TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	Descriptive Analysis of Neuropsychiatric Diagnoses in Patients taking Dolutegravir in the OPERA® Observational Database

Compound Number: GSK1349572, GSK2619619

Development Phase IV

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Subject: Dolutegravir, neuropsychiatric events

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Introduction:

Dolutegravir (DTG), an integrase strand transfer inhibitor formulated as a once-daily, single agent tablet (Tivicay®) and as a single tablet regimen (Triumeq®) with abacavir and lamivudine (ABC/3TC) has been recently introduced to the antiretroviral therapy (ART) marketplace. Both Tivicay and Triumeq have demonstrated a favorable safety profile and high tolerability during their clinical development programs. Grade 4 neuropsychiatric safety events were rarely seen (<1%) with individual grade 1 or grade 2 events being seen in up to 3% of the patients. Similarly, post-marketing spontaneous adverse event surveillance has reported neuropsychiatric diagnoses as non-serious adverse events infrequently and as serious adverse events rarely.

In contrast, a recent study from CROI 2016 (Poster #948, van den Berk et. al.) presented an unexpectedly high rate of intolerance to DTG, including various neuropsychiatric symptoms, in a real-world setting. Given the safety profile seen in the development programs and the low spontaneous reporting rates, a finding of unexpectedly high rates seen by van den Berk et. al. should be evaluated in an independent real-world setting to see if these rates can be reproduced.

Objectives:

To summarize neuropsychiatric tolerability diagnoses in a population of HIV-positive males and females who have been prescribed DTG including both ART naïve and ART experienced patients.

Study Design:

A descriptive analysis of neuropsychiatric diagnoses made within a large, geographically-diverse, real-world clinical setting utilizing prospectively-collected electronic medical record (EMR) data obtained from the OPERA® Observational Database will be performed. The observation period will begin on January 1, 2007 (the STR era) with study participants identified through April 30, 2015 on data through April 30, 2016. The study population will be limited to HIV-positive patients who have been prescribed DTG-based, efavirenz (EFV)-based, ralutegravir (RAL)-based, or darunavir (DRV)-based regimens by an OPERA caregiver including both treatment naïve and treatment experienced patients. Each patient will be followed from the first occurrence of one of these regimens until regimen change, lost to follow up or death. Multiple endpoints will be allowed per patient to capture all events a patient experienceds while on regimen of interest.

Study Endpoints:

The study endpoints will include the following neuropsychiatric diagnoses of interest (grading/severity not available) and time to discontinuation:

1) abnormal behavior
2) abnormal dreams
3) aboulia/diminished motivation
4) affective disorder
5) aggression
6) agitation

7) alcoholism
8) anger
9) anxiety
10) bipolar disorder
11) bulimia nervosa
12) suicide (ideation, attempted, completed)
13) confused state
14) delusion
15) depressed mood
16) depression
17) depressive symptoms
18) disinhibition
19) disorientation
20) dissociation
21) dissociative disorder
22) drug dependence
23) elevated mood
24) emotional disorder
25) emotional distress
26) encopresis
27) euphoric mood
28) hallucination, auditory
29) hallucination, visual
30) impatience
31) impulsive behavior
32) insomnia
33) intentional self-injury
34) irritability
35) libido increased
36) loss of libido
37) mania
38) mental disorder
39) mental status changes
40) middle insomnia
41) mood alteration
42) mood swings
43) nervousness
44) nightmares
45) obsessive rumination
46) obsessive thoughts
47) orgasm abnormal
48) panic attack
49) panic reaction
50) paranoia
51) persecutory delusion
52) personality change
53) psychiatric symptom
54) psychotic disorder
55) restlessness
56) self injurious behavior
57) sleep disorders
58) somnambulism
59) stress
60) suicidal ideation
61) suicide attempt
62) thinking abnormal
63) time perception altered

Study Covariates:

The following patient demographic and clinical characteristics will be assessed at baseline, the initiation of the first DTG, EFV, RAL or DRV-containing regimen in the study period.

Demographic variables

- Age
- Gender
- Race (African American or not)
- Ethnicity (Hispanic or not)
- Possible Route of Infection (MSM or not)

Clinical variables

- HIV Status at baseline
  - HIV RNA viral load
  - CD4 count

  - AIDS status
  - ART experience (naïve or not)
  - Backbone ARTs given
- Neuropsychiatric comorbidities at baseline
  - Major Depressive Disorder
  - Bipolar Disorder
  - Alcoholism
  - Alcohol Use
  - Illicit drug/chem sex drug use
  - Other mental/emotional/behavioral disorder
  - Presence of neuropsychiatric concomitant medications

Statistical Analysis:

Patient demographics, baseline clinical characteristics and neuropsychiatric diagnoses will be described using frequency distributions. Medians with interquartile ranges will be used to describe time to neuropsychiatric event.

1. Addendum 1 (original neuropsychiatric event analysis; due May 27, 2016)
    a. Frequency of events distributions for:
        i. DTG-based regimens (with dose stratification)
2. Addendum 1a (due May 27, 2016)
    a. Frequency of events distributions for:
        i. EFV-based regimens
        ii. RAL-based regimens
        iii. DRV-based regimens
3. Addendum 1b (due August 20, 2016)
    a. Frequency of events distributions for:
        i. Complera regimens
        ii. Stribild regimens
4. Addendum 1c (due October 14, 2016)
    a. Comparison of demographics for:
        i. Patients on DTG with neuropsychiatric events
        ii. Patients on DTG without neuropsychiatric events

Regulatory and Ethical Considerations:

Data Aggregation, Informed Consent, Data Privacy, and the handling of Personally Identifiable Information (PII) follow the guidance of the HIPAA and HITECH guidelines.

Clinical 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. No personally identifiable information is available in the OPERA® Database. The OPERA® Clinical Advisory Board provides clinical and methodological review & oversight.

Business Associate Agreements (BAA) in place between Epividian and all medical practices govern 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 BAA's in place, a separate informed consent for each individual, non-interventional study is not required.

The study design is to analyse the patient level information recorded in the OPERA database from electronic health records in an aggregate manner. Reporting of adverse events by Epividian to competent authorities is not applicable as the healthcare information used in this study will not contain physician attribution of adverse event causality to any medicinal product.

References:

1. van den Berk G, Oryszczyn J, Blok W, van der Meche N, Regez R, Ait Moha D, Brinkman K. Unexpectedly High Rate of Intolerance for Dolutegravir in Real-Life Setting. Poster #948. Conference on Retroviruses and Opportunistic Infections. Boston. February 22-25, 2016.