TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	Comparison of Dolutegravir Effectiveness vs. Other Anchor Agent Effectiveness among Hepatitis C Virus Co-infected patients in the OPERA® Observational Database

Compound Number: GSK1349572, GSK2619619

Development Phase IV

Effective Date: xx-xx-xxxx

Subject: HIV+/HCV+ Co-infected, Dolutegravir, Virologic Outcome

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1. LIST OF ABBREVIATIONS

Abbreviation	Medication Name
3TC	Lamivudine
ABC	Abacavir
COBI, c or /c	cobicistat
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
EFV/c/TDF/FTC	efavirenz/cobicistat/tenofovir disoproxil fumarate/emtricitabine
EVG	elvitegravir
FTC	emtricitabine
RAL	raltegravir
TDF	tenofovir disoproxil fumarate
	Drug Class Name
INSTI	integrase strand transfer inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
PI	protease inhibitor
	General Terminology
ADAP	AIDS drug assistance payer
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral Therapy
BAA	business associates agreement

BID	twice daily
DDI	Drug-drug interaction
DHHS	Department of Health and Human Services
ELISA	enzyme-linked immunosorbent assay
EMR	Electronic medical records
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
IQR	Inter-Quartile Range
OPERA	Observational Pharmaco-Epidemiology Research & Analysis
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
QA	quality assurance
STR	single tablet regimen
US	United States
VACS	Veterans aging cohort study
VL	viral load (HIV-1 RNA)

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

MARKETING AUTHORISATION HOLDER

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

3. ABSTRACT

Introduction:

The complexity of human immunodeficiency virus (HIV) care can be reduced by increasing efficacy, reducing adverse events, minimizing potential contraindications (e.g. hepatitis C virus (HCV) therapy, anti-diabetics, statins), and improving clinical effectiveness through dosing simplicity (e.g. reduced frequency and total pill burden). Dolutegravir (DTG) is available as a fixed-dose combination single table regiment (STR), does not require a boosting agent, and has a minimal drug-drug interaction (DDI) profile. With these properties, DTG may be easier to take and better tolerated, therefore, improving the quality of life for HIV patients, especially those with the complexities of co-morbid conditions such as HCV infection.

Objectives:

Primary:

1) To describe the baseline demographic and clinical characteristics, including co-morbid conditions, of HIV+/HCV+ patients.
2) To describe the baseline demographic and clinical characteristics, including co-morbid conditions, of HIV+/HCV+ patients initiating raltegravir (RAL), elvitegravir (EVG), darunavir (DRV) and those initiating DTG.
3) To estimate and compare the frequency of liver enzyme elevations by grade and discontinuation due to hepatotoxicity among HIV+/HCV+ patients who have initiated RAL, EVG, DRV or DTG.
4) To describe and compare time to virologic suppression (<50 copies/ml) among HIV+/HCV+ patients who have initiated RAL, EVG, DRV or DTG.

Study Design:

An observational clinical cohort analysis utilizing prospectively collected electronic medical record (EMR) data obtained from the Observational Pharmaco-Epidemiology Research & Analysis (OPERA®) Observational Database will be used to address the study objectives. The observation period will begin on August 12, 2013 (approval of Tivicay®) with study participants identified through June 30, 2016 to allow for a minimum potential follow-up of one year.

Endpoints & Outcomes:

Descriptive statistics will be used to summarize baseline demographic and clinical characteristics (including comorbid conditions, pregnancy, and history of anti-retroviral therapy (ART) in HIV+/HCV+ patients), as well as clinical outcomes (i.e., liver enzyme elevations, discontinuation of anchor drug in initial regimen of interest). Chi-square tests will be used to compare categorical variables and Wilcoxon rank-sum tests will be used to compare continuous variables by category of exposure. Kaplan Meier methods will be used to estimate time to virologic suppression in each group of patients by anchor-of-

interest-based regimen prescribed. Multivariable Cox proportional hazards models will be used to model time to virologic suppression among HIV+/HCV+ patients initiating an anchor-of-interest-based regimen to understand the hazard ratio of the outcomes adjusted for various patient characteristics of interest.

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
Registration on the EU PAS register	26-JUN-2017
Start of data analysis	27-JUN-2017
End of data analysis	08-AUG-2017
Preliminary tables	05-SEP-2017
Abstract submission	26-SEP-2017
Final report of study results	24-OCT-2017

6. BACKGROUND AND RATIONALE

6.1. Background

Highly active ART has changed HIV infection from a fatal illness to a chronic disease [1]. Since the mid-1990's, regimens containing multiple antiretroviral drugs from at least two classes have been the standard of care in HIV treatment. [2] Combination therapy presents multiple barriers to viral replication and limits the development of drug-resistant mutations. Co-morbid conditions present additional complexities for the management of HIV infection.

One of the most important co-morbid conditions with respect to HIV positive individuals is hepatitis C virus (HCV) infection. HCV is a small positive-strand ribonucleic acid (RNA) virus in the *Flaviviridae* family with at least seven different HCV genotypes, numbered 1 to 7; most genotypes have been divided into multiple subtypes (e.g., genotype 1 subtypes 1a and 1b). [3] In the United States, genotype 1 is the most common (70 to 80 percent), followed by genotypes 2 and 3. The remaining genotypes occur most frequently outside of the US. [4]

HCV infection is a major global health burden and is the leading cause of chronic liver disease worldwide. It is estimated that 185 million individuals worldwide are infected with HCV and about 3.2 million persons in the United States have chronic HCV infection. [5] About one-third of hepatocellular carcinoma (HCC) cases in the US are

attributed to HCV-related liver damage and HCV is the leading cause of liver transplantation. [6] Estimates indicate that three to four million people are newly infected each year putting each at risk of developing a liver-related disease such as cirrhosis or HCC, with an additional 350,000 deaths occurring each year also due to HCV-related causes. [7] With new and promising drugs recently available and more in the pipeline, hepatitis C is now considered curable in up to 70% of treated patients. [8] Therapy for HCV can be instrumental in the prevention of advanced liver disease. [9]

In recent years, several direct-acting antivirals (DAAs) have been approved by the FDA. In late 2013, FDA approved the second-generation protease inhibitor simeprevir (Olysio®) and polymerase inhibitor sofosbuvir (Sovaldi®). Ledipasvir/sofosbuvir (Harvoni®) and ombitasvir, paritaprevir and dasabuvir (Viekira Pak®) were approved in 2014, respectively. In January 2016, the FDA approved elbasvir/grazoprevir (Zepatier™) for the treatment of chronic HCV genotypes 1 and 4 infections. Clinical trials results of these recently-approved agents reported very high rates of SVR (between 90% to 100%). (9-14).

Unboosted regimens such as those containing DTG may provide significant flexibility for treating HIV infection, such as not requiring a change in regimen and reducing the possibility of DDIs, while either simultaneously monitoring or treating HCV infection. Integrase strand transfer inhibitors (INSTI), such as DTG, 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 efavirenz (EFV) based regimens. [15] Raltegravir was the first such agent approved for clinical use by the Food and Drug Administration (FDA) in 2007. Multiple trials demonstrated it to be a very effective agent in both naïve and treatment-experienced patients when used with either tenofovir (TDF)/emtricitabine (FTC) or abacavir (ABC)/lamivudine (3TC). [16,17] Elvitegravir followed in 2012, achieving non-inferiority to both boosted PI and EFV containing regimens along with improved lipid profiles in several studies. [18,19]

Dolutegravir, the newest INSTI, was approved in 2013. Unlike RAL, it does not require twice daily (BID) dosing, and, 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 nucleoside analogue reverse-transcriptase inhibitor (NRTI) mutations found in the DTG arm. [20] The SPRING-2 study compared DTG to RAL in naïve subjects and demonstrated that DTG was non-inferior to RAL. [21] A third study comparing DTG to DRV showed non-inferiority and superiority with a better lipid response in the DTG arm. [22,23] As a result of these pivotal studies, the most recent United States (US) Department of Health and Human Services (DHHS) antiretroviral treatment guidelines (April 2015) moved DTG with ABC/3TC or TDF/FTC to the recommended list along with the other INSTIs for treatment-naïve patients. [24]

A recent goal of clinical development in HIV has been to reduce the complexity of care by increasing efficacy, reducing adverse side effects, minimizing potential contraindications (e.g. HCV therapy, anti-diabetics, statins), and improving clinical effectiveness through dosing simplicity (e.g. reduced frequency and total pill burden).

Dolutegravir's availability as a fixed-dose combination STR, its lack of boosting requirements coupled with its pharmacokinetic properties contributing to a minimal DDI profile all suggest that DTG could be easier to take and better tolerated and could, therefore, improve the quality of life for HIV patients, especially those with the complexities of co-morbid conditions as HCV infection.

6.2. Rationale

Considering DTG's higher barrier to resistance, and its performance compared to other anchor agents, DTG could be preferentially prescribed in patients with advanced disease, have significant co-morbidities, and who are at greater risk of accumulating numerous resistance mutations over the course of their disease. Evaluating the effectiveness and safety of DTG-based regimens in patients with HCV co-infection in a real-world setting will provide evidence for the development of treatment strategies for patients in a more precarious state of health.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objectives of this study are:

1) To describe the baseline demographic and clinical characteristics, including co-morbid conditions, of HIV+/HCV+ patients.
2) To describe the baseline demographic and clinical characteristics, including co-morbid conditions, of HIV+/HCV+ patients initiating RAL, EVG, DRV and those initiating DTG.
3) To estimate and compare the frequency of liver enzyme elevations and discontinuation due to hepatotoxicity among HIV+/HCV+ patients who have initiated RAL, EVG, DRV or DTG.
4) To describe and compare time to virologic suppression among HIV+/HCV+ patients who have initiated RAL, EVG, DRV or DTG.

8. RESEARCH METHODS

8.1. Study Design

An observational analysis of a clinical cohort utilizing prospectively-collected EMR data obtained from the OPERA Database to address study objectives. 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 12, 2013 (approval date of Tivicay) and proceed until the data are frozen for aggregation into the database. Study participants can only be included into the analysis population until June 30, 2016 to allow a minimum of 12 months of potential follow up for all those followed.

Index date: The index date for an eligible patient is defined as the first date of the first anchor-of-interest-based regimen ever prescribed to a patient

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) discontinuation due to any cause of the anchor-of-interest-based regimen (defined as a gap of 45 days or more), b) cessation of continuous clinical activity, c) death or d) study end (June 30, 2017). 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 study sample will be identified from the OPERA Database for analysis according to the inclusion criteria defined below.

Patients initiating an anchor-of-interest-based regimen between August 12, 2013 and June 30, 2016 will be included in the study sample if they meet the following inclusion criteria:

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) A diagnosis of HCV and PCR or serology positive.
3) At least 13 years of age at the index date.
4) At least one HIV-1 viral load test on or up to 120 days prior to index date.
5) Continuous clinical activity in the year following anchor-of-interest-based regimen initiation, defined as at least one clinical contact (visit or telephone contact)

Subjects with the following criteria will be excluded from the study sample:

1) HIV negative.
2) HCV negative.
3) A diagnosis of HIV-2, a positive HIV-1/HIV-2 Multispot, a positive HIV-2-specific ELISA, a positive HIV-2 Western Blot or a detectable HIV-2 viral load test.
4) Initial anchor-of-interest-based regimen treatment identified as a component of post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP).

8.3. Variables

8.3.1. Exposure definitions

The index INSTI or DRV regimen is defined as the first complete anchor-of-interest-based regimen a patient receives.

Table 1, below, lists the most frequently used combination regimens for anchor agents of interest. All FDA approved ARTs and formulations are present in the OPERA Database from the time they are approved by the FDA. Any regimen with an anchor-of-interest will be included in the analysis and described, excluding dual-anchor agent regimens.

Table 1. Commonly prescribed Anchor-of-interest-based regimens stratified by pill burden

Single Tablet Regimens	Multi-tablet Regimens
1-pill	**2-pills**
• Stribild® (EVG/c/TDF/FTC) • Triumeq® (DTG/ABC/3TC) • Genvoya® (EVG/c/TAF/FTC)	• DTG + Truvada® (TDF/FTC) • DTG + Epzicom® (ABC/3TC) • RAL + Truvada® (TDF/FTC) • RAL + Epzicom® (ABC/3TC) • DRV + Epzicom® (ABC/3TC) • DRV + Truvada® (TDF/FTC) • DRV + Descovy® (TAF/FTC)

8.3.2. Outcome definitions

Stratification:

A. Treatment experienced
B. Treatment naïve

1. Incidence of viral suppression (viral load < 50 copies/mL) on an anchor-of-interest-based regimen at 12 months after initiation
    - Achievement of, and time to, suppression among naïve patients
    - Achieving re-suppression among experienced patients

2. Incidence of, and time to, liver enzyme elevations (grade 3 or higher) on an anchor-of-interest-based regimen after initiation

3. Incidence of discontinuation/switching due to hepatotoxicities

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 initial INSTI regimen
  - Continuous (copies/mL and $\log^{10}$ copies/mL)
  - Categorical:
    - Low (<10,000 copies/mL)
    - Moderate (≥10,000 to <100,000 copies/mL)
    - High (≥100,000 copies/mL)
- HCV viral load
  - Continuous (copies/mL and $\log^{10}$ copies/mL)
  - Categorical:
    - Low (<10,000 copies/mL)
    - Moderate (≥10,000 to <200,000 copies/mL)
    - High (≥200,000 copies/mL)

Immunologic variables

- CD4 cell count at initiation of initial ART regimen
  - 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 and laboratory variables

- ART naïve at baseline (initiation of INSTI-based regimen)
- Number of classes of ART experience
- Backbone ART given with INSTI
- Year of ART initiation
- Year of INSTI initiation

- Time from first active date to baseline (months)
- Follow up time (months)
- Pregnancy status at baseline (yes/no)
- AIDS defining illnesses at baseline
- Mortality Risk (Veterans Aging Cohort Study (VACS) Mortality Index)
- HCV viral load at initiation of ART
- HCV genotype
- HCV therapy
- HCV SVR
- HBV infection
- Active syphilis diagnosis at initiation of ART

Comorbid Conditions at baseline

- Autoimmune Disease
- Cardiovascular Disease
- Invasive Cancers
- Endocrine Disorders
- Mental Health Disorders
- Liver Disease
- Bone Disorders
- Peripheral Neuropathy
- Renal Disease
- Hypertension
- Substance Abuse

8.4. Data sources

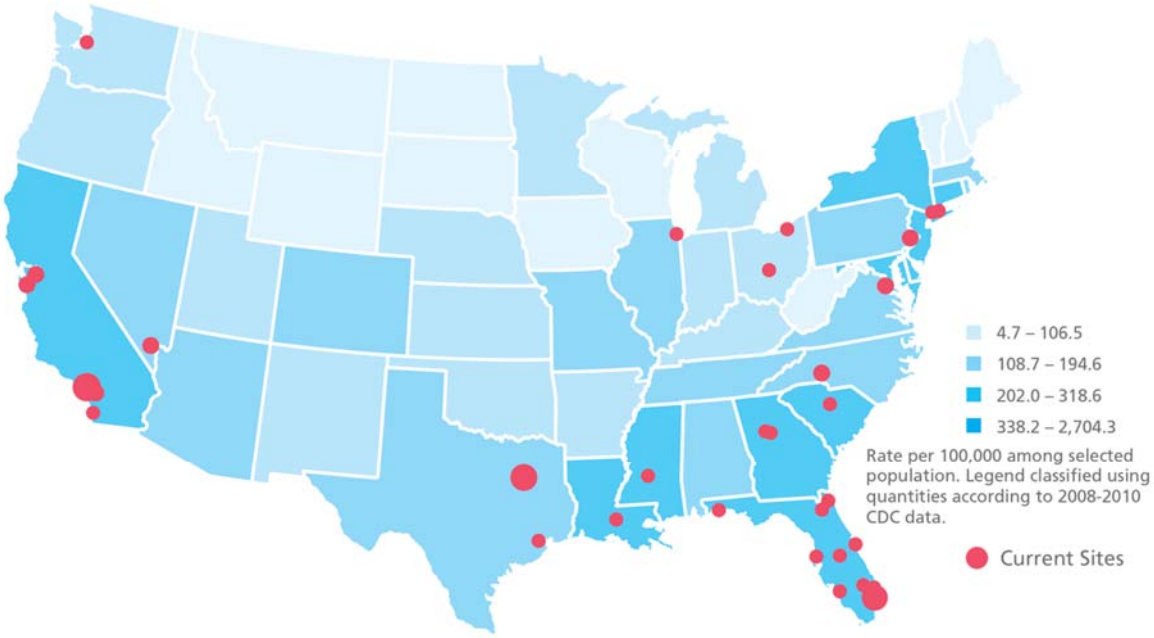
The OPERA database and research network is a multi-site observational database built from the complete patient health records collected through EMR systems from more than 400 participating caregivers across 79 separate outpatient clinical locations throughout the US (Figure 1).

These physicians and allied healthcare providers have documented the care of over 700,000 patients, including 70,807 patients living with HIV, representing 7 percent of all the HIV+ patients linked to care in the US. The database captures all of the usual care of an HIV patient including their physical exams, diagnoses, laboratory findings, medication prescriptions, social history, and payer information. As a result of the size and diversity of the clinics participating in the OPERA database, 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 on a daily basis, making the OPERA database one of the largest continuously operating cohorts of HIV+ patients in the US. 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 the OPERA database is 3.7 years with 4,620 HIV+ patients who have ten or more years of follow-up.

Figure 1: U.S. Map of OPERA HIV+ Population & CDC (2010) State-by-State Estimates



Patients will be identified from August 08, 2013 (approval of Tivicay) to ensure that there is equal opportunity for follow up in all the arms of the study. The patients will be included through June 30, 2016 and followed through June 30, 2017 to allow all patients at least 12 months of follow up after index.

Endpoint Definitions: Viral load after initiating an anchor-agent-of-interest regimen with virologic suppression defined as a viral load test <50 copies/ mL in both naïve and experienced patients. The patients whose viral load values are >50, but <200 copies/mL

can be either switched to a different regimen or continued the same regimen depending on the patient's treatment history & the optimal treatment plan for the patient. This sub group of patients will be described in detail with respect to the clinical characteristics and treatment history (naïve or experienced, how many regimens in the past, switched/continued on the same regimen).

8.5. Data analysis

8.5.1. Analysis of demographics/baseline characteristics

Descriptive statistics will be used to describe clinical and demographic patient characteristics of the overall HIV+/HCV+ population and those co-infected and initiating anchor-of-interest-based regimens. Results will be summarized using medians with interquartile ranges (IQR) for continuous variables and as frequencies and proportions for categorical variables. Where applicable, pairwise comparisons of patient characteristics will be determined by Pearson's chi-square or Fisher exact tests for categorical variables and Wilcoxon rank-sum test for continuous variables.

8.5.2. Analysis of primary objectives

Clinical outcomes, including liver enzyme elevations (grading) and discontinuation due to hepatotoxicity, will be described using frequency distributions for categorical variables and medians with IQRs for continuous variables. Chi-square tests will be used to compare categorical outcomes and Wilcoxon rank-sum tests will be used to compare continuous outcomes by category of exposure.

Kaplan Meier methods will be used to estimate time to virologic suppression in each group of patients by anchor-of-interest-based regimen prescribed. Patients will be censored upon death, modification or discontinuation of the anchor-of-interest-based regimen, or the end of study date. Survival distributions of the anchor-of-interest-based regimen treatment groups will be compared using log-rank tests.

Multivariable Cox proportional hazards models will model time to virologic suppression among HIV+/HCV+ patients initiating an anchor-of-interest-based regimen, adjusted for potential confounders. Proportional hazards assumptions (constant ratio of hazards independent of time) will be evaluated by the addition of an interaction term between treatment group (i.e. regimen) and time. In the absence of a suppression event, patients will be censored upon death, discontinuation of the anchor-of-interest-based regimen, or end of follow-up time. Hazard ratios and 95% confidence intervals will be reported for naïve and experienced populations.

8.5.3. Analysis of secondary objectives

Not Applicable.

8.5.4. Sensitivity analyses

To be determined as needed to evaluate various restrictions on inclusion and exclusion criteria, distinctive clinical profiles or particular treatment patterns.

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 the OPERA database 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 to a peer reviewed journal.

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