TITLE PAGE

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Title:	Rates of Suspected Hypersensitivity Reaction in HIV infected Adult treatment populations screened HLA-B*5701 negative prior to commencing Abacavir therapy: Meta-analysis of Data from GlaxoSmithKline and ViiV Healthcare Sponsored Clinical Trials

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1. ABBREVIATIONS AND TRADEMARKS

3TC	Lamivudine
ABC	Abacavir
AE	Adverse Event
ART	Antiretroviral Therapy
ARV	Antiretroviral
ATV	Atazanavir
CI	Confidence Interval
CSI	Core safety information
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
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
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
IMP	Investigational medicinal product
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PI	Prescribing Information
PT	Preferred Term
QD	Once daily
RAL	Raltegravir
RCT	Randomized Controlled Trial
RTV	Ritonavir
SAE	Serious Adverse Event
SAS	Statistical analysis system
SmPC	Summary of Product Characteristics
TDF	Tenofovir Disoproxil Fumarate
TTO	Time to onset
VH	ViiV Healthcare

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2. RESPONSIBLE PARTIES: SPONSOR INFORMATION PAGE

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3. ABSTRACT

Title: Rates of suspected hypersensitivity reaction in HIV infected Adult treatment populations screened HLA-B*5701 negative prior to commencing abacavir therapy: Meta-analysis of data from GlaxoSmithKline and ViiV Healthcare sponsored clinical trials.

Rationale and background: The last GSK clinical trial meta-analysis on abacavir hypersensitivity was undertaken in 2006, and involved studies conducted before the era of routine screening for HLAB*5701 prior to commencing abacavir therapy. Since then, several marketing authorisation holder (MAH) sponsored studies have been conducted that have investigated abacavir- containing study medications in HIV- infected adult treatment populations, that were screened for the HLA-B*5701 allele. Depending on individual study protocol/design, patients testing positive for this allele were then excluded from participation or from receiving an ABC- containing product in these studies. Additionally, as part of CNA106030 (PREDICT-1), Investigators were blinded to the subjects HLA-B*5701 status during the study [Mallal, 2008], which could be considered a limitation of the reported data, because this would not be the case in clinical practice. It is hypothesized that the more recent MAH sponsored trials that investigated abacavir- containing study medications in HLA-B*5701 negative, HIV- infected adult treatment populations, will more accurately reflect experience and reporting rates in clinical practice, because subject HLA-B*5701 status was not blinded.

Research question and objectives: The primary objective is to estimate the incidence rate of clinically suspected abacavir hypersensitivity reaction cases reported in HLA-B*5701 negative subjects treated with ABC-containing ART regimens.

Study design: This meta-analysis will include data that were previously collected for 12 GSK/VH-sponsored randomized clinical trials (RCTs) from Phase IIb–IV of drug development for either ABC/lamivudine (3TC) [EPZICOM®, KIVEXA®], dolutegravir (DTG) [TIVICAY®], ABC/DTG/3TC [TRIUMEQ®] or cabotegravir, conducted since January 2007. HLAB*5701 negative, HIV infected Adult Subjects were either randomized to ABC vs. other ARTs, or ABC was prescribed as a background medication by investigator as part of these RCTs.

Study size: Overall, 3063 HLA-B*5701 negative, HIV infected Adult subjects were exposed to regimens that included ABC, for a minimum of 20 Weeks, as part of the above RCTs. In a sub-population of seven of these RCTs, during which 1,494 such subjects were exposed to either TRIUMEQ, or its equivalent component actives (given as the single active preparation of dolutegravir [DTG; TIVICAY] in combination with the ABC/3TC fixed dose combination (FDC) tablet), for a minimum of 24 Weeks.

Data analysis: Incidence rates of both: Investigator diagnosed; and MAH adjudicated, clinically suspected abacavir hypersensitivity reactions will be estimated. The exposure to an abacavir-containing regimen will be reported. 95% CIs will be based on exact binomial 2-sided confidence intervals. These analyses will be repeated in a sub-population of subjects, who received TRIUMEQ or its equivalent component actives (given as DTG in combination with the ABC/3TC FDC Tablet).

4. AMENDMENTS AND UPDATES

N/A

5. MILESTONES

Milestone	Planned date
Start of data analysis	10 Apr 2017
Draft report	30 Jun 2017
Final report of study results	30 Sep 2017

6. BACKGROUND AND RATIONALE

6.1. Background

Abacavir sulfate is a carbocyclic 2'-deoxyguanosine nucleoside analogue, which was approved by the FDA in December 1998, for the treatment of adults and children with HIV infection. The approval of abacavir (ABC) was based on studies that showed improved CD4 profile and decreased plasma HIV RNA levels in patients who took abacavir in combination with other nucleoside analogues versus those who took antiretroviral regimens without abacavir [Saag, 1998; Staszewski, 1998]. Abacavir is converted intracellularly by enzymes, into the active compound carbovir triphosphate. This, in turn, competitively inhibits HIV reverse transcriptase and terminates proviral DNA chain extension [Hervey, 2000].

Originally marketed as ZIAGEN®, abacavir has since been co-formulated with two other nucleoside reverse transcriptase inhibitors, zidovudine and lamivudine (3TC), approved as TRIZIVIR®, followed by co-formulations with lamivudine, approved as EPZICOM® and KIVEXA® and with lamivudine and dolutegravir (DTG) approved as TRIUMEQ®. With all formulations, abacavir is widely used to achieve viral suppression and immunologic improvement in patients with HIV infection. Factors that make abacavir a suitable choice for HIV therapy are its high oral bioavailability (geometric mean of absolute bioavailability is 83%), no significant effect of food on the extent of absorption, pharmacokinetics that support once daily dosing, good central nervous system penetration, no significant drug interactions, and slow development of drug-resistant mutants [Chittick, 1999; McDowell, 2000; Tisdale, 1997; Wang, 1999; Weller, 2000].

Early phase I/II trials with abacavir indicated the occurrence of side effects like headache, gastrointestinal disturbances, rash, malaise, fatigue and asthenia. Like many antiretroviral drugs, abacavir is metabolized by cytochrome P450 in the liver. Nucleoside analogues are associated with the class effect of mitochondrial toxicity and its secondary clinical syndromes, such as lactic acidosis, hepatomegaly with steatosis and metabolic disorders [Bleeker-Rovers, 2000]. Among nucleoside analogues, abacavir is believed to have a lower propensity for causing mitochondrial toxicity. Studies show that switching patients with symptomatic hyperlactatemia or lactic acidosis from stavudine and/or didanosine to abacavir and lamivudine results in lower lactate levels, that are generally asymptomatic [Lonergan, 2003].

Hypersensitivity is the term used for an extreme form of adaptive immune response. Such responses occur when the immune system reacts inappropriately to certain antigens, and may lead to inflammatory reactions and tissue damage [Brostoff, 1996]. Hypersensitivity to abacavir is a well-characterized systemic syndrome that usually presents with multiple symptoms and involves several organ systems. The majority of patients have fever and/or rash as part of the syndrome; however, reactions have occurred without rash or fever. Other signs and symptoms commonly include gastrointestinal complaints (nausea, vomiting, diarrhea or abdominal pain), lethargy and malaise, musculoskeletal symptoms (e.g., arthralgia and myalgia) and respiratory symptoms (such as dyspnea, cough and pharyngitis).

The vast majority of patients (95%) present with symptoms from two or more body systems [Symonds, 2002]. The symptoms of this HSR can occur at any time during treatment with ABC, but usually occur within the first six weeks of therapy (median time to onset [TTO] 9-11 days) [ZIAGEN US Package Insert, 2015; Symonds, 2002].

Other symptoms of hypersensitivity include myolysis, edema, abnormal chest X-ray, paresthesia, liver failure, renal failure, hypotension, adult respiratory distress syndrome and respiratory failure. Reports of anaphylaxis with initial and re-challenge exposure to abacavir have been documented [Walensky, 1999; Frissen, 2001; Shapiro, 2001; Clay, 2000].

The reaction generally evolves over a number of days, can be detected early with clinical monitoring, and is reversible when abacavir is discontinued. However, more severe and rarely fatal or life threatening reactions can occur, and are generally the result of either prolonged abacavir treatment in the face of evolving symptoms of HSR, or inappropriate re-challenge. Following a diagnosis of hypersensitivity, patients must not take abacavir again. Restarting the drug following a hypersensitivity reaction has resulted in cases of life-threatening hypotension and fatal re-challenge reactions. Additionally, there have been reports of individuals who developed re-challenge hypersensitivity to abacavir after having been asymptomatic during initial use of the drug [Frissen, 2001; El-Sahly, 2004]. Therefore, it is recommended that all patients receiving abacavir be monitored closely for signs of a hypersensitivity reaction, especially in the initial weeks of treatment [Clay, 2002].

Early studies examining the demographic and clinical predictors of hypersensitivity found higher risks for white race, female gender, elevated baseline CD8 and lower risks for antiretroviral treatment experienced patients and those of African American descent [Easterbrook, 2003; Cutrell, 2004; Symonds, 2002; Hewitt, 2003]. Genetic susceptibility factors have been suggested because of the occurrence of the reaction in a small sub-population of patients receiving abacavir, familial disposition, the low incidence of the reaction in patients of African American origin and involvement of the major histocompatibility complex alleles in other similar multi-organ hypersensitivity reactions [Martin, 2004; Mallal, 2002]. Later studies found an association between abacavir hypersensitivity and specific human leukocyte antigen (HLA) alleles [Mallal, 2008].

Following the identification of a genetic link to abacavir hypersensitivity reaction, HLA-B*5701 testing entered clinical use in 2008 with the demonstration of the clinical utility

of HLA screening where it was found that screening eliminated immunologically confirmed hypersensitivity reaction with a negative predictive value of 100% and a positive predictive value of 47.9% [Mallal, 2008]. Guidelines subsequently recommended HLA testing for all patients when considering an abacavir-containing regimen. It also became standard practice in 2007 for GlaxoSmithKline (GSK), and then ViiV Healthcare (VH), Sponsored Clinical Trials to require study participants to have tested HLA-B*5701 negative prior to initiating an abacavir- containing study medication (i.e., HLA-B*5701 positive patients were excluded from either participating or receiving an abacavir-containing product in such clinical trials, depending on individual protocol designs).

Until recently, the exact mechanism of the abacavir hypersensitivity reaction was not clearly understood. Features of this reaction suggest an immune mediated mechanism but do not match any of the four Gell and Coombs classifications for hypersensitivity reaction [Hetherington, 2001]. The most significant development in understanding the mechanism of abacavir hypersensitivity reaction was the resolution of the crystal structure of the abacavir-MHC-peptide complex, which was reported by two groups in 2012 [Illing, 2013; Ostrov, 2012].

Illingham et al. showed that unmodified ABC binds non-covalently to HLA-B*57:01, and these findings provide a general theoretical mechanism for HLA-linked hypersensitivities that involve small-molecule drugs [Illing, 2013]. Ostrov et al. found that specific peptides showed significantly increased affinity for binding to HLA-B*57:01 in the presence of abacavir, providing an explanation for HLA-linked idiosyncratic adverse drug reactions. Specifically, drugs can alter the repertoire of self-peptides presented to T cells, thus causing the equivalent of an alloreactive T-cell response. Furthermore specific self-peptides that are presented only in the presence of abacavir were identified and these were recognised by T cells of hypersensitive patients [Ostrov, 2012]. Additional studies further demonstrated that ABC-specific T-cell stimulation does not require the formation of covalent bonds [Adam, 2012] and that ABC can alter the quantity and quality of self-peptide loading into HLA-B*57:01 in the absence of drug metabolism [Norcross, 2012].

The current body of evidence supports the ‘altered repertoire model’, in which ABC can alter the repertoire of self-peptides presented to T-cells resulting in an immune response. This is heightened in patients carrying HLA-B*5701 due to a direct, metabolism-independent and non-covalent interaction of abacavir with HLA-B*5701.

Reporting rates for hypersensitivity reactions from clinical trials with abacavir, which were conducted before the era of routine screening for HLA-B*5701 pre-abacavir therapy, have ranged from 4 to 8%. A retrospective review of data from 200,000 patients who received abacavir through clinical trials or by prescription initially identified a total of 1,803 cases of suspected hypersensitivity to the drug. Upon further review of these cases, the calculated incidence rate in the clinical trials was determined to be 4.3%. The mortality rate in patients who received abacavir in clinical trials was 0.03% [Hetherington, 2001].

In a subsequent meta-analysis of 8,038 subjects receiving ABC through participation in 34 GSK Sponsored clinical trials with at least 24 Weeks exposure through to January

2002, approximately 5% (403) were diagnosed with a suspected hypersensitivity reaction. In a sub- analysis of nine such GSK Sponsored clinical trials conducted between November 1999 and January 2002, which employed the abacavir hypersensitivity reaction case report form (CRF) and involved 2,670 patients exposed to abacavir, the reporting rate for patients diagnosed with a suspected hypersensitivity reaction increased to 8% (range 2-9%) [Cutrell, 2004; Hernandez, 2003]. The most recent update to these GSK analyses was conducted with data through to March 2006. This included a total of 39 clinical trials involving 10,888 patients with at least 12 Weeks of exposure to ABC pre- routine HLA-B*5701 screening, 590 (5%) of which developed a clinically suspected abacavir hypersensitivity reaction. At this point the sub- group of clinical trials utilizing the ABC HSR CRF had expanded to 14 studies, involving 5,521 patients of whom 393 (7%) were diagnoses with a clinically suspected ABC HSR [Data on file].

External researchers in Australia and Europe began publishing data in 2006 from small treatment cohorts, in which they had prospectively screened for HLA-B*5701 and excluded subjects testing positive for this allele from receiving ABC, resulting in reporting rates for abacavir hypersensitivity of 0 to <1% [Rauch, 2006; Reeves, 2006; Zucman, 2006].

6.2. Rationale

The last GSK clinical trial meta-analysis on abacavir hypersensitivity in 2006 involved studies conducted before the era of routine screening for HLA-B*5701 pre-abacavir therapy. Since then, several marketing authorisation holder (MAH) sponsored studies have been conducted that have investigated abacavir- containing study medications in HIV- infected adult treatment populations, that were screened for the HLA-B*5701 allele. Patients testing positive for this allele were then excluded from participation or from receiving an ABC- containing product in these studies, depending on individual study protocol/design.

Additionally, Investigators were blinded to the subjects HLA-B*5701 status during CNA106030 (PREDICT-1) [Mallal, 2008], which could be considered a limitation of the study data, because this would not be the case in clinical practice, and may have resulted in an over reporting of ABC HSR in this study. It is hypothesized that the more recent MAH sponsored trials that investigated abacavir- containing study medications in HLA-B*5701 negative, HIV- infected adult treatment populations, will more accurately reflect experience and reporting rates in clinical practice, because subject HLA-B*5701 status was not blinded.

The proposed meta-analysis is part of VH’s continued pharmacovigilance efforts to monitor this risk. This analysis will assess the use of HLA-B*5701 testing in Clinical Trials along with the Clinical Trial reporting rates of suspected hypersensitivity reaction due to abacavir in the post-testing era.

7. RESEARCH QUESTION AND OBJECTIVE(S)

1. To describe the baseline demographic and clinical characteristics of HIV positive patients screened HLA-B*5701 negative prior to commencing an abacavir-based antiretroviral therapy (ART) regimen in randomised clinical trials (RCTs).
2. To estimate the incidence rate of clinically suspected abacavir hypersensitivity reaction cases (both Investigator diagnosed and MAH adjudicated), reported in HLA-B*5701 negative subjects treated with ABC-containing ART regimens.

8. RESEARCH METHODS

8.1. Study Design

The current analysis will include data that were collected as part of GSK/VH-sponsored clinical trials in HLA-B*5701 negative, HIV infected adult treatment populations, from Phase IIb–IV of drug development for the ABC/3TC FDC, DTG, ABC/DTG/3TC or cabotegravir, conducted since January 2007. Subjects were either randomized to abacavir (ABC) vs. other antiretrovirals (ARV) as investigational medicinal product (IMP), or ABC was given as Investigators choice background medication, per individual study protocol/design. ARVs taken by subjects prior to entering a GSK/VH-sponsored study will be ignored in this meta-analysis.

Data for 3063 HLA-B*5701 negative, HIV-infected adult subjects from the 12 post-2006 GSK/VH-sponsored clinical trials will be investigated, with the aim of calculating a reporting rate for clinical suspected abacavir hypersensitivity reaction in such a treatment population. In addition, these analyses will be repeated in a sub-population of seven of these RCTs, during which 1,494 such subjects were exposed to either TRIUMEQ, or its equivalent component actives (given as the single active preparation of dolutegravir [DTG; TIVICAY] in combination with the ABC/3TC fixed dose combination).

8.2. Study Population and Setting

Clinical trials conducted since the 2006 meta-analysis with at least 20 weeks of ABC exposure in HLA-B*5701 negative, HIV-infected adult subjects will be included in this analysis. Only studies that were completed or for which the primary objective was completed, will be included. This analysis will be based on all treated population defined by subjects who received at least one dose of an ABC- containing product (i.e., ABC/3TC or ABC/DTG/3TC) as either randomized IMP or background medication (i.e., randomization was not based on ABC). Table 1 briefly describes the 12 studies that will be included in this analysis.

Table 1 Overview of post-2006 GSK/VH-sponsored clinical trials included in the meta-analysis.

Study name	Study identifier	Study duration included	Primary objective Abbreviations defined in Section 1	ABC exposed
ARIA[1,2]	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[3]
ARIES[4,5]	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.	515
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
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
FLAMINGO[2]	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
LATTE[4,6]	LAI116482	96	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

Study name	Study identifier	Study duration included	Primary objective Abbreviations defined in Section 1	ABC exposed
LATTE-2[1,4,7]	200056	32	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	309
SINGLE[1,2]	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
SPRING-1[2]	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.	68[8]
SPRING-2[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.	333
STRIIVING[1,2,4,9]	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.	519
	ING116070[2]	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

1. Randomized with respect to ABC therapy (i.e. an experimental control for ABC).
2. Trial included in the sub-analysis of subjects who received TRIUMEQ (or the equivalent components given as the single active preparation of DTG [TIVICAY] in combination with the ABC/3TC fixed dose combination tablet)
3. One HLA-B*5701 positive patient included in total subject numbers, but is not counted in the number of events
4. Exposure calculation for each phase of the study
5. 515 subjects in induction phase (36 weeks), 419 in randomization phase (48 weeks), 369 in extension phase (60 weeks)
6. 94 subjects in induction phase (24 weeks), 62 in maintenance phase (72 weeks).
7. 309 subjects in induction phase (20 weeks), 54 in maintenance phase (32 weeks)
8. PPD in the DTG 25 mg treatment arm was switched from TDF/FTC to ABC/3TC at Day 22 due to renal impairment
9. 275 subjects in early switch (48 weeks), 244 in late switch (24 weeks).

8.3. Variables

8.3.1. Exposure definitions

Extent of exposure in mean days will be collected from published trial results exposure summary tables. For trials where dose-modifications or switch were allowed for different study phases (including extension phases) – the exposure will be calculated according to the number of subjects and mean days of exposure in each phase.

8.3.2. Outcome definitions

In all of the 12 GSK/VH-sponsored clinical trials, HSRs were captured through adverse event (AE) and serious AE (SAE) reporting post baseline at scheduled study visits.

A definition for clinically suspected abacavir hypersensitivity reaction, similar to the MAH- case definition included in Appendix 1, was provided in the study protocols for all 12 GSK/VH-sponsored clinical trials. Investigators were instructed to record any cases meeting this protocol definition as an abacavir hypersensitivity reaction in the study case report form (which codes to the Medical Dictionary for Regulatory Activities [MedDRA] AE preferred term [PT] of “drug hypersensitivity”).

In order to meet post-marketing commitments with FDA for increased monitoring of all suspected ABC HSR cases occurring during MAH Sponsored clinical trials, GSK and then VH employed a Company and product specific safety criterion, which required Investigators to report all cases of clinically suspected ABC HSR cases as serious adverse events (SAEs), regardless of whether or not any of the associated signs and symptoms met the standard ICH-E2A definitions for seriousness [ICH E2A, 1994]. This requirement was put in place with the FDA following the approval of the original NDA for ZIAGEN, until circa 2012 when FDA considered this post-marketing commitment to be fulfilled. As such, cases of clinically suspected ABC HSR developed during more recent MAH Sponsored clinical trials 200056, 201147 ING117172 and LAI116482 (see Table 1), should only have been reported as serious by Investigators if the case met the standard ICH-E2A definitions for seriousness. In addition to completing SAE CRF pages, for all studies included in this analysis, Investigators were also required per-protocol to complete a separate ABC HSR CRF module, a specialised data collection tool that allows the collection of relevant standardised follow up details for the event as part of the reporting process, and hence thorough case assessment.

To identify cases for this analysis from the Clinical Study Reports described in Table 1, relevant statistical analysis system (SAS) SAE and AE outputs will be reviewed for MedDRA AE PTs considered indicative of hypersensitivity reactions; these include the following MedDRA AE PTs only, and no derivatives:

- hypersensitivity
- drug hypersensitivity, and
- anaphylactic reaction

Additionally, SAS outputs relating to the ABC HSR CRF Module will also be reviewed for the individual studies included in Table 1.

Investigator diagnosed clinically suspected abacavir hypersensitivity reaction cases

All cases identified through these means will be included in the analysis of Investigator diagnosed cases, UNLESS any of the following are clearly recorded for the above MedDRA AE PTs:

1. A negative rechallenge with abacavir (i.e., reintroduction of abacavir did not result in a rechallenge reaction);
2. Event resolution with continued abacavir treatment; or
3. An Investigator attributability statement that rules out causal associated with abacavir

Clinically suspected, MAH adjudicated abacavir hypersensitivity reaction cases

All cases identified from the review of the above detailed SAS outputs will also be adjudicated against the MAH Case Definition for ABC HSR (see Appendix 1), by a Safety Evaluation and Risk Management Product Specialist with 12 years experience of assessing both clinical trials and post-marketing cases for the ABC- containing products against this MAH definition. As part of this adjudication a small number of cases, originally assessed as clinically suspected ABC HSRs by reporting Investigators, may not be considered to meet the MAH Case Definition for ABC HSR by the Sponsor and therefore will be excluded from this analysis. Equally, a small number of cases, which were not originally considered indicative of clinically suspected ABC HSRs by reporting Investigators, may subsequently be considered to meet the MAH Case Definition for ABC HSR by the Sponsor and therefore included in this analysis.

Clinical Characteristics

The clinical characteristics for any data set of identified clinically suspected abacavir hypersensitivity reaction cases (e.g., in terms of symptomatology or median TTO), will not be formally analysed. However, a brief description of their presentation including TTO will be provided in the study report from review of the identified cases.

8.3.3. Confounders and effect modifiers

Confounding may occur with the use of other ART that causes similar symptoms (e.g. nevirapine and rash), concurrent conditions, other illnesses (e.g. influenza season) and environmental allergens (e.g., hay fever or food allergies), HIV disease characteristics and previous ART-experience at baseline. There will be no statistical analysis exploring the impact of confounder effects.

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 in patients screened negative for the HLA-B*5701 allele prior to commencing ABC therapy.

8.5. Study size

12 GSK/VH-sponsored clinical trials since January 2007, will contribute to the analysis with 3063 subjects who were exposed to regimens that included ABC, which will provide a cumulative summary of the clinical trial evidence on the reporting rate of HSR in HIV infected Adults pre-screened and found to be negative for HLA-B*5701.

8.6. Data management

8.6.1. Timings of Assessment during follow-up

The timing of follow-up in the original clinical trials varies from 20 weeks up to 144 weeks post-treatment initiation.

Data analysis

Descriptive statistics will be used to summarize baseline demographics and clinical characteristics of HIV+ patients exposed to an abacavir-containing regimen. Incidence rates of suspected hypersensitivity reaction to abacavir-containing regimens will be estimated. The exposure to an abacavir-containing regimen will be reported.

8.6.2. Essential analysis

Incidence rates with percentages will be based on the frequency of: Investigator diagnosed; and MAH- adjudicated, cases of clinically suspected abacavir hypersensitivity reactions occuring during the conduct of clinical trials. 95% CIs will be based on exact binomial 2-sided confidence intervals (CIs). Incidence rate for clinical suspected abacavir hypersensitivity reaction will be repeated in a sub-population of subjects who received TRIUMEQ (or the equivalent components given as the single active preparation of dolutegravir [TIVICAY] in combination with the ABC/3TC FDC Tablet).

8.6.3. General considerations for data analyses

None of the patients had multiple events, but it is possible that patients who had clinically suspected HSR event were excluded from the remainder of the study, or were lost to follow-up. 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 HSR.

8.7. Quality control and Quality Assurance

Quality control and quality assurance processes will be 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-GSK/VH-sponsored clinical trials that were not included in this analysis.

Data is collected from randomized clinical trial patients and was intended for research purposes, hence might not represent the real world patient populations or the utilisation of abacavir.

Conversely, because of the careful monitoring for ABC HSR in randomised clinical trials, the quality of information on any reported cases would be better than information received from other sources (e.g., post-marketing/spontaneous reporting and epidemiological cohorts).

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 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.

12. REFERENCES

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Appendix 1 MAH Case Definition for ABC HSR

The HSR case definition shown below is consistent with the description of HSR in the Company Core Safety Information (CSI) and worldwide product labels for ZIAGEN, TRIZIVIR, KIVEXA [EPZICOM] and TRIUMEQ, including the European Union Summary of Product Characteristics (SmPC) and the United States Prescribing Information (PI). The definition was developed based on minimum criteria required to make a diagnosis of HSR as described in the CSI. Cumulative analyses of adverse event reports from clinical trials and post-marketing experience with abacavir have shown that the case definition is a conservative way to identify HSR cases.

HSR Case Definition

A case of abacavir HSR is one in which conditions in A or B are fulfilled and where the exclusion criteria do not apply.

A. Hypersensitivity / anaphylactic reaction / allergic reaction / drug allergy to abacavir is reported.

OR

B. Two or more events are reported from two or more of the following groups of signs/symptoms:
    - rash
    - fever
    - gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain)
    - constitutional symptoms (lethargy, fatigue, malaise, myalgia, arthralgia, general ill feeling)
    - respiratory symptoms (dyspnoea, sore throat, cough, chest X-ray changes, predominantly infiltrates, which can be localised).

Exclusion Criteria

- Other causes of the HSR-like events appear significantly more likely (this assessment is carried out by a company physician)
- Cases where there is a negative re-challenge with abacavir
- Cases where symptoms resolved with continued abacavir treatment
- Cases of possible hypersensitivity to abacavir which do not fulfil the criteria in B