# TITLE PAGE

**Information Type:** ViiV Healthcare Epidemiology Study Protocol

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| **Title:** | Dolutegravir Use and Predictors of CNS events: Meta-analysis of Data from Phase III/IIIb Clinical Trials |

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**Author(s):**

PPD

## TABLE OF CONTENTS

**PAGE**

# 1. LIST OF ABBREVIATIONS

| | |
|---|---|
| ABC | Abacavir |
| AE | Adverse Event |
| ATV | Atazanavir |
| cART | Combination Antiretroviral Therapy |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| D:A:D | Data Collection on Adverse Events of Anti-HIV Drugs |
| DRV | Darunavir |
| DTG | Dolutegravir |
| EFV | Efavirenz |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| FDA | Food and Drug Administration |
| FDC | Fixed Dose Combination |
| GSK | GlaxoSmithKline |
| HIV | Human Immunodeficiency Virus |
| RAL | Raltegravir |
| RCT | Randomized Controlled Trial |
| US | United States |
| VH | ViiV Healthcare |

## 2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

**MARKETING AUTHORISATION HOLDER**

ViiV Healthcare UK Limited

**Sponsor Legal Registered Address:**

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom

**SPONSOR SIGNATORY:**

| | |
|---|---|
| Primary Author/ Project officer | **Date** |
| VP, Global Medical Sciences | **Date** |
| VP, Safety and Pharmacovigilance | **Date** |

# 3. ABSTRACT

**Title:** Dolutegravir Use and CNS events: Meta-analysis of Data from Phase III/IIIb Clinical Trials

**Rationale and background:** In treatment-naïve Phase III/IIIb trials of DTG compared with either RAL, EFV, DRV/r or ATV/r, CNS AE rates were low, and most CNS AEs were of mild-to-moderate severity and rarely resulted in treatment discontinuation. A couple of observational HIV cohorts (see references) suggest that CNS AEs may result in somewhat higher rates of discontinuation in clinical practice than documented in clinical trials, and that this might occur more frequently in women, those >50yrs old, and with concomitant ABC use. Therefore, we are proposing to re-examine data from the phase III adult naive studies Spring 2, Single, Flamingo and Aria as well as the adult experienced Sailing study to identify if there are any predictors (from a pre-specified list) of development of a CNS AE during the course of the trials which could explain what is observed in the cohorts.

**Research question and objectives:**

The primary objective is to assess if there are any predictors for the development of a CNS AE during the course of the trials.

**Study design:** This meta-analysis will include data that were previously collected for VH-sponsored clinical trials in adult Phase III/IIIb of drug development for dolutegravir.

**Study size:** Studies included in the meta-analysis will be Spring 2, Single, Flamingo, Aria and Sailing

**Data analysis:** The incidence of CNS events will be calculated from frequencies of reported adverse events (AEs) in the included clinical trials; 95% CIs will be based on exact binomial 2-sided CIs. To assess the effect of pre-specified predictors on the exposure adjusted incidence rate and relative rate of CNS events in human immunodeficiency virus (HIV) patients treated with DTG containing versus non DTG containing regimens as well as DTG + ABC exposure vs DTG + other regimens Poisson mixed effects meta-regression models will be used. 95% CIs will be calculated for rates and relative rates.

# 4. AMENDMENTS AND UPDATES

N/A

# 5. MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data analysis | 01 May 2017 |
| Draft report | 30 JUN 2017 |
| Final report of study results | 30 JUL 2017 |

# 6. BACKGROUND AND RATIONALE

## 6.1. Background

In treatment-naïve Phase III/IIIb trials of DTG compared with either RAL, EFV, DRV/r or ATV/r, CNS AE rates were low, and most CNS AEs were of mild-to-moderate severity and rarely resulted in treatment discontinuation. Evolving observational HIV cohort data (1,2,4,5,6,7,8) suggest that CNS AEs may result in somewhat higher rates of DTG discontinuation in clinical practice than documented in clinical trials and that this might occur more frequently in women, those >50yrs old, and with concomitant ABC use.

## 6.2. Rationale

Therefore, we are proposing to re-examine patient level data from the phase III/IIIb adult naive studies Spring 2, Single, Flamingo and Aria as well as the adult experienced Sailing study to identify if there are any predictors of development of a CNS AE during the course of the trials which could explain what is observed in the cohorts. These are the same studies as were included in the Fettiplace et al manuscript (2017).

# 7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective is to identify if there are any predictors of the development of a CNS AE during the course of the trials.

# 8. RESEARCH METHODS

## 8.1. Study Design

This meta-analysis will include individual patient level data that were previously collected for VH-sponsored randomized clinical trials in adult Phase III/IIIb of drug development for dolutegravir.

## 8.2. Study Population and Setting

The total number of patients exposed to DTG from all 5 studies is 1672 and the total number of comparator regimen exposed patients included will be 1681. The number of patients exposed to DTG + ABC containing regimen is 930. Trials included in the meta-analysis are listed in Table 1.

**Table 1. Overview of GSK/VH-sponsored clinical trials included in the meta-analysis.**

| Study name | Study identifier | Study duration included in meta-analysis | Primary objective | DTG exposed | DTG unexposed |
|---|---|---|---|---|---|
| ARIA[1] | ING117172 | 48 | A Phase IIIb study to demonstrate the non-inferior antiviral activity, safety and tolerability of DTG/ABC/3TC FDC compared to ATV+RTV and TDF/FTC FDC in HIV-1 infected, ART-naïve women. | 248 | 247 |
| FLAMINGO | ING114915 | 96 | A Phase IIIb study to demonstrate the non-inferior antiviral activity of DTG 50mg administered once daily compared to DRV+RTV 800mg + 100mg once daily both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve subjects. | 242 | 242 |
| SINGLE[1] | ING114467 | 144 | A Phase III study to demonstrate the non-inferior antiviral activity of DTG + ABC/3TC once daily therapy compared to EFV/TDF/FTC in HIV-1 infected ART-naïve subjects. | 414 | 419 |
| SPRING-2 | ING113086 | 96 | A Phase III study to demonstrate the antiviral activity of DTG 50 mg administered once daily compared to RAL 400 mg twice daily, both administered with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naive subjects. | 411 | 411 |
| SAILING | ING111762 | 48 | A Phase III Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults | 357 | 362 |

[1]Randomized with respect to ABC therapy (i.e. an experimental control for ABC).

## 8.3. Variables

### 8.3.1. Exposure definitions

Two sets of analyses will be carried out reflecting the different exposures of interest – DTG and DTG + ABC. For the first set of analyses the exposed group was treated with DTG as part of cART. The comparator group was exposed to non-DTG-containing cART regimen. A single subject may only contribute to one of the exposure categories. For the second set of analyses we will consider DTG + ABC exposure vs DTG + Other exposure.

The mean exposure in days will be calculated from patient level data available for each study. Exposure categories will be constructed according to exposure to DTG or not in the cART as well as DTG + ABC vs not. The total exposure time in person-years will be obtained by taking the sum of each subjects' exposure time from start to end of treatment and dividing it by 365.25.

### 8.3.2. Outcome definitions

For the 5 VH-sponsored clinical trials, outcomes were identified on the basis of reported AEs listed in an aggregated clinical trials database maintained by VH.

The same definitions as described in the Fettiplace et al. JAIDS paper (2017) will be used to select the events of interest based on selected psychiatric symptoms occurring in HIV-positive patients during dolutegravir treatment as classified by company physicians. The following specific preferred terms will be used to define a CNS event in this analysis:

- Insomnia
- Anxiety
- Depression
- Suicidality
- Nightmares/abnormal dreams
- Headache

As described in Fettiplace et al the category *insomnia* includes the terms *insomnia*, *initial insomnia, terminal insomnia*, and *middle insomnia*. The category *anxiety* includes the terms *anxiety* and *anxiety disorder*. The category *depression* includes the terms *depression*, *major depression*, *depressed mood*, *depressive symptom*, and *bipolar disorder*. The category *suicidality* includes *suicide attempt*, *suicidal ideation*, *completed suicide*, *intentional self-injury*, and *self-injurious behavior*. The category headache includes the terms *headache* and *migraine*.

The analysis will be carried out for both all AEs and all drug related AEs during the course of the trials and will model both events and patients with an event as an outcome. Treatment of recurrent events will depend on how many re-occurring events are found to be present in the data. If there are 15% or more re-occurring events a sensitivity analysis will be carried out taking these into account. If fewer recurrent events are present in the data then only the first event for each patient will be included.

### 8.3.3. Predictors

The following set of variables are hypothesized based on the cohort data to be predictors of the development of a CNS AE during the course of the trials and will therefore be included and tested for in the analysis:

- Gender (M vs F)
- Age (< and ≥ 50)
- Race (White vs Other)
- Region
- Country
- Previous psychiatric history (Y vs N)
- Any chronic co-morbidity, including HCV, Diabetes, Hypertension (Y vs N)
- HIV acquisition risk factor
- History of drug use (Y vs N)
- Baseline viral load (< and ≥ 100,000 copies/ml)
- CD4 nadir (< and ≥ 200)
- BMI

## 8.4. Data sources

The studies that will be included in the meta-analysis were initially identified in the VH clinical-trial repository that includes prospectively collected data from VH-sponsored trials and contains clinical studies from phases III/IIIb of drug development shown in table 1.

## 8.5. Study size

The total number of patients exposed to DTG from all 5 studies is 1672 and the total number of comparator regimen exposed patients included will be 1681. The number of patients exposed to DTG + ABC containing regimen is 930. Trials included in the meta-analysis are listed in Table 1.

## 8.6. Data analysis

This analysis will look at studies with a follow-up of ≥48 weeks. This analysis will calculate incidence of a CNS AE as defined by the psychiatric symptoms described in section 8.3.2 for both definitions of exposure and evaluate if there are any predictors described in section 8.3.3. Since this is an exploratory analysis we will use a p-value of 0.10 for significance testing of those predictors. Prior to inclusion in the analysis the incidence of a CNS AE will be tabulated by predictor and any predictors with zero counts in categories will be excluded from the Poisson regression model.

### 8.6.1. Essential analysis

*Incidence of CNS events by predictor*

Percentages will be based on the frequency of AEs collected during the conduct of clinical trials and presented by levels of a predictor and study as well as aggregate. 95% CIs will be based on exact binomial 2-sided confidence intervals (CIs).

*Relationship between exposure to DTG, predictors and development of outcome*

Exposure adjusted incidence rates per 1,000 person-years will be calculated, and Poisson regression models will used to calculate relative rates, adjusted for predictors described in section 8.3.3. Study will be fitted as an indicator within the pooled model. 95% CIs will be calculated for rates and relative rates. P-values will be calculated for predictors. A stepwise approach will be used to identify significant predictors with a significance level of 10%. Results will be presented in a forest plot (by study and aggregate). The characteristics of those subjects at highest risk of a CNS event will be identified and the difference versus the remainder of the subjects quoted.

*Sensitivity analyses*

If there are 15% or more recurrent events a sensitivity analysis will be carried out taking these into account.

To consider whether insomnia is a pre cursor to other CNS AEs events, a tabular display of insomnia followed by other CNS AE yes/no will be created.

### 8.6.2. General considerations for data analyses

The possibility of multiple events in one patient may need to be taken into account. Therefore, the analysis of AE incidence is carried out both at the event and patient level.

## 8.7. Quality control and Quality Assurance

Quality control and quality assurance processes have been performed as part of the clinical trial protocols. Two statisticians will independently program for this analysis to ensure quality control of highest level.

Additionally, the analyses will be performed per European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (2010).

## 8.8. Limitations of the research methods

Only a review of the GSK/VH clinical trial database was performed to identify studies for inclusion. It is possible that more data has been published from non- VH-sponsored clinical trials that were not included in this analysis.

As the clinical trials were not specifically designed to evaluate CNS outcomes, the collection of additional predictors for CNS events may not have been incorporated in the original study protocols. Additionally, there will be no additional adjudication for CNS events for the current meta-analysis. Based on these limitations of the available data, the current meta-analysis will mainly be explorative in nature.

The included studies were generally designed as efficacy studies, and the primary endpoint was not CNS outcomes, thus the total drug exposure in person-years will be defined as an average time exposed to the treatment rather than calculated until time to event or end of study, whichever occurred first. Due to the small number of events, the post-CNS event follow-up time will have a very limited effect on the overall exposure.

Absence of any effect may be due to size and therefore power of the study and not because there is no relationship between predictors and outcome. The results will therefore need to be treated as exploratory.

### 8.8.1. Study closure/uninterpretability of results

N/A

# 9. PROTECTION OF HUMAN SUBJECTS

## 9.1. Ethical approval and subject consent

N/A, ethical approval was obtained for primary data collection as part of the clinical trials. This meta-analysis will use previously collected, anonymized clinical trial data.

## 9.2. Subject confidentiality

This meta-analysis will use previously collected, anonymized clinical trial data. No identifying information will be provided.

# 10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves secondary use of anonymized data from RCTs. All serious and non-serious AEs, pregnancy exposures and incidents related to any VH product during the conduct of the RCTs have already been reported to the case management and regulatory authorities per the RCT protocols. There is no potential for identification of any additional AEs or SAEs. Hence there will not be a study specific pharmacovigilance plan developed.

# 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

## 11.1. Target Audience

The target audience includes healthcare providers, regulatory and health authorities. The study results will be made available externally through conference presentation.

## 11.2. Study reporting and publications

Study results will be included in safety and regulatory reports as appropriate. Results will also be submitted for publication at a relevant conference.

# 12. REFERENCES

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