TITLE PAGE

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Title:	Abacavir Use and Risk for Myocardial Infarction and Coronary Artery Disease: Meta-analysis of Data from Clinical Trials

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1. LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
ATV	Atazanavir
CAD	Coronary Artery Disease
cART	Combination Antiretroviral Therapy
CI	Confidence Interval
CVD	Cardiovascular Disease
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs
DTG	Dolutegravir
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FTC	Emtricitabine
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
LPV	Lopinavir
MI	Myocardial Infarction
RCT	Randomized Controlled Trial
RTV	Ritonavir
TDF	Tenofovir Disoproxil Fumarate
US	United States
VH	ViiV Healthcare

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

MARKETING AUTHORISATION HOLDER

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3. ABSTRACT

Title: Abacavir Use and Risk for Myocardial Infarction and Coronary Artery Disease: Meta-analysis of Data from Clinical Trials

Rationale and background: While some observational studies and randomized controlled trials (RCTs) suggest an association between abacavir (ABC) use and myocardial infarction (MI), other observational studies and RCTs do not confirm this, including meta-analyses conducted on clinical trial data by GlaxoSmithKline (GSK), the United States (US) Food and Drug Administration (FDA) and independent researchers. Although the published evidence remains conflicting, and a plausible biological mechanism for this potential association has not yet been identified, ViiV Healthcare (VH) continues to monitor data as it becomes available. The proposed meta-analysis will include summary data from the previous meta-analysis performed by GSK (Brothers et al. 2009) and aggregate data on ABC exposure from GSK/VH-sponsored clinical trials conducted since then.

Research question and objectives:

The primary objective is to estimate the exposure adjusted incidence rate and relative rate of MI and coronary artery disease (CAD) events reported in subjects treated with ABC-containing combination antiretroviral therapy (cART) regimens and in subjects treated with non-ABC-containing cART regimens.

Study design: This meta-analysis will include data that were previously collected for GSK/VH-sponsored clinical trials from Phase II–IV of drug development. Subjects were either randomized to ABC vs other ARTs, or ABC was prescribed as a background medication by investigator.

Study size: The previous GSK meta-analysis (Brothers et al. 2009) and 14 GSK/VH-sponsored clinical trials completed since then comprise a total of approximately 20,000 subjects contributed to the analysis. Nearly 14,000 patients were exposed to regimens that included ABC, and 7,500 were in comparator groups with regimens that did not include ABC.

Data analysis: The incidence of MIs and CADs 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 exposure adjusted incidence rate and relative rate of MI and CAD in human immunodeficiency virus (HIV) patients treated with ABC-containing cART regimens compared with subjects treated with non-ABC containing cART regimens Poisson regression models will be used. 95% CIs will be calculated for rates and relative rates. The main analysis will include ABC-randomized trials with a duration of 48 weeks or longer. Sensitivity analyses will be performed to investigate the impact of including trials with follow-up shorter than 48 weeks and non-ABC-randomized trials.

4. AMENDMENTS AND UPDATES

N/A

5. MILESTONES

Milestone	Planned date
Start of data analysis	01 DEC 2106
Draft report	31 MAR 2017
Final report of study results	30 APR 2017

6. BACKGROUND AND RATIONALE

6.1. Background

Cardiovascular disease (CVD) is a leading cause of death in HIV-infected individuals, accounting for approximately 11% of total deaths in this population (Smith et al. 2014). The risk of CVD is higher in HIV-infected individuals compared with uninfected individuals (Bedimo et al. 2011; Hemkens and Bucher 2014; Triant et al. 2007). The reported incidence of MI in cohort studies ranges from 3–11 cases per 1000 patient-years in HIV-infected individuals compared with 2–7 cases per 1000 patient-years in HIV uninfected individuals (Durand et al. 2011; Klein et al. 2002; Triant et al. 2007; Worm et al. 2010).

Mechanisms for increased CVD risk in HIV remain incompletely defined and probably include both direct effects of HIV infection, including HIV-associated inflammation and immune activation, and exacerbation of risk factors by HIV infection and/or cART (Triant 2013; Triant et al. 2010). The prevalence of many CVD risk factors tends to be higher among HIV-infected individuals than among uninfected individuals, and these must be accounted for in any assessment of the relative incidence of CVD (Bedimo et al. 2011; Durand et al. 2011; Triant 2013; Triant et al. 2007). For example, data collected in two large US hospitals between 1996 and 2004 found a significantly higher prevalence between HIV-infected and uninfected individuals of smoking (38 vs. 18%), hypertension (21 vs. 16%) diabetes (12 vs. 7%) and dyslipidaemia (23 vs. 18%) (Triant et al. 2007).

One of the largest and most comprehensive data sets on CVD risk in HIV-infected individuals is the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, an international multi-cohort collaboration set up to prospectively assess the incidence of MI among HIV-infected individuals receiving cART (Friis-Moller, Sabin, et al. 2003; Friis-Moller, Weber, et al. 2003). The primary objective of the study was to determine whether exposure to cART is independently associated with risk of MI (Friis-Moller, Sabin, et al. 2003). Among the findings of the D:A:D study was an association between recent use of ABC and an increased rate of MI (Sabin et al. 2008). This was unexpected since ABC is not known to adversely affect lipids and glucose metabolism, factors that are normally considered to be pro-atherogenic.

Following the initial publication of MI results from the D:A:D study (Sabin et al. 2008), an increased risk of MI was also reported among patients who received ABC in three observational studies and a retrospective analysis of one randomised clinical trial (RCT). In consideration of these data, VH proposed a safety update to the SmPC for ABC/3TC (lamivudine):

"Observational studies have shown an association between myocardial infarction and the use of abacavir. Those studied were mainly antiretroviral experienced patients. Data from clinical trials showed limited numbers of myocardial infarction and could not exclude a small increase in risk. Overall the available data from observational cohorts and from randomised trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction. To date there is no established biological mechanism to explain a potential increase in risk. When prescribing Kivexa, action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia)."

The current Global Datasheet (GDS) includes the following on MI

Some observational, epidemiological studies have reported an association with abacavir use and the risk of myocardial infarction. Meta-analyses of randomised controlled trials have demonstrated no excess risk of myocardial infarction with abacavir use. To date, there is no established biological mechanism to explain a potential increase in risk. In totality the available data from observational studies and from controlled clinical trials show some inconsistency so can neither confirm nor refute a causal relationship between abacavir treatment and the risk of myocardial infarction.

As a precaution the underlying risk of coronary heart disease should be considered when prescribing antiretroviral therapies, including abacavir, and action taken to minimize all modifiable risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking).

While some observational studies (Choi et al. 2011; Durand et al. 2011; Lundgren et al. 2008; Obel et al. 2010; Sabin et al. 2016; Sabin et al. 2008; Worm et al. 2010) and RCTs (Martin et al. 2009) suggest an association between ABC use and MI, other observational studies (Bedimo et al. 2011; Lang et al. 2010; Lichtenstein et al. 2010; Triant et al. 2010) and RCTs (Daar et al. 2011; Martinez et al. 2010; Moyle et al. 2013; Sax et al. 2011; Smith et al. 2009; Squires et al. 2012) do not confirm this, including meta-analyses conducted on clinical trial data by GSK (Brothers et al. 2009), the US Food and Drug Administration (FDA) (Ding et al. 2012) and independent researchers (Cruciani et al. 2011; Ribaudo et al. 2011). Although strict inclusion/exclusion criteria make RCTs less prone to selection and classification bias and confounding, they may also limit comparability with HIV patients in clinical practice as clinical trial subjects are generally healthier and have a lower cardiovascular risk. On the other hand, observational studies are subject to channelling bias; a difference in baseline characteristics of patients resulting from the way that they are assigned to a particular treatment. Channelling bias could not be ruled out in previous observational studies, e.g. D:A:D or SMART study (Lundgren et al. 2008; Sabin et al. 2008). Neither study excluded patients with chronic kidney disease (an important cardiovascular risk factor) and patients had cART

experience prior to receiving ABC. In both studies, the investigators acknowledged the potential for high-risk individuals to be channelled towards ABC (Lundgren et al. 2008; Post and Campbell 2008; Sabin et al. 2008).

Overall, the available data from observational cohorts and RCTs are inconclusive regarding the relationship between ABC treatment and the risk of MI or cardiovascular events. However, the differences in effect size seen between the observational and the RCT evidence cannot be attributed to differences in cardiovascular risk among the study populations. In the D:A:D study, the association between ABC use and MI incidence was strongest, in relative terms, in individuals with low cardiovascular risk. This would predict that an association between ABC use and MI incidence should be visible in the lower-risk populations included in RCTs.

While the published evidence remains conflicting, and a plausible biological mechanism for this potential association has not yet been identified, VH continues to monitor data as it becomes available. The proposed meta-analysis will include aggregate data on ABC exposure from VH-sponsored clinical trials, conducted since the last such meta-analysis (Brothers et al. 2009).

6.2. Rationale

Since the last analysis of GSK clinical trial data in 2009, several new studies have been conducted, generating additional data on ABC use and risk for MI and CAD. The proposed meta-analysis is part of VH's continued pharmacovigilance efforts to monitor this risk.

7. RESEARCH QUESTION AND OBJECTIVE(S)

The primary objective is to estimate the exposure adjusted incidence rate and relative rate of MI and CAD events reported in subjects treated with ABC-containing cART regimens and in subjects treated with non-ABC-containing cART regimens.

8. RESEARCH METHODS

8.1. Study Design

This study is formed to update the previously established Brothers et al. (2009) meta-analysis results of 52 GSK-sponsored clinical trials in adult subjects. In addition to summary data from the previous meta-analysis, the current analysis will include data that were collected as part of GSK/VH-sponsored clinical trials from Phase II–IV of drug development since 2009. Subjects were either randomized to ABC vs other ARTs, or ABC was prescribed as a background medication by the investigator. ARTs taken by subjects prior to entering a VH-sponsored study will be ignored in this meta-analysis.

Data for nearly 6,000 HIV-infected adult subjects from the 14 post-2009 GSK/VH-sponsored clinical trials will be investigated with the aim of evaluating the association between ABC and the risk of MI and CAD as outcomes in addition to the 14,174 HIV-infected individuals which were included in the previous meta-analysis (Brothers et al. 2009).

8.2. Study Population and Setting

In addition to data from the previous GSK meta-analysis (Brothers et al. 2009), data from 14 GSK/VH-sponsored clinical trials conducted since the 2009 meta-analysis, with at least 24 weeks of cART exposure will be included in this analysis (see Table 1). Only studies that were completed or for which the primary objective was completed, will be included. Overall, this analysis will be based on 66 studies, in which a total of approximately 20,000 subjects were randomized to various treatment regimen, some ABC containing and others non-ABC regimen, but in many studies randomization was not based on ABC.

Table 1. Overview of post-2009 GSK/VH-sponsored clinical trials included in the meta-analysis.

Study name	Study identifier	Study duration included in meta-analysis	Primary objective	ABC exposed	ABC 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
ARIES	EPZ108859	144	A Phase IIIb study to compare the safety and efficacy of ATV/r administered once daily (QD) followed by randomization (1:1) to a simplification regimen of ATV QD or continuation of ATV/r QD, each in combination with ABC/3TC FDC QD in ART-naïve, HIV-1 infected, HLA-B*5701 negative subjects.	369	0
ASSERT[1]	CNA109586	96	A Phase IV study to demonstrate a superior renal safety profile in subjects who received ABC/3TC FDC compared to TDF/FTC FDC, both administered with efavirenz.	192	193
ASSURE[1]	EPZ113734	48	A Phase IV study to evaluate the efficacy, safety, and tolerability of the antiviral response between ATV/RTV+ TDF/FTC and ATV + ABC/3TC without ritonavir in HIV-1 infected, HLA-B*5701 negative subjects previously suppressed on ATV/RTV + TDF/FTC.	199	97
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.	159	325

HEAT[1]	EPZ104057	96	A Phase IV study to establish that ABC/3TC is virologically non-inferior to TDF/FTC when administered in combination with LPV/r in ART-naïve, HIV-1 infected subjects and to compare the safety and tolerability of ABC/3TC versus TDF/FTC when administered in combination with LPV/r.	343	345
LATTE	LAI116482	24	A Phase IIb study to select a dose of Cabotegravir for further evaluation as part of a two drug combination ART regimen with rilpivirine, following a 24 week induction period of Cabotegravir with two NRTIs (either ABC/3TC or TDF/FTC, in HIV-1 infected, antiretroviral naïve subjects.	94	149
LATTE-2[1]	200056	32[2]	A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 For The Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects	56	230
MERIT	APV109141	48	A Phase IIIb study To demonstrate non-inferior antiviral activity of FPV/RTV 1400 mg/100 mg once daily compared to FPV/RTV 700 mg/100 mg BID, both administered with abacavir/lamivudine fixed dose combination (ABC/3TC FDC) once daily.	212	0
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-1	ING112276	96	A Phase II study to select a DTG once daily dose for further evaluation in Phase III based on a comparison of the antiviral activity and tolerability of a range of oral doses of DTG taken in combination with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naïve adult subjects.	67	138
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	333	489

			with either ABC/3TC or TDF/FTC in HIV-1 infected therapy-naive subjects.		
STRIIVING[1]	201147	48	A Phase IIIb study to compare switching from current antiretroviral regimen to ABC/DTG/3TC administered once daily in the treatment of human immunodeficiency virus type 1 (HIV-1) infected adults who are virologically suppressed.	275	276[3]
	ING116070	96	A single-arm study of the safety, efficacy and central nervous system and plasma PK of GSK1349572 (dolutegravir, DTG) 50 mg once daily in combination with the abacavir/lamivudine fixed dose combination tablet over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects.	13	0

[1]Randomized with respect to ABC therapy (i.e. an experimental control for ABC).
[2]Additional 20 weeks of the induction phase where all subjects (n=309) took CAB+ABC/3TC will be included in the analysis
[3]At Week 24, individuals originally randomly assigned to CAR switched to ABC/DTG/3TC FDC and were followed for an additional 24 weeks (n=244).

8.3. Variables

8.3.1. Exposure definitions

The exposed group was treated with ABC as part of cART. The comparator group was treated with non-ABC-containing cART regimen. A single subject may only contribute to one of the exposure categories (except in STRIIVING where some subjects switched from cART to ABC/DTG/3TC after 24 weeks, and LATTE-2 where all subjects received CAB+ABC/3TC during the induction phase).

The mean exposure in days will be collected from published trial results from exposure summary tabulations information for each trial for each treatment. Exposure categories will be constructed according to exposure to ABC or not in the cART. The total exposure time in person-years to the cART regimen, will be obtained by taking the mean exposure in days and multiplying it with the total number of subjects for each treatment group in each trial, and dividing it by 365.25.

8.3.2. Outcome definitions

For the additional 14 GSK/VH-sponsored clinical trials, outcomes were identified on the basis of reported AEs listed in an aggregated clinical trials database maintained by GSK/VH. Any pre-existing AEs were not collected unless there was a change in severity during treatment, therefore any pre-treatment MIs and CADs were not collected and therefore not included in the database.

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The same definitions as in the initial meta-analysis Brothers et al. (2009) will be used to select the events of interest based on MedDRA High-Level Terms of Coronary artery disorders not elsewhere classified and Ischemic coronary Aartery disease. The following specific preferred terms will be used:

- Arteriosclerosis coronary artery,
- Coronary artery disease,
- Coronary artery occlusion,
- Acute myocardial infarction
- Myocardial infarction
-
- Myocardial ischemia.

MedDRA terms for angina (angina pectoris and angina unstable) will also be included as CADs, as these were included in the 2009 meta-analysis.
In addition, MedDRA terms for the outcome of MI will include acute MIs and MIs.

8.3.3. Confounders and effect modifiers

Concurrent ARTs, baseline demographics, HIV disease characteristics, established cardiovascular risk factors, presence or absence of preexisting CVD before enrolment could have potential confounding effects in the analysis. Due to the relatively small

number of events, a full statistical analysis exploring the impact of other covariates is not viable.

8.4. Data sources

The studies that will be included in the meta-analysis were initially identified in the GSK/VH clinical-trial repository that includes prospectively collected data from GSK/VH-sponsored trials and contains clinical studies from phases II–IV of drug development.

8.5. Study size

From the current 14 GSK/VH-sponsored clinical trials since 2009, nearly 6,000 subjects contributed to the analysis. In these trials, over 3,500 were exposed to regimens that included ABC, and nearly 3,000 were in comparator groups with regimens that did not include ABC (as noted in Section 8.3.1 some subjects in STRIIVING and LATTE-2 received both regimens). Including data from the previous meta-analysis (Brothers et al. 2009), the current analysis will be based on a total of approximately 20,000 subjects, with adults who received ABC (n= ~14,000) or not (n= ~7,500), that will provide a cumulative summary of the clinical trial evidence on the relationship between ABC and MI risk.

8.6. Data management

8.6.1. Timings of Assessment during follow-up

The timing of follow-up in the original clinical trials varied from 24 weeks up to 144 weeks post-treatment initiation. A sensitivity analysis will be performed to identify potential differences in signal detection between follow-up periods of at least 48 weeks and follow-up periods that are shorter than 48 weeks.

8.7. Data analysis

The main analysis will combine data from studies that were randomized to ABC or control, from studies included in the previous meta-analysis (Brothers et al. 2009) as well as from GSK/VH-sponsored studies identified post-2009. This analysis will look at studies with a follow-up of ≥48 weeks. This analysis will be conducted for MI.

The following sensitivity analyses will be performed:

- Randomized to ABC or control studies including studies of <48 weeks duration conducted for MI.
- Randomized and non-randomized to ABC or control studies of ≥48 weeks duration conducted for MIs and CADs
- Randomized and non-randomized studies including studies of <48 weeks duration conducted for MIs and CADs

8.7.1. Essential analysis

Incidence of MI and CAD

Percentages will be based on the frequency of AEs collected during the conduct of clinical trials. 95% CIs will be based on exact binomial 2-sided confidence intervals (CIs).

Relationship between exposure to ABC and development of outcome

Exposure adjusted incidence rates per 1,000 person-years will be calculated, and Poisson regression models will used to calculate unadjusted relative rates, no adjustment for confounders will be performed. 95% CIs will be calculated for rates and relative rates.

Sensitivity analyses

Table 1 includes several trials that included relatively short periods of follow-up. Sensitivity analyses will be performed including trials in which subjects were randomized to ABC or control, and the follow-up time was shorter than 48 weeks.
Additional analyses will be performed including all studies which were randomized with respect to ABC or not. This will be conducted excluding studies of <48 weeks duration, and also including these studies
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8.7.2. General considerations for data analyses

None of the patients had multiple cardiac events, but it is possible that patients who had a cardiac event were excluded from the remainder of the study, or were lost to follow-up. This will be further investigated as part of the data analysis. The possibility of multiple events in one patient may not need to be taken into account. The clinical trials from which the data is derived were designed to investigate the safety and efficacy of various antiretroviral agents, including ABC, and the primary endpoint was not cardiovascular outcomes.

8.8. 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).

8.9. 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-GSK/VH-sponsored clinical trials that were not included in this analysis.

As the clinical trials were not specifically designed to evaluate cardiovascular outcomes, the collection of baseline risk factors for cardiovascular events may not have been incorporated in the original study protocols. Additionally, there will be no additional adjudication for MI and CAD events for the current meta-analysis. Furthermore, pre-treatment events were not recorded, making it impossible to determine whether the event reported during the clinical trials were a recurrence or a new event. Based on these limitations of the available data, the current meta-analysis will mainly be descriptive in nature.

This analysis used summary data rather than patient level data to calculate exposure time. The included studies were generally designed as efficacy studies, and the primary endpoint was not cardiovascular 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. Thus, the fact that once the event occurred the subject was no longer at risk of having an outcome of interest will not be taken into account. Due to the small number of events, the post-MI/CAD follow-up time will have a very limited effect on the exposure.

Finally, due to the relatively small number of events, it is not possible to perform a full statistical analysis exploring the impact of potential confounders.

8.9.1. 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 peer reviewed manuscript and 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 in a peer reviewed journal, and for consideration to be presented at relevant conference.

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