31, 2016:

1) A diagnosis of HIV-1, a positive HIV-1 Western Blot, or a positive HIV-1 enzyme-linked immunosorbent assay (ELISA); and a detectable HIV-1 viral load test.
2) At least 13 years of age at the index date.
3) ART naïve or experienced.
4) Initiation of DTG or EVG or RAL or DRV between August 01, 2013 and December 31, 2016.

Subjects with the following criteria will be excluded:

1) HIV negative
2) A diagnosis of HIV-2, a positive HIV-1/HIV-2 Multi-spot, a positive HIV-2-specific ELISA, a positive HIV-2 Western Blot or a detectable HIV-2 viral load test
3) Patients prescribed monotherapy regimens (includes 1 core agent with or without a PK boosting agent)

4) Patients prescribed PEP or PrEP

8.3 Variables

8.3.1 Exposure definitions

Eligible patients will be identified who have initiated treatment with a regimen of interest at least 90 days after their first active visit in the OPERA database so that prospectively collected clinical data was available for the entire time a patient was taking the drug.

8.3.2 Outcome definitions

Stratification:

A. ART naïve
B. ART experienced

Definition:

- **A.** Discontinuation:
  - a. change in INSTI or DRV (not formulation change) due to (B:)
- **B.** Diagnoses:
  - a. Hypersensitivity reactions (HSR)*
  - b. Hepatobiliary disorders*
    - i. DILI
    - ii. Liver chemistry (ALT, AST, alkaline phosphatase) elevations >2x ULN & grade 3 or 4 elevations
    - iii. Drug interaction:*
      1. Dofetilide
    - iv.
  - c. Dermatologic disorders**
    - i. Systemic rash (grade 3 or 4)
  - d. Renal disorders**
  - e. Gastrointestinal intolerance and erosions**
  - f. Pancreatitis and Pancreatic enzyme elevations**
    - i. Lipase elevations (grade 3 or 4)
  - g. Rhabdomyolysis and Musculoskeletal events
    - i. Elevated creatinine phosphokinase (CPK)**
  - h. Immune Reconstitution Inflammatory Syndrome (IRIS)**
  - i. Redistribution/accumulation of body fat^
    - i. Lipodystrophy
    - ii. Lipoatrophy

*identified risks in RMP, **potential risks in RMP, ^risk in product label

8.3.3 Study covariates

The following patient demographic and clinical characteristics will be assessed at baseline.

Demographic variables

- Age
  - Continuous (years)
  - Categorical:
    i. 13-25 years old
    ii. 26-49 years old
    iii. 50+ years old
- Race (African American or not)
- Ethnicity (Hispanic or not)
- History of syphilis (an indicator of a risky lifestyle)
- Marital status (i.e., single, married, widowed, divorced, unknown)
- Geographic region (i.e., Northeast, Midwest, South, West)
- Payer (i.e. Medicaid, Medicare, commercial ins, AIDS drug assistance programs (ADAP)/Ryan White, cash)

Virologic variables

- HIV viral load at initiation of each INSTI or DRV
  - Continuous (copies/mL and $\log^{10}$ copies/mL)
  - Categorical (Naïve):
    - Low (<10,000 copies/mL)
    - Moderate (≥10,000 to <100,000 copies/mL)
    - High (≥100,000 copies/mL)
  - Categorical (Experienced):
    - Suppressed (<50 copies/mL)
    - Detectable (>=50 copies/mL)

Immunologic variables

- CD4 cell count at initiation of each INSTI or DRV
  - Nadir CD4 levels
  - Continuous (cells/µL)
  - Categorical:
    - High (CD4 > 500 cells/µL)
    - Moderate (CD4 count >350 to ≤500 cells/µL)
    - Low (CD4 count >200 to ≤350 cells/µL)
    - Lower (CD4 count >50 to ≤200 cells/µL)
    - Lowest (CD4 count ≤50 cells/µL)

Clinical variables

- ART naïve at index date
- Number of classes of ART experience
- INSTI exposure

- Year of ART initiation
- Year of regimen of interest initiation
- Length of previous regimen
- Time from first active date to index date(months)
- Time between index and end of follow-up (months)
- Pregnancy status at index date (yes/no)
- AIDS defining illnesses at index date
- Mortality Risk (VACS Mortality Index)
- Comorbid Conditions occurring on or before the index date:
    - Autoimmune Disease
    - Cardiovascular Disease
    - Invasive Cancers
    - Endocrine Disorders
    - Mental Health Disorders
    - Liver Disease
    - Bone Disorders
    - Peripheral Neuropathy
    - Renal Disease
    - Hypertension

- Concomitant medications

    - Hepatitis drugs (direct acting antivirals-DAAs)
    - Antidepressants
    - Oral hypoglycemic drugs
    - Non-steroidal anti-inflammatory agents
    - Immuno-modulators
    - Antibiotics
    - Sedatives and hypnotics (sleeping pills)
    - Lipid lowering agents (HMG co-enzyme reductase inhibitors)
    - Anti-diabetic agents

8.4 Data sources

The OPERA® database and research network is a multi-site observational database built from the complete patient health records collected through EMR systems from more than 400 participating caregivers across 81 separate outpatient clinical locations throughout the US.

These physicians and allied healthcare providers have documented the care of over 802,338 patients, including 78,698 patients living with HIV, representing 7 percent of all the HIV+ patients linked to care in the U.S. The database captures all the usual care of an HIV patient including their physical exams, diagnoses, laboratory findings, medication prescriptions, social history, and payer information. Because of the size and diversity of

the clinics participating in OPERA, a wide variety of care patterns, outcomes, and payer types are observable within the database.

The OPERA database is refreshed from the EMR databases at each clinic daily, making the OPERA database one of the largest continuously operating cohorts of HIV+ patients in the U.S. In total, there are more than 2.4 million documented prospective visits in the EMR systems for these HIV+ patients and 2.6 million prescriptions written for ART medications. The average prospective follow-up for patients in OPERA is 4.4 years with 7,076 HIV+ patients who have ten or more years of follow-up.

8.5 Data analysis

8.5.1 Analysis of demographics/baseline characteristics

Descriptive analyses will be conducted for patients treated with their first INSTI or DRV between August 1, 2013 and December 31, 2016. Patient characteristics will include basic demographics such as age, sex, race, ethnicity, marital status, MSM status, and geographic region. Clinical characteristics such treatment experience, ART backbone, history of AIDS defining events, baseline HIV-1 RNA viral load and CD4 cell counts will be presented. Adverse events at or before baseline will be described.

8.5.2 Analysis of primary objectives

Descriptive statistics including medians and interquartile ranges will be provided for continuous variables with frequencies (counts and percentages) for categorical variables. For the events that have higher incidence among DTG users (and if numbers permit), time-to-event and duration of treatment will be described. a follow up period will be examined to assess if the AEs resolve with continued use or if the event is followed by discontinuation of DTG. Adverse events will be classified by the system-organ-class (SOC) hierarchical categorization deemed most appropriate for incidence rate (IR) calculations and the frequency of drug discontinuations due to respective events/risks along with time to discontinuations will be estimated.

Differences between groups will be evaluated by p-values calculated from Pearson Chi-Square test for categorical variables. Fisher's exact test will be used to compare frequencies with few events. Wilcoxon Rank Sum test will be used to calculate p-values for continuous variables. Kaplan-Meier curves will be used to describe time to event graphically. To account for multiplicity and false positive findings, a p-value of 0.01 will be used for statistical significance.

The occurrence of adverse events will be stratified by the presence of adverse event at baseline. Pre-existing adverse events will be defined as all adverse events that occur for that SOC during follow-up that were already present at baseline. Incident adverse events will be defined as all new adverse events for that SOC during follow-up, excluding pre-existing events.

8.5.3 Analysis of secondary objectives

NA.

8.5.4 Sensitivity analyses

NA.

8.6 Quality control and quality assurance

Epividian has working practices & procedures governing the use of observational data, the development of analysis specifications and plans, the development of analytical programming and the analytical quality assurance (QA) process and the scientific review of reports as well as clinical advisory charters for the clinical review of output intended for public domain. Working practices for the development of analysis specifications include basic identifying information, background material, relevant definitions of key study variables, population definitions, baseline definitions, specific requirements for dataset creation, and statistical requirements such as eligibility criteria, exposures, outcomes and model fitting. Working practices for programming include naming conventions, proper code documentation and commentary, content, appearance, efficiencies (i.e. use of macros), and organization of output, maintainability and generalizability. Working practices for programming QA include self-reviews of observational counts, missing data values, many-to-many merges, variable formatting, numeric-character & character-numeric conversions, uninitialized variables, unresolved macro references, report completeness and report-to-specification correspondence, and system errors and logs. The QA team review may include small sample spot-checking, coding log reviews, complete coding review, selected observations from intermediary dataset reviews, and/or independent programming to reproduce the results. Documentation of non-public domain reports includes market, scientific, statistical, and clinical review. Documentation of scientific protocols, reports and manuscripts intended for public domain follows two sequential steps: an internal-to-Epividian epidemiological, statistical, and clinical review, followed by a clinical/epidemiological external advisory council review.

All analytical data, coding algorithms, QA documentation and report outputs will be retained per Epividian standard practices.

9. PROTECTION OF HUMAN SUBJECTS

Clinical information is aggregated into the OPERA® Database following the guidelines of the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH). Data aggregation occurs via a secure and encrypted connection with security and confidentiality maintained through Epividian's validated de-identification algorithms with regular and routine statistical audits of the de-identification process.

9.1. Ethical approval and subject consent

Business Associate Agreements (BAAs) in place between Epividian and all medical practices govern, following the guidelines established in HIPAA and HITECH, the encryption, transportation, aggregation, de-identification and use of all clinical data in the OPERA® Database. All medical practices are responsible for obtaining proper HIPAA consent for their patients. With BAAs in place, a separate informed consent for each individual, non-interventional study is not required.

9.2. Subject confidentiality

All clinical data is de-identified as per HIPAA and HITECH in OPERA® with all reports submitted at the aggregated population level. No personally identifiable information is available in the OPERA® Database. The OPERA® Clinical Advisory Board provides clinical and methodological review & oversight.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

There is no potential to collect serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual patient using a ViiV Healthcare product as the study design is to analyse the patient level information recorded in the OPERA database from electronic health records in an aggregate manner. Therefore, a study specific pharmacovigilance plan will not be developed.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

Health care practitioners, regulatory authorities

11.2. Study reporting and publications

Final report to be submitted to sponsor. Study results will be submitted as an abstract to a congress and/or to a peer reviewed journal.

12. REFERENCES

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