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- *Aggregate data will be included; with any direct reference to individual patients excluded*

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TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Final Study Report

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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SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of study [207831]

PPD

15 DEC 2017.

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1. LIST OF ABBREVIATIONS

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 leucocyte antigen
HSR	Hypersensitivity reaction
IMP	Investigational medicinal product
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PI	Prescribing Information
PT	Preferred Term
QD	Once daily
RAL	Raltegravir
RCT	Randomised 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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Statistical analysis system

2. RESPONSIBLE PARTIES

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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.

Keywords: Safety, Abacavir, hypersensitivity reaction, HLA-B*5701 screening.

Rationale and background: The last GSK clinical trial meta-analysis on abacavir (ABC) hypersensitivity reaction (HSR) was undertaken in 2006, and involved studies conducted before the era of routine screening for HLA-B*5701 prior to commencing ABC therapy. Since then, several marketing authorisation holder (MAH) sponsored studies have been conducted that have investigated ABC-containing study medications in HIV-infected adult treatment populations, that were screened for the HLA-B*5701 allele. Depending on individual study protocol/design, subjects 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 subject's 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 was hypothesised that the more recent MAH-sponsored trials that investigated ABC-containing study medications in HLA-B*5701-negative, HIV-infected

adult treatment populations, would more accurately reflect experience and reporting rates in current clinical practice, because subject HLA-B*5701 status was not blinded.

Research questions and objectives: The primary objective was to calculate the incidence rate of clinically suspected ABC HSR cases reported in HLA-B*5701-negative subjects treated with ABC-containing ART regimens.

Study design: This meta-analysis included 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 (CAB), conducted since January 2007. HLA-B*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.

Setting: Meta-analysis

Subjects and study size, including dropouts: 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 (the 'All ABC-Exposed Subjects' population). This overall population consisted of two sub-populations:

1. 1,494 subjects exposed to either TRIUMEQ or its equivalent active components (given as the single active preparation of dolutegravir [DTG; TIVICAY] in combination with the ABC/3TC fixed-dose combination (FDC) tablet) in seven of these RCTs for a minimum of 24 weeks (the 'ABC/DTG/3TC sub-population'); and
2. 1,569 subjects exposed to the ABC/3TC FDC tablet in combination with a non-DTG anchor drug, which were atazanavir (ATV)+ritonavir (RTV), CAB, darunavir (DRV)+RTV, efavirenz (EFV) or raltegravir (RAL), in eight of these RCTs for a minimum of 20 weeks (the 'ABC/3TC sub-population')

Data analysis: Incidence rates for investigator diagnosed, MAH-adjudicated and all possible cases of clinically suspected ABC HSR were calculated for the 'all ABC-Exposed Subjects' population. Exposure to an ABC-containing regimen was reported. 95% CIs were based on exact binomial 2-sided confidence intervals. These analyses were repeated in the two sub-populations of subjects (i.e., both the ABC/DTG/3TC sub-population and the ABC/3TC sub-population.

Variables and data sources: Investigator-diagnosed ABC HSR, MAH-adjudicated ABC HSR, all possible cases of ABC HSR, all ABC-Exposed Subjects, ABC/DTG/3TC sub-population (i.e., subjects exposed to TRIUMEQ or DTG+ABC/3TC), ABC/3TC sub-population (i.e. subjects exposed to the ABC/3TC FDC tablet in combination with a non-DTG anchor drug).

Results: In the All ABC-Exposed Subjects population, at Baseline, the median age was 39 years (range 18-80) and participants were predominately: white (69%); male (77%); recruited from the North America (61%); acquired HIV through homosexual contact (60%); and had HIV CDC class A disease (79%). The median HIV-1 RNA viral load

(VL) was 4.35 log_{10} copies/mL (1.59-6.93) and median CD4+ cell count was 363.0 cells/mm^3 (10.0-1831.0). The baseline demographic characteristics of the treatment sub-populations were generally similar, although the ABC/DTG/3TC sub-population had: more study participants who were female (30%), ART experienced (35%) and acquired HIV through heterosexual transmission (40%); lower median VL (4.02 log_{10} copies/mL) and higher median CD4 count (411 cells/mm^3), compared with the ABC/3TC sub-population (16%, 13%, 23%, 4.64 log_{10} copies/mL and 313 cells/mm^3 respectively).

The median exposure to ABC- containing study regimens was 342 days (1-1126) overall, and was similar for both the ABC/DTG/3TC sub-population and the ABC/3TC sub-population (340 and 347 days, respectively).

Suspected ABC HSR occurred at a lower frequency in HLA-B*5701- negative subjects treated with ABC in clinical trials, compared to equivalent historical analyses of MAH sponsored clinical trials in which participants were not screened for HLA-B*5701 before receiving ABC- containing regimens. All calculations performed for this clinical trial meta-analysis resulted in incidence rates of ≤1% for suspected ABC HSR (range 0.3%-1.3%), and rates were lower for subjects receiving ABC/DTG/3TC (range 0.3%-0.4%) than for those exposed to ABC/3TC (range 0.8%-1.3%) with an alternative anchor drug to DTG. Incidence rates for Investigator- diagnosed ABC HSR were similar to those for MAH- Adjudicated Cases (Section 15.1), in each of the three ABC-exposed populations analysed (Table 4) (ranges 0.3%-0.8% and 0.3%-1.0%, respectively).

Conclusion: Clinically suspected ABC HSR occurs at a rate of ≤1% in HLA-B*5701 negative clinical trial subjects. However, just as in PREDICT-1, whilst excluding HLA-B*5701 positive subjects from receiving ABC-containing study regimens reduced the risk of developing ABC HSR, cases of clinically suspected ABC HSR were still reported from HLA-B*5701- negative subjects in the current meta-analysis. This emphasises the importance of adhering to the product labelling when managing patients with suspected ABC HSR, as follows: 1) where HLA-B*5701 testing is standard of care, the results must be available and confirmed negative before starting ABC treatment; 2) for any patient receiving treatment with ABC, the clinical diagnosis of suspected HSR must remain the basis of clinical decision making; and 3) regardless of HLA-B*5701 status, it is important to permanently discontinue ABC and not re-challenge with ABC if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

4. AMENDMENTS AND UPDATES

The protocol indicated that analyses would only be performed on the 'all ABC- Exposed Subjects' population and the 'ABC/DTG/3TC sub-population' (i.e., subjects exposed to either TRIUMEQ or DTG + the ABC/3TC FDC). However, upon the analysis of data, the MAH considered it useful to present data for the 'ABC/3TC sub-population' as well (i.e. subjects exposed to the ABC/3TC FDC tablet in combination with a non-DTG anchor drug). The protocol was not updated to reflect this.

The planned date for the final report of study results was initially 30 September 2017; however, the MAH subsequently amended this to 31 December 2017 on both the

European Union (EU) Post Authorisation Study (PAS) Registry and the ViiV Healthcare Clinical Studies Register.

5. MILESTONES

Start of data analysis:	10-April-2017
Draft report	03-October-2017
Final report of study results	20-December-2017

6. RATIONALE AND BACKGROUND

6.1. Background

Abacavir sulfate (ABC) 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 ABC was based on studies that showed improved CD4 profile and decreased plasma HIV RNA levels in patients who took ABC in combination with other nucleoside analogues versus those who took antiretroviral regimens without ABC [Saag, 1998; Staszewski, 1998]. ABC 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®, ABC 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, ABC is widely used to achieve viral suppression and immunologic improvement in patients with HIV infection. Factors that make ABC 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].

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 ABC is a well-characterised 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, diarrhoea or abdominal pain), lethargy and malaise, musculoskeletal symptoms (e.g., arthralgia and myalgia) and respiratory symptoms (such as dyspnoea, cough and pharyngitis) (see Section 15.1).

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 US Package Insert, 2015; Symonds, 2002].

Other symptoms of hypersensitivity include myolysis, oedema, 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 ABC 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 ABC is discontinued. However, more severe and rarely fatal or life-threatening reactions can occur, and are generally the result of either prolonged ABC treatment in the face of evolving symptoms of HSR, or inappropriate re-challenge. Following a diagnosis of hypersensitivity, patients must not take ABC again. Restarting the drug following an HSR has resulted in cases of life-threatening hypotension and fatal rechallenge reactions. Additionally, there have been reports of individuals who developed re-challenge hypersensitivity to ABC after having been asymptomatic during initial use of the drug [Frissen, 2001; El-Sahly, 2004]. Therefore, it is recommended that all patients receiving ABC be monitored closely for signs of a HSR, 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 subjects 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 subjects receiving ABC, familial disposition, the low incidence of the reaction in subjects of African American origin and involvement of the major histocompatibility complex alleles in other similar multi-organ HSR [Martin, 2004; Mallal, 2002]. Later studies found an association between ABC hypersensitivity and specific human leukocyte antigen (HLA) alleles [Mallal, 2008].

Following the identification of a genetic link to ABC HSR, 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 HSR with a negative predictive value of 100% and a positive predictive value of 47.9% [Mallal, 2008]. Guidelines subsequently recommended HLA testing for all subjects when considering an ABC-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 ABC-containing study medication (i.e., HLA-B*5701-positive subjects were excluded from either participating or receiving an ABC-containing product in such clinical trials, depending on individual protocol designs).

Until recently, the exact mechanism of the ABC HSR 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 HSR [Hetherington, 2001]. However, recent research supports an '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 ABC with HLA-B*5701 [Adam, 2012; Norcross, 2012; Ostrov, 2012; Illing, 2013].

Incidence rates for HSR from clinical trials with ABC, which were conducted before the era of routine screening for HLA-B*5701 pre-ABC therapy, have ranged from 4 to 8%. A retrospective review of data from 200,000 subjects who received ABC 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 subjects who received ABC 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 of exposure through to January 2002, approximately 5% (403) were diagnosed with a suspected HSR. In a sub- analysis of nine such GSK Sponsored clinical trials conducted between November 1999 and January 2002, which employed the ABC HSR case report form (CRF) and involved 2,670 subjects exposed to ABC, the incidence rate for subjects diagnosed with a suspected HSR 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 subjects with at least 12 weeks of exposure to ABC pre-routine HLA-B*5701 screening, 590 (5%) of which developed a clinically suspected ABC HSR. At this point the sub-group of clinical trials utilising the ABC HSR CRF had expanded to 14 studies, involving 5,521 subjects 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 incidence rates for ABC hypersensitivity of 0 to <1% [Rauch, 2006; Reeves, 2006; Zucman, 2006].

6.2. Rationale

The last GSK clinical trial meta-analysis on ABC hypersensitivity in 2006 involved studies conducted before the era of routine screening for HLA-B*5701 pre-ABC therapy. Since then, several marketing authorisation holder (MAH)-sponsored studies have been conducted that have investigated ABC-containing study medications in HIV- infected adult treatment populations, that were screened for the HLA-B*5701 allele. Subjects 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 subject's 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 was hypothesised that the more recent MAH-sponsored trials that investigated ABC-containing study medications in HLA-B*5701-negative, HIV- infected adult treatment populations, would more accurately reflect experience and reporting rates in clinical practice, because subject HLA-B*5701 status was not blinded.

This meta-analysis was part of VH's continued pharmacovigilance efforts to monitor this risk. This analysis assessed the use of HLA-B*5701 testing in Clinical Trials along with the Clinical Trial incidence rates of suspected HSR due to ABC in the post-testing era.

7. RESEARCH QUESTION AND OBJECTIVES

1. To describe the baseline demographic and clinical characteristics of HIV-positive subjects screened HLA-B*5701 negative prior to commencing an ABC-based antiretroviral therapy (ART) regimen in randomised clinical trials (RCTs).
2. To calculate the incidence rate of clinically suspected ABC HSR 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 included 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 CAB, conducted since January 2007. Subjects were either randomised to 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 were ignored in this meta-analysis.

Data for 3063 HLA-B*5701-negative, HIV-infected adult subjects from the 12 GSK/VH-sponsored clinical trials conducted since 2007 were investigated, with the aim of calculating an incidence rate for clinical suspected ABC HSR in such a treatment population (the 'All ABC- Exposed Subjects' population). In addition, these analyses were repeated in two sub-populations:

1. 1,494 subjects exposed to either TRIUMEQ or its equivalent active components (given as the single active preparation of DTG [TIVICAY] in combination with the ABC/3TC FDC tablet) in seven of these RCTs for a minimum of 24 weeks (the 'ABC/DTG/3TC sub-population'); and
2. 1,569 subjects exposed to the ABC/3TC FDC tablet in combination with a non-DTG anchor drug, which were atazanavir (ATV)+ritonavir (RTV), CAB, darunavir

(DRV)+RTV, efavirenz (EFV) or raltegravir (RAL), in eight of these RCTs for a minimum of 20 weeks (the 'ABC/3TC sub-population').

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 were included in this analysis. Only studies that were completed or for which the primary objective was completed, were included in the analysis. This analysis was based on an 'All ABC-Exposed Subjects' 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 randomised IMP or background medication (i.e., randomisation was not based on ABC). Table 1 briefly describes the 12 studies that were included in this analysis.

Table 1 Overview of GSK/VH-sponsored Clinical Trials Included in the Meta-analysis

Study name	Study identifier	Study duration (Weeks)	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
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

Study name	Study identifier	Study duration (Weeks)	Primary objective Abbreviations defined in Section 1	ABC-exposed
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. Randomised 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 subject 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. Subject PP 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)

8.2.1. Exposure definitions

Extent of exposure in mean days were 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 was calculated according to the number of subjects and mean days of exposure in each phase. These were presented for the All ABC- Exposed Subjects population and the two sub-populations.

8.2.2. Outcome definitions

For all 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 ABC HSR, similar to the MAH- case definition included in Section 15.1, 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 ABC HSR 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 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, 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 allowed 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, relevant statistical analysis system (SAS) SAE and non- serious AE outputs were reviewed for MedDRA AE PTs considered indicative of HSR; these included 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 were reviewed for the individual studies included in Table 1.

Investigator-diagnosed clinically suspected ABC HSR cases

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

1. A negative rechallenge with ABC (i.e., reintroduction of ABC did not result in a re-challenge reaction);
2. Event resolution with continued ABC treatment; or
3. An Investigator attributability statement that ruled out causal association with ABC

Clinically suspected, MAH-adjudicated ABC HSR cases

All cases identified from the review of the above detailed SAS outputs were also adjudicated against the MAH Case Definition for ABC HSR (see Section 15.1), by a Safety Evaluation and Risk Management Product Specialist with 12 years' experience in assessing both clinical trials and post-marketing cases for the ABC-containing products against this MAH definition. The protocol for this meta-analysis specified that, 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 would be excluded. Equally, a small number of cases, which were not originally considered as 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 be included in this dataset.

Clinical Characteristics

The clinical characteristics for any data set of identified clinically suspected ABC HSR cases (e.g., in terms of symptomatology or median TTO), were not be formally analysed. However, the MAH-Adjudicated ABC HSR Cases were reviewed to provide a brief description of their presentation, including TTO, in this study report.

8.2.3. Confounders and effect modifiers

Potential confounding was considered likely due to the use of other ART that causes similar symptoms (e.g. EFV 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 was no statistical analysis exploring the impact of confounder effects.

8.3. Data Sources

The studies that were 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 subjects screened negative for the HLA-B*5701 allele prior to commencing ABC therapy.

8.4. Study Size

Twelve GSK/VH-sponsored clinical trials since January 2007 contributed to the analysis, with 3063 subjects who were exposed to regimens that included ABC. This provided a cumulative summary of the clinical trial evidence on the incidence rate of HSR in HIV-infected adults pre-screened and found to be negative for HLA-B*5701.

8.5. Data Management

8.5.1. Essential analysis

Incidence rates with percentages were based on the frequency of investigator-diagnosed, MAH-adjudicated and all possible cases of clinically suspected ABC hypersensitivity reactions occurring during the conduct of clinical trials. 95% CIs were based on exact binomial 2-sided confidence intervals (CIs). Incidence rate for clinical suspected ABC HSR was repeated in both the ABC/DTG/3TC sub-population and the ABC/DTG/3TC sub-population.

8.5.2. General considerations for data analyses

None of the subjects had multiple ABC HSR events, because subjects who had clinically suspected HSR events were withdrawn from study, per protocol. The clinical trials from which the data were derived were designed to investigate the safety and efficacy of various antiretroviral agents, including ABC, and the primary endpoint was not HSR.

Although more recent MAH-Sponsored clinical trials 200056, 201147, ING117172 and LAI116482 did not employ the Company and product-specific ABC HSR seriousness criterion (see Section 8.2.2), any clinically suspected cases which were not considered to meet the standard ICH-E2A definitions for seriousness [ICH E2A, 1994] were identified from reviewing the non-serious AE listings.

8.6. Quality Control and Quality Assurance

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

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

8.7. 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 were collected from randomised clinical trial subjects and were intended for research purposes. Therefore, they might not represent the real-world patient populations or the utilisation of ABC.

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

8.8. 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 used previously collected, anonymised clinical trial data.

9.2. Subject Confidentiality

This meta-analysis used previously collected, anonymised clinical trial data. No identifying information was provided.

10. RESULTS

10.1. Participants

Of the 3063 All ABC-Exposed Subjects, the ABC/DTG/3TC sub-population comprised 1494 subjects and the ABC/3TC sub-population comprised 1569 subjects (Table 2).

10.2. Descriptive Data including Baseline Characteristics

In the All ABC- Exposed Subject population, at Baseline, the median age was 39 years and participants were predominately: white; male; recruited from North America; acquired HIV through homosexual contact; and had HIV CDC class A disease. The median baseline HIV-1 RNA was 4.35 $\log_{10}$ copies/mL and CD4+ cell count was 363.0 cells/mm^3 (Table 2).

The baseline demographic characteristics of the treatment sub-populations were generally similar, although the ABC/DTG/3TC sub-population had: more study participants who were female, ART experienced and acquired HIV through heterosexual transmission; lower median VL and higher median CD4+ cell count, compared with the ABC/3TC sub-population.

The median exposure to ABC- containing study regimens was 342.00 days overall. The median exposure was similar in the ABC/DTG/3TC sub-population (340.00 days) and the ABC/3TC sub-population (347.00 days) (Table 3).

Table 2 Baseline Demographics and Clinical Characteristics

Characteristic	All ABC- Exposed Subjects[1] (N=3063)	ABC/DTG/3TC sub-population[2] (N=1494)	ABC/3TC sub-population[3] (N=1569)
Age in Years, median (min, max)	38.0 (18.0, 80.0)	39.0 (18.0, 80.0)	37.0 (18.0, 75.0)
Gender, n (%)			
Female	699 (22.8)	454 (30.4)	245 (15.6)
Male	2364 (77.2)	1040 (69.6)	1324 (84.4)
Race, n (%)			
White	2105 (68.7)	987 (66.1)	1118 (71.3)
Non-White	956 (31.2)	505 (33.8)	451 (28.7)
Missing	2 (0.1)	2 (0.1)	0
Geographic Region, n (%)			
Europe[4]	911 (29.7)	416 (27.8)	495 (31.5)
North America[5]	1881 (61.4)	881 (59.0)	1000 (63.7)
South America[6]	38 (1.2)	34 (2.3)	4 (0.3)
Rest of World[7]	233 (7.6)	163 (10.9)	70 (4.5)
ART Status, n (%)			
Naïve	2345 (76.6)	975 (65.3)	1370 (87)
Experienced	718 (23.4)	519 (34.7)	199 (13)
Baseline Values, median (range)			
HIV-1 RNA PCR (log_{10} copies/mL)	4.36 (1.59, 6.93)	4.02 (1.59, 6.66)	4.64 (1.59, 6.93)
CD4+ cell count (cells/mm^3)	363.0 (10.0, 1831.0)	411.0 (19.0, 1831.0)	313.0 (10.0, 1196.0)
CDC Classification of HIV, n (%)			
A: Asymptomatic,	2408 (78.6)	1132 (79.2)	1225 (78.1)
Lymphadenopathy or Acute HIV	415 (13.6)	190 (12.7)	225 (14.3)
B: Symptomatic, Not AIDS	240 (7.8)	121 (8.1)	119 (7.6)
C: AIDS			
HIV Risk Factor			
Hemophilia-associated injections	1 (0)	1 (0.1)	0
Heterosexual contact	960 (31.4)	600 (42)	360 (22.9)
Homosexual contact	1828 (59.7)	788 (52.7)	1040 (66.3)
Injectable drug use	71 (2.3)	40 (2.7)	31 (2.0)
Occupational exposure	7 (0.2)	2 (0.1)	5 (0.3)
Transfusion	6 (0.2)	3 (0.2)	3 (0.2)
Other	89 (2.9)	6 (0.4)	83 (5.3)
Missing	101 (3.3)	54 (3.6)	47 (3.0)

Data Source: Section 15.5

1. Subjects exposed to ABC/3TC or ABC/DTG/3TC
2. Subjects exposed to ABC/DTG/3TC or DTG+ABC/3TC
3. Subjects exposed to ABC/3TC in combination with a non-DTG anchor drug, which were ATV+RTV, CAB, DRV+RTV, EFV or RAL
4. Europe designated countries: Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Latvia, Netherlands, Portugal, Romania, Spain, Switzerland, United Kingdom.
5. North America designated countries: Canada, United States of America
6. South America designated countries: Argentina, Mexico, Puerto Rico
7. Rest of World designated countries: Australia, Russia, South Africa, Thailand

Table 3 Subject Exposure to ABC- Containing Study Regimens

	All ABC- Exposed Subjects[1] (N=3063)	ABC/DTG/3TC sub-population[2] (N=1494)	ABC/3TC sub-population[3] (N=1569)
Exposure in Days, median (min, max)	342.00 (1.00, 1126.00)	340.00 (1.00, 1124.00)	347.00 (1.00, 1126.00)

Data Source: Section 15.5

1. Subjects exposed to ABC/3TC or ABC/DTG/3TC
2. Subjects exposed to ABC/DTG/3TC or DTG+ABC/3TC
3. Subjects exposed to ABC/3TC in combination with a non-DTG anchor drug, which were ATV+RTV, CAB, DRV+RTV, EFV or RAL

10.3. Results of Essential Analyses

Case identification and classification results are detailed in Section 15.2.

Incidence rates of possible ABC HSR in HLA-B*5701-negative subjects were <1% for the All ABC-Exposed Subject population (range 0.6%-0.9%) and the ABC/DTG/3TC sub-population (range 0.3%-0.4%), in each of the three case analyses (Table 4). Incidence rates were lower for the ABC/DTG/3TC sub-population than for the ABC/3TC sub-population (range 0.8%-1.3%), in each of the three case analyses (Table 4). None of the suspected ABC HSR cases resulted in a fatal outcome.

The MAH case adjudication is also outlined in Section 15.2. Incidence rates for Investigator-diagnosed ABC HSR were similar to those for MAH-Adjudicated Cases (Section 15.1), in each of the three ABC-exposed populations analysed (Table 4) (range 0.3%-0.8% and 0.3%-1.0%, respectively).

Table 4 Clinical Trial Incidence Rates of Possible ABC HSR Amongst HLA-B*5701-negative Subjects Treated with ABC/3TC or ABC/DTG/3TC

Population/Case Analysis	All ABC- Exposed Subjects[1] N=3063	ABC/DTG/3TC sub-population[2] N=1494	ABC/3TC sub-population[3] N=1569
Investigator-Diagnosed ABC HSR	0.6% (n=17; 95% CI: 0.32-0.89)	0.3% (n=4; 95% CI: 0.07-0.68)	0.8% (n=13; 95% CI: 0.44-1.41)
MAH-Adjudicated Cases	0.7% (n=21; 95% CI: 0.42-1.05)	0.3% (n=5; 95% CI: 0.11-0.78)	1.0% (n=16; 95% CI: 0.58-1.65)
All Possible Cases of ABC HSR	0.9% (n=27; 95% CI: 0.58-1.28)	0.4% (n=6; 95% CI: 0.15-0.87)	1.3% (n=21; 95% CI: 0.83-2.04)

Data Source: Section 15.3 and Section 15.4

1. Subjects exposed to ABC/3TC+anchor drug or ABC/DTG/3TC
2. Subjects exposed to ABC/DTG/3TC or DTG+ABC/3TC
3. Subjects exposed to ABC/3TC in combination with a non-DTG anchor drug, which were ATV+RTV, CAB, DRV+RTV, EFV or RAL

Eleven of the 17 Investigator-Diagnosed ABC HSR cases were included in the 21 MAH Adjudicated Cases; however, 6/17 did not meet Part B of the MAH ABC HSR Case Definition (Section 15.1), because reported symptomatology indicated single body system involvement only (i.e., rash with or without other skin and subcutaneous disorders, Section 15.2 and Section 15.3).

Ten additional MAH-Adjudicated Cases were identified, which were not reported as Investigator-diagnosed ABC HSR: all 10 cases met the MAH Definition (5 met Part A only and 5 met both Part A and Part B; Section 15.1) and resolved following the permanent discontinuation of ABC/3TC (along with the anchor drug in 9/10 cases).

A total of 16 cases did not overlap between the Investigator-Diagnosed ABC HSR and MAH-Adjudicated Case datasets, the majority of which involved ABC/3TC in combination with non-VH anchor drugs (n=13).

The 21 MAH-Adjudicated cases were characterised as follows. The majority occurred within 6 weeks of initiating ABC treatment, had a median TTO of 10 Days (range 2-89), were mainly of Grade 2 intensity (16/21; Grade 3: n=3; Grade 4: n=2) and resolved within a median of 20 Days (range 4-172; upper limit due to normalisation of liver chemistries in one case). Three resulted in hospitalisation, and no cases were life-threatening or disabling. Where symptom details were reported (16/21), the majority of cases (11/16) involved key symptoms from at least 3 groups (Section 15.1, Part B; by definition, all cases had symptoms from at least 2 groups); all 16 cases involved either rash (n=14) or fever (n=12), with 10/16 involving both. GI complaints and lethargy/malaise were also frequently reported (10/16 and 11/16, respectively), with musculoskeletal and respiratory symptoms reported less so (4/16 and 6/16, respectively). The majority reported classic reactions in line with the MAH Case Definition. However, 4 presented with symptoms suggesting more severe reactions, including liver dysfunction in 2 cases involving DTG from SPRING-2 that resulted in hospitalisation (previously well described [Curtis, 2016; Raffi, 2013]) and one each with erythema multiforme (ARIES) or hypotension (ASSERT). (Data Source: Section 15.4)

As noted in Table 1 and Section 15.2, ING117172 (ARIA) Subject PPD was excluded from all analyses, because she tested HLA-B*5701 positive at screening and therefore, per protocol, should have been excluded from participating in the original clinical trial. This HLA-B*5701 positive result was erroneously missed by the site, and the subject was mistakenly randomized; an action that was considered a protocol deviation in the study report for ING117172. This HLA-B*5701 positive subject developed ‘flu-like illness’ and an oral lesion with a TTO of 8 Days, which resulted in the investigator diagnosing a Grade 1, non-serious ABC HSR and withdrawing ABC/DTG/3TC treatment.

11. DISCUSSION

11.1. Results

This analysis evaluated the effectiveness of HLA-B*5701 screening as a risk mitigation measure for ABC HSR, by assessing incidence rates for suspected ABC HSR in the 10 years since adoption of this test by ARV treatment guidelines and clinical practice.

Baseline demographics and clinical characteristics for the All ABC-Exposed Subject population were typical of HIV infected adults recruited into phase IIIb/IV clinical trials for ARVs, conducted in North America, Europe and Australia, during the past decade. The baseline demographic and clinical characteristics of the treatment sub-populations were generally similar, although the ABC/DTG/3TC sub-population had: more study participants who were female, ART experienced and acquired HIV through heterosexual transmission; lower median VL and higher median CD4+ cell count, compared with the ABC/3TC sub-population. These observable differences were due to the populations for two specific TRIUMEQ studies: ARIA, which investigated an exclusively female subject population; and STRIIVING, which was a stable switch study in over 500 ART experienced subjects. These differences in demographics and clinical characteristics between the two sub-population of ABC- exposed subjects is not believed to have influenced ABC HSR incidence rates.

As would be expected from previous published research on this risk mitigation measure, suspected ABC HSR occurred at a lower frequency in HLA-B*5701-negative subjects treated with ABC in clinical trials. All calculations performed for this clinical trial meta-analysis resulted in incidence rates of ≤1% for suspected ABC HSR, and rates were lower for subjects receiving ABC/DTG/3TC than for those exposed to ABC/3TC with an alternative anchor drug to DTG. Equivalent, historical meta-analyses of MAH sponsored clinical trials that did not screen for HLA-B*5701 prior to commencing ABC- therapy, resulted in incidence rate of between 4% to 8% for clinically suspected ABC HSR [Hetherington, 2001; Hernandez, 2003; Cutrell, 2004].

In the current analysis, rates calculated for Investigator-Diagnosed ABC HSR and MAH-Adjudicated Cases were similar. However, a total of 16 cases were discordant between these datasets, 13 of which involved ABC/3TC in combination with non-DTG anchor drugs with adverse drug reaction (ADR) profiles significant for rash and/or HSR (i.e., ATV+RTV, DRV+RTV, EFV and RAL). Eight of these cases were from ASSERT, which involved EFV, and were the main contributor to differences in results: across each of the three separate case analyses; and between the two sub-populations of ABC-exposed subjects. ASSERT was also one of the first MAH-sponsored trials to employ HLA-B*5701 screening, and these eight discordant cases from this study may have indicated a lack of Investigator confidence in diagnosing/managing clinically suspected ABC HSR in HLA-B*5701 negative subjects, especially with the overlapping ADR profile from EFV, resulting in potential over reporting (discussed below).

Six Investigator-diagnosed cases across ASSERT, ARIES, FLAMINGO and ARIA that reported symptoms indicating only single body system involvement (i.e., rash with or without other skin disorders), were not considered to meet the MAH ABC HSR Case

Definition. The 10 additional MAH-Adjudicated Cases may not have been diagnosed as suspected ABC HSR by the reporting Investigators, because alternative causes may have appeared more likely (e.g., the anchor drug, as indicated by the verbatim event term of 'allergy to EFV' [or equivalent] in 6 cases from ASSERT). However, although the majority (9/10) specified a positive dechallenge to the anchor drug, a diagnosis of suspected ABC HSR could not be ruled out by the Company because all 10 involved a positive dechallenge to ABC.

The MAH ABC HSR Case Definition is a pragmatic and conservative definition used for the purposes of all MAH regulatory reporting activities for, and analyses of, suspected ABC HSR and is not meant to replace medical diagnoses. The Investigator diagnosis of suspected ABC HSR in the 6 cases of 'rash' only, and withdrawal of ABC treatment in all 16 discordant cases, may have been clinically appropriate at the time of patient presentation. This highlights the difficulty in differentiating causality for HSR between co-administered drugs with overlapping ADR profiles, and particularly in the presence of rash. As was also specifically demonstrated in the double-blinded SINGLE clinical trial (Table 1), where prior to investigator un-blinding for subject management, the rate of clinically suspected ABC HSR was greater for the blinded EFV/FTC/TDF treatment group (5/419, 1%) compared to the blinded DTG+ABC/3TC treatment group (2/414, <1%) [ViiV Healthcare Document No. 2014N198290_01, 2015].

Ultimately, however, per guidance in the product label and reproduced in study protocols, when a distinction cannot be made, ABC should always be discontinued, regardless of a subject's HLA-B*5701 status. None of the ABC HSR cases identified in this meta-analysis involved either an ABC rechallenge or a fatal outcome, which is also an indication of effective product labelling/protocol guidance on patient management for this risk.

Whilst the PREDICT-1 study represented pioneering research in both the field of pharmacogenetics and in reducing the risk from ABC HSR, Investigators were blinded to the subject's HLA-B*5701 status, which may have resulted in an over reporting of ABC HSR in this study (27/803, 3.4%) [Mallal, 2008]. The current meta-analysis could more accurately reflects experience and reporting rates in current clinical practice, because subject HLA-B*5701 status was not blinded in the individual clinical trials.

11.2. Limitations

Clinical trials are a valuable data source because Investigator training and controlled protocol conditions allow for more consistent clinical care and thorough classification, reporting and safety assessment of events. However, clinical trial data has limitations, because patients enrolled in clinical trials are screened to meet specific inclusion criteria and therefore might not accurately represent real-world populations.

The impact from potential confounders such as concomitant use of ART with overlapping ADR profiles, 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, was not explored as part of this analysis.

More recent MAH-Sponsored clinical trials 200056, 201147, ING117172 and LAI116482 did not employ the Company and product-specific ABC HSR seriousness criterion (see Section 8.2.2). However, clinically suspected cases which were not considered to meet the standard ICH-E2A definitions for seriousness [ICH E2A, 1994] were identified from reviewing the data from non- serious AE listings for these studies.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Clinically suspected ABC HSR occurs at a rate of ≤1% in HLA-B*5701- negative clinical trial subjects. However, just as in PREDICT-1, whilst excluding HLA-B*5701 positive subjects from receiving ABC-containing study regimens reduced the risk of developing ABC HSR, cases of clinically suspected ABC HSR were still reported from HLA-B*5701-negative subjects in the current meta-analysis. This emphasises the importance of adhering to the product labelling when managing patients with suspected ABC HSR, as follows: 1) where HLA-B*5701 testing is standard of care, the results must be available and confirmed negative before starting ABC treatment; 2) for any patient receiving treatment with ABC, the clinical diagnosis of suspected HSR must remain the basis of clinical decision making; and 3) regardless of HLA-B*5701 status, it is important to permanently discontinue ABC and not re-challenge with ABC if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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15. APPENDICES

15.1. 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 ABC have shown that the case definition is a conservative way to identify HSR cases.

HSR Case Definition

A case of ABC 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 ABC is reported.

OR

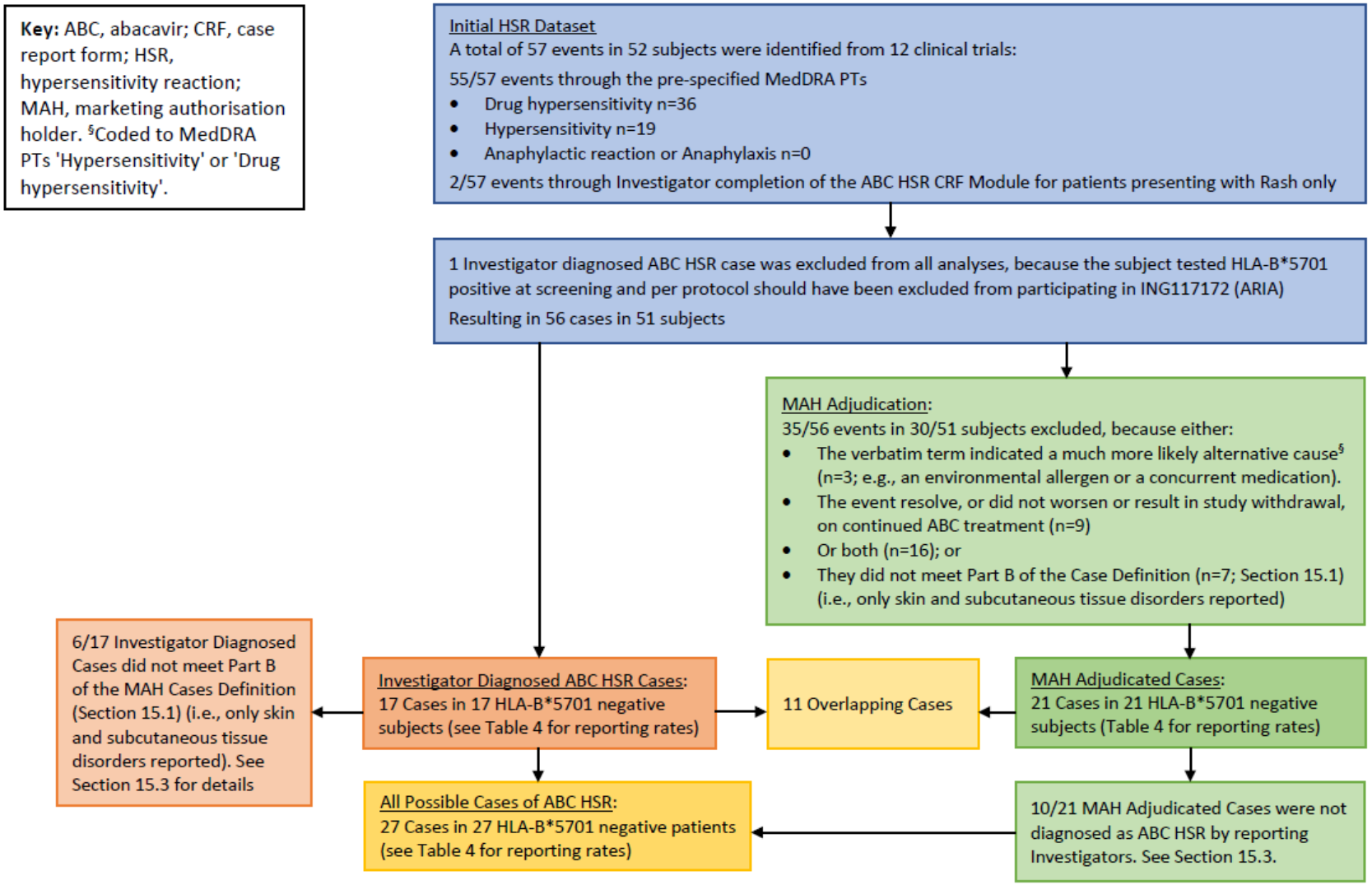
b. Two or more events are reported from two or more of the following groups of signs/symptoms:

- 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 rechallenge with ABC
- Cases where symptoms resolved with continued ABC treatment
- Cases of possible hypersensitivity to ABC in Part A, which do not fulfil the criteria in B

15.2. Appendix 2: Case Identification and Classification Results



15.3. Appendix 3: Breakdown of Investigator Diagnosed and MAH-Adjudicated Cases of Suspected ABC HSR

Study Details	ABC Study Regimen (Non- ABC Comparator Arm)	Investigator-Diagnosed Cases (n)	MAH-Adjudicated Cases (n)	MAH Adjudication Details
ING112276 (SPRING-1) ART Naïve Open Label Week 96	ABC/3TC+DTG[1,2] ABC/3TC+EFV[1,3]	0	0	N/A
ING113086 (SPRING-2) ART Naïve Open Label NRTI backbone Week 96	ABC/3TC+DTG[1,2] ABC/3TC+RAL[1, 3]	2	5	3 additional cases. 2 met Part A & B of the case definition: 1/2 with positive dechallenge to ABC & DTG, investigator implicated DTG only, however MAH could not rule out ABC causality; 1/2 with positive dechallenge to ABC & RAL, and was confounded by confirmed influenza infection and amoxicillin use. Remaining case was a non-serious AE, met Part A of the definition only and reported a positive de-challenge to ABC and a negative rechallenge to RAL.
ING114467 (SINGLE) ART Naïve Double Blind[5] Week 144	ABC/3TC+DTG[2,4] (EFV/TDF/FTC)	1	2	1 additional case. Met Part A & B of the case definition, with a positive de-challenge to ABC & DTG. Investigator implicated DTG only, however MAH could not rule out ABC causality.
ING114915 (FLAMINGO) ART Naïve Open Label Week 96	ABC/3TC+DTG[1,2] ABC/3TC+DRV+RTV[1, 3]	2	0	2 unconvincing cases. 1 met Part A of the case definition, the other was reported as Rash only (i.e, met neither Part A nor Part B) but an ABC HSR CRF Module was completed. Symptoms for both indicated single body system involvement only (i.e., skin and subcutaneous disorders MedDRA SOC), thus were excluded from the MAH-adjudicated analysis. Positive dechallenge to ABC for both and DRV+RTV for 1/2.
ING116070 ART Naïve Open Label Week 96	ABC/3TC+DTG[2] (None)	0	0	N/A

Study Details	ABC Study Regimen (Non- ABC Comparator Arm)	Investigator-Diagnosed Cases (n)	MAH-Adjudicated Cases (n)	MAH Adjudication Details
ING117172 (ARIA) ART Naïve Open Label Week 48	ABC/DTG/3TC[2,4] (ATV+RTV+TDF/FTC)	1	0	1 unconvincing case. Met Part A but not Part B of the case definition, with symptoms indicating single body system involvement only (i.e., skin and subcutaneous disorders MedDRA SOC), thus excluded from the MAH adjudicated analysis. Positive dechallenge to ABC/DTG/3TC.
201147 (STRIIVING) ART Experienced Open Label Week 48	ABC/DTG/3TC[2,4] (CAR)[6]	0	0	N/A
CNA109586 (ASSERT) ART Naïve Open Label Week 96	ABC/3TC+EFV[3,4] (TDF/FTC+EFV)	6	10	6 additional cases. 2 met Part A & B of the case definition. Investigator implicated EFV or NVP only. 4 were non-serious and met Part A only, verbatim terms implicated EFV only. Positive dechallenge to ABC & EFV (or NVP) in all 6, thus MAH could not rule out a possible ABC HSR for all cases. 2 unconvincing cases. Both met Part A but not Part B, with symptoms indicating single body system involvement only (i.e., skin and subcutaneous disorders MedDRA SOC), 1/2 with Rash only, thus both excluded from the MAH adjudicated analysis. Positive dechallenge to ABC for both and EFV for 1/2.
EPZ108859 (ARIES) ART Naïve Open Label Week 144	ABC/3TC+ATV+RTV[3] ABC/3TC+ATV[3]	4	3	1 unconvincing case. Met Part A but not Part B with symptoms indicating single body system involvement only (i.e., skin and subcutaneous disorders MedDRA SOC), thus excluded from the MAH adjudicated analysis. Positive dechallenge to ABC and negative rechallenge to ATV+RTV.
EPZ113734 (ASSURE) ART Experienced Open Label Week 48	ABC/3TC+ATV[3,4] (TDF/FTC+ATV+RTV)	1	1	Complete concordance with Investigator diagnosed cases.
LAI116482 (LATTE) ART Naïve Open Label Week 96	ABC/3TC+CAB[1,3] (CAB+RTV)	0	0	N/A

Study Details	ABC Study Regimen (Non- ABC Comparator Arm)	Investigator-Diagnosed Cases (n)	MAH-Adjudicated Cases (n)	MAH Adjudication Details
200056 (LATTE-2) ART Naïve Open Label Week 32	ABC/3TC+CAB[3,4] (CAB+RTV)	0	0	N/A

Data Source: CNA109586 Week 96 CSR Listings 10, 12 & 36; EPZ108859 Week 144 CSR Listings 8.4, 8.6 & 8.9; EPZ113734 Week 48 CSR Listings 8.4, 8.6 & 8.9; ING112276 Week 96 CSR Listings 12, 15 & 29; ING113086 Week 96 CSR Listings 13, 16 & 29; ING114467 Week 144 Listings 12, 14 & 30; ING114915 Week 96 CSR Listings 12, 14 & 31; ING116070 Week 96 CSR Listing 11, 14 & 27; ING117172 Week 48 CSR Listings 16, 18 & 57; LAI116482 Week 96 CSR Listings 8.3, 8.5 & 8.15; 200056 Week 32 CSR Listings 8.1002, 8.1004 & 8.1016; 201147 Week 48 CSR Listings 12.12, 12.14 & 13.22.

ABC, abacavir; ATV, atazanavir; CAB, cabotegravir; CAR, current antiretroviral regimen; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine

1. Investigators choice background therapy was either ABC/3TC or TDF/FTC
2. Included in the sub-analysis of patients who received ABC/DTG/3TC (or the equivalent components of DTG in combination with the ABC/3TC) – 'ABC/DTG/3TC sub-population'
3. Included in the sub-analysis of patients who received ABC/3TC in combination with a none DTG- anchor drug: the 'ABC/3TC sub- population'
4. Randomized with respect to ABC therapy (i.e., an experimental control for ABC)
5. Double-blind phase occurred from initiation to Week 96 followed by an open-label phase from Week 96 to Week 144
6. Late switch to ABC/DTG/3TC at 24 Weeks

15.4. Appendix 4: Listing of all possible ABC HSR Cases (n=27)

Study ID Subject No. Study Drugs	MedDRA AE PT 'Verbatim Term'	Symptoms	Reported TTO MAH TTO[1] (Days)	Action Taken[2] Outcome Duration (Days)	Severity SAE (Reason)	Investigator Causality[2] ABC CRF Module	MAH Adjudicated Case[3] Comment
Investigator-Diagnosed ABC HSR (n=17)							
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Hypersensitivity to abacavir'	Fever, Rash, Hypotension, Malaise, Myalgia, Fatigue, Cough, Pharyngitis Hyperaemia, Eyelid oedema	13 13	Withdrawn Resolved 10	Grade 4 Yes (Clinically Significant)	Yes Yes	Yes (Cannot be ruled out) Key symptoms from 2 body systems Positive dechallenge to ABC and EFV
CNA109586 PPD EFV+ABC/3TC	Hypersensitivity 'Hypersensitivity reaction'	Rash, Nausea, Diarrhea, Abdominal pain, Malaise, Fatigue, Cough, Dyspnea	12 12	Withdrawn Resolved 10	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes (Cannot be ruled out) Key symptoms from 2 body systems. Positive dechallenge to ABC Causality statement also implicated amoxicilin Negative rechallenge to EFV
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Abacavir hypersensitivity reaction'	Rash	10 10	Withdrawn Resolved 25	Grade 2 Yes (Clinically Significant)	Yes Yes	No (Unconvincing)[4] Single key symptom/body system. Positive dechallenge to ABC and EFV
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Possible abacavir hypersensitivity reaction'	Rash, Fever Pruritus, Erythema	4 8	Withdrawn Resolved 30	Grade 3 Yes (Hospitalised)	Yes Yes	Yes (Cannot be ruled out) Key symptoms from 2 body systems Positive dechallenge to ABC and EFV
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Abacavir hypersensitivity'	Rash Papule, Pruritus	10 10	Withdrawn Resolved 6	Grade 3 Yes Clinically Significant)	Yes Yes	No (Unconvincing)[4] Single key symptom/body system Resolved on continued EFV"
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Possible abacavir hypersensitivity reaction'	Rash generalised, Malaise, Fatigue	10 10	Withdrawn Resolved 12	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes (Cannot be ruled out) Key symptoms from 2 body systems Positive dechallenge to ABC and EFV
EPZ108859 PPD ATV+RTV+ABC/3TC	Drug hypersensitivity 'Abacavir hypersensitivity'	Rash generalised, Rash maculo-papular	9 9	Withdrawn Resolved 6	Grade 1 Yes (Clinically Significant)	Yes Yes	No (Unconvincing)[4] Single key symptom/body system. Investigator confirmed that there was no malaise, fever, fatigue, gastrointestinal symptoms, myalgia or athralgia. Positive dechallenge to ABC Negative rechallenge to ATV+RTV

Study ID Subject No. Study Drugs	MedDRA AE PT 'Verbatim Term'	Symptoms	Reported TTO MAH TTO[1] (Days)	Action Taken[2] Outcome Duration (Days)	Severity SAE (Reason)	Investigator Causality[2] ABC CRF Module	MAH Adjudicated Case[3] Comment
EPZ108859 PPD ATV+RTV+ABC/3TC	Hypersensitivity 'Hypersensitivity reaction'	Rash, Pyrexia, Rash, Nausea, Diarrhoea, Abdominal pain, Malaise, Myalgia, Fatigue, Arthralgia Chest pain, Pruritus, Erythema multiforme, Erythema,	13 13	Withdrawn Resolved 4	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes Key symptoms from 2 body systems. Positive dechallenge to ABC Negative rechallenge to ATV+RTV
EPZ108859 PPD ATV+RTV+ABC/3TC	Drug hypersensitivity 'Suspected abacavir hypersensitivity'	Rash generalised, Pyrexia Pruritus, Rash maculo-papular, Erythema,	11 11	Withdrawn Resolved 50	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes "Key symptoms from 2 body systems. Positive dechallenge to ABC Negative rechallenge to ATV+RTV"
EPZ108859 PPD ATV+RTV+ABC/3TC	Drug hypersensitivity 'Abacavir hypersensitivity reaction'	Rash generalised, Fatigue, Nausea, Pyrexia, Myalgia, Arthralgia, Cough, Rash maculo-papular, Pruritus, Rash papular, Erythema, Influenza like illness	12 11	Withdrawn Resolved 20	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes Key symptoms from 2 body systems. Positive dechallenge to ABC Negative rechallenge to ATV+RTV
EPZ113734 PPD ATV+ABC/3TC	Drug hypersensitivity 'Abacavir hypersensitivity reaction'	Pyrexia, Rash generalised, Nausea, Diarrhoea, Malaise, Fatigue, Headache, Insomnia	8 8	Withdrawn Resolved 20	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes Key symptoms from 2 body systems. Positive dechallenge to ABC Negative rechallenge to ATV
ING113086 PPD DTG+ABC/FTC	Drug hypersensitivity 'Presumptive Abacavir Hypersensitivity reaction'	Fever, Nausea, Fatigue, Malaise Other: anorexia, night sweats, periorbital tenderness, Lymphadenopathy, headache	16 16	Withdrawn Resolved 10	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes Key symptoms from 2 body systems. Positive dechallenge to ABC
ING113086 PPD DTG+ABC/FTC	Drug hypersensitivity 'Hypersensitivity reaction to KIVEXA'	Fever, Nausea, Abdominal pain, Fatigue, Rash Loss of appetite	7 7	Withdrawn Resolved 8	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes Key symptoms from 2 body systems. Positive dechallenge to ABC
ING114467 PPD DTG+ABC/3TC	Drug hypersensitivity 'Suspected Abacavir hypersensitivity reaction'	Fever, Cough, Pharyngitis, Nausea, Diarrhea, Fatigue	2 2	Withdrawn Resolved 11	Grade 2 Yes (Clinically Significant)	Yes Yes	Yes Key symptoms from 2 body systems. Patient initiated rechallenge Positive dechallenge to ABC and DTG

Study ID Subject No. Study Drugs	MedDRA AE PT 'Verbatim Term'	Symptoms	Reported TTO MAH TTO[1] (Days)	Action Taken[2] Outcome Duration (Days)	Severity SAE (Reason)	Investigator Causality[2] ABC CRF Module	MAH Adjudicated Case[3] Comment
ING114915 PPD DRV+RTV+ABC/3TC	Rash Rash	Rash	10 N/A	Withdrawn Resolved 11	Grade 2 No	Yes Yes	No (Unconvincing)[4] Single symptom of rash only. Positive dechallenge to ABC. Negative rechallenge to DRV+RTV
ING114915 PPD DRV+RTV+ABC/3TC	Drug hypersensitivity Suspected Abacavir hypersensitivity (maculopapular rash without other symptoms)	Rash, Erythema	11 11	Withdrawn Recovering	Grade 2 Yes (Clinically Significant)	Yes Yes	No (Unconvincing)[4] Single Key symptom/body system. Other symptoms didn't develop despite continued ABC Rx for 4 days Positive dechallenge to ABC and DRV+RTV
ING117172 PPD DTG/ABC/3TC	Drug hypersensitivity Possible abacavir hypersensitivity reaction	Pruritic macular-papular rash, Conjunctivitis	7 N/A	Withdrawn Resolved 30	Grade 2 No	Yes No	No (Unconvincing)[4] Single Key symptom/body system.
Additional MAH Adjudicated Cases (n=10)							
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Allergy to efavirenz'	N/A	9 9	Withdrawn Resolved 21	Grade 3 No	No No	Yes (Cannot be ruled out) Positive dechallenge to ABC+EFV EFV withdrawn 1st followed by ABC 4 days later
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Skin rash (allergy to nevirapine)'	Diarrhoea	89 89	Withdrawn Not Resolved N/A	Grade 2 No	No No	Yes (Cannot be ruled out) Key symptoms from 2 body systems. Positive dechallenge to ABC and NVP, both withdrawn on the same day
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Sustiva allergy reaction'	N/A	30 30	Withdrawn Resolved 13	Grade 2 No	Yes[5] No	Yes (Cannot be ruled out) Positive dechallenge to ABC and EFV, both withdrawn on the same day
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Sustiva allergy reaction'	N/A	14 14	Withdrawn Resolved 36	Grade 2 No	Yes[5] No	Yes (Cannot be ruled out) Positive dechallenge to ABC and EFV, both withdrawn on the same day
CNA109586 PPD EFV+ABC/3TC	Hypersensitivity 'Hypersensitivity reaction'	Rash macular, Dyspnoea, Hyperhidrosis, Sleep disorder, Euphoric mood	12 10	Withdrawn Resolved 52	Grade 2 Yes (Clinically Significant)	Yes[5] No	Yes (Cannot be ruled out) Key symptoms from 2x body systems. SAE Narrative implies dyspnoea resolved following ABC withdrawal. Rash persisted on continued EFV, ultimate positive dechallenge to EFV

Study ID Subject No. Study Drugs	MedDRA AE PT 'Verbatim Term'	Symptoms	Reported TTO MAH TTO[1] (Days)	Action Taken[2] Outcome Duration (Days)	Severity SAE (Reason)	Investigator Causality[2] ABC CRF Module	MAH Adjudicated Case[3] Comment
CNA109586 PPD EFV+ABC/3TC	Drug hypersensitivity 'Stocrin allergy'	N/A	9 9	Withdrawn Resolved 52	Grade 2 No	Yes[5] No	Yes (Cannot be ruled out) Positive dechallenge to ABC and EFV, both withdrawn on the same day
ING113086 PPD DTG+ABC/3TC	Drug hypersensitivity 'Hypersensitivity reaction'	Rash, pyrexia, arthralgia, lethargy, myalgia, jaundice, ALT increased, hyperbilirubinaemia, gammaglutamyltransferase increased, atrial fibrillation, headache, neck pain, 'heavy chest', paresthesia	10 10	Withdrawn Resolved 172[6]	Grade 4 Yes (Hospitalised)	No No	Yes (Cannot be ruled out) Investigator considered related to DTG only. MAH could not rule out ABC Key symptoms from 2 body systems. Positive dechallenge to ABC and DTG
ING113086 PPD RAL+ABC/3TC	Hypersensitivity 'Systemic allergic reaction'	N/A	85 85	Withdrawn Resolved 58	Grade 2 No	N/A No	Yes (Cannot be ruled out) Positive dechallenge to ABC Negative rechellenge to RAL
ING113086 PPD RAL+ABC/3TC	Hypersensitivity 'Toxico-allergic reaction'	Rash, Fever, Fatigue Watery stools, influenza, cytolytic hepatitis, viral cervical lymphadenitis, insominai, conjunctival injection, palpable spleen	8 8	Withdrawn Resolved 23	Grade 2 Yes (Hospitalised)	Yes No	Yes (Cannot be ruled out) Key symptoms from 2 body systems. Positive dechallenge to ABC and RAL This case was also confounded by confirmed influenza infection and amoxicillin administration. Lymphadenitis viral also reported."
ING114467 PPD DTG+ABC/3TC	Hypersensitivity 'Acute systemic allergic reaction'	Fever, Pharyngitis, Diarrhea, Rash Chills	5 5	Withdrawn Resolved 8	Grade 3 No	No Yes	Yes (Cannot be ruled out) Investigator considered related to DTG only. MAH could not rule out ABC, Key symptoms from 2 body systems. Positive dechallenge to both ABC+DTG

Data Source: CNA109586 Week 96 CSR Listings 10, 12 & 36; EPZ108859 Week 144 CSR Listings 8.4, 8.6 & 8.9; EPZ113734 Week 48 CSR Listings 8.4, 8.6 & 8.9; ING113086 Week 96 CSR Listings 13, 16 & 29; ING114467 Week 144 Listings 12, 14 & 30; ING114915 Week 96 CSR Listings 12, 14 & 31; ING117172 Week 48 CSR Listings 16, 18 & 57; Argus Safety Database (OASIS)

ABC, abacavir; AE PT, adverse event preferred term; ATV, atazanavir; CRF, case report form; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; ID, identifier; MAH, marketing authorization holder; MedDRA, Medical Dictionary for Regulatory Activities; No., number; RAL, raltegravir; RTV, ritonavir; SAE, serious adverse event; TDF, tenofovir disoproxil fumarate; TTO, time to onset, 3TC, lamivudine

1. Day on which symptomatology met the MAH ABC HSR Cases definition (i.e., at least 2 symptoms for 2 different body symptoms), derived from the SAE narrative
2. With ABC. For Investigator causality with ABC where received as Investigators choice dual NRTI backbone, this could only be determined where specified in the SAE narrative
3. Adjudicated against the MAH Case Definition in Section 15.1, which is pragmatic and conservative definition, and is not meant to replace medical diagnoses
4. The Investigator diagnosis of suspected ABC HSR in this case, and withdrawal of ABC treatment, may have been clinically appropriate at the time of patient presentation.
5. For CNA109586, it was unclear if investigator relationship to study drug was defined as either: EFV+ABC/3TC vs. EFV+TDF/FTC; OR ABC/3TC vs TDF/FTC
6. Prolonged duration due to normalisation of liver chemistries

15.5. Appendix 5: Summary of Baseline Demographics, Clinical Characteristics and Exposure Data Summary

Protocol: 207831

Table 1: Demographic and Baseline Characteristics
Summary of Patients Exposed to ABC and DTG or ABC and Non-DTG

Baseline variables		TRIUMEQ (N=1494)	ABC + Non-DTG (N=1569)	TRIUMEQ or ABC + Non-DTG (N=3063)
Age (years)	N	1494	1569	3063
	Mean	39.52	38.00	38.74
	SD	11.25	10.23	10.76
	Median	39.00	37.00	38.00
	Min	18.00	18.00	18.00
	Max	80.00	75.00	80.00
Sex	M	1040 (69.6%)	1324 (84.4%)	2364 (77.2%)
	F	454 (30.4%)	245 (15.6%)	699 (22.8%)
Race	White	987 (66.1%)	1118 (71.3%)	2105 (68.7%)
	Non-White	505 (33.8%)	451 (28.7%)	956 (31.2%)
	Missing	2 (0.1%)	0	2 (0.1%)
Country	Argentina	24 (1.6%)	0	24 (0.8%)
	Australia	17 (1.1%)	9 (0.6%)	26 (0.8%)
	Austria	0	9 (0.6%)	9 (0.3%)
	Belgium	8 (0.5%)	12 (0.8%)	20 (0.7%)
	Canada	143 (9.6%)	163 (10.4%)	306 (10.0%)

Denmark	2 (0.1%)	6 (0.4%)	8 (0.3%)
France	44 (2.9%)	59 (3.8%)	103 (3.4%)
Germany	51 (3.4%)	77 (4.9%)	128 (4.2%)
Ireland	0	4 (0.3%)	4 (0.1%)
Italy	48 (3.2%)	38 (2.4%)	86 (2.8%)

Data Source: Data presented is from the following studies: ARIA (ING117172), ARIES (EPZ108859), ASSERT (CNA109586), ASSURE (EPZ113734), LATTE (LAI116482), LATTE-2 (200056),
SINGLE (ING114467), SPRING-1 (ING112276), SPRING-2 (ING113086), FLAMINGO (ING114915), STRIIVING (201147), ING116070.

Protocol: 207831

Table 1: Demographic and Baseline Characteristics
Summary of Patients Exposed to ABC and DTG or ABC and Non-DTG

Baseline variables		**TRIUMEQ (N=1494)**	**ABC + Non-DTG (N=1569)**	**TRIUMEQ or ABC + Non-DTG (N=3063)**
	Latvia	0	1 (0.1%)	1 (0.0%)
	Mexico	6 (0.4%)	0	6 (0.2%)
	Netherlands	7 (0.5%)	9 (0.6%)	16 (0.5%)
	Portugal	4 (0.3%)	1 (0.1%)	5 (0.2%)
	Puerto Rico	4 (0.3%)	4 (0.3%)	8 (0.3%)
	Romania	12 (0.8%)	3 (0.2%)	15 (0.5%)
	Russia	94 (6.3%)	61 (3.9%)	155 (5.1%)
	South Africa	33 (2.2%)	0	33 (1.1%)
	Spain	209 (14.0%)	213 (13.6%)	422 (13.8%)
	Switzerland	2 (0.1%)	15 (1.0%)	17 (0.6%)
	Thailand	19 (1.3%)	0	19 (0.6%)
	United Kingdom	29 (1.9%)	48 (3.1%)	77 (2.5%)
	United States	738 (49.4%)	837 (53.3%)	1575 (51.4%)
Regions	Europe	416 (27.8%)	495 (31.5%)	911 (29.7%)
	Latin America	34 (2.3%)	4 (0.3%)	38 (1.2%)
	North-America	881 (59.0%)	1000 (63.7%)	1881 (61.4%)
	Rest of the World	163 (10.9%)	70 (4.5%)	233 (7.6%)
CDC Category	A: Asymptomatic or Lymphadenopathy or Acute HIV	1183 (79.2%)	1225 (78.1%)	2408 (78.6%)

B: Symptomatic, Not AIDS	190 (12.7%)	225 (14.3%)	415 (13.5%)

Data Source: Data presented is from the following studies: ARIA (ING117172), ARIES (EPZ108859), ASSERT (CNA109586), ASSURE (EPZ113734), LATTE (LAI116482), LATTE-2 (200056),
SINGLE (ING114467), SPRING-1 (ING112276), SPRING-2 (ING113086), FLAMINGO (ING114915), STRIIVING (201147), ING116070.

Protocol: 207831

Table 1: Demographic and Baseline Characteristics
Summary of Patients Exposed to ABC and DTG or ABC and Non-DTG

Baseline variables		TRIUMEQ (N=1494)	ABC + Non-DTG (N=1569)	TRIUMEQ or ABC + Non-DTG (N=3063)
	C: AIDS	121 (8.1%)	119 (7.6%)	240 (7.8%)
HIV Risk Factor	Hemophilia-associated injections	1 (0.1%)	0	1 (0.0%)
	Heterosexual contact	600 (40.2%)	360 (22.9%)	960 (31.3%)
	Homosexual contact	788 (52.7%)	1040 (66.3%)	1828 (59.7%)
	Injectable drug use	40 (2.7%)	31 (2.0%)	71 (2.3%)
	Occupational exposure	2 (0.1%)	5 (0.3%)	7 (0.2%)
	Transfusion	3 (0.2%)	3 (0.2%)	6 (0.2%)
	Other	6 (0.4%)	83 (5.3%)	89 (2.9%)
	Missing	54 (3.6%)	47 (3.0%)	101 (3.3%)
Baseline Log HIV-1 RNA Class (copies/mL)	N	1485	1546	3031
	Mean	3.55	4.33	3.95
	SD	1.53	1.25	1.45
	Median	4.02	4.64	4.36
	Min	1.59	1.59	1.59
	Max	6.66	6.93	6.93
Baseline HIV-1 RNA Class (copies/mL)	N	1485	1546	3031
	Mean	98235.12	174041.33	136901.03
	SD	335672.75	480890.43	417779.02

Median	10493.00	43700.00	22669.00

Data Source: Data presented is from the following studies: ARIA (ING117172), ARIES (EPZ108859), ASSERT (CNA109586), ASSURE (EPZ113734), LATTE (LAI116482), LATTE-2 (200056),
SINGLE (ING114467), SPRING-1 (ING112276), SPRING-2 (ING113086), FLAMINGO (ING114915), STRIIVING (201147), ING116070.

Protocol: 207831

Table 1: Demographic and Baseline Characteristics
Summary of Patients Exposed to ABC and DTG or ABC and Non-DTG

Baseline variables		TRIUMEQ (N=1494)	ABC + Non-DTG (N=1569)	TRIUMEQ or ABC + Non-DTG (N=3063)
	Min	39.00	39.00	39.00
	Max	4618267.00	8425886.00	8425886.00
Baseline HIV-1 RNA Class (copies/mL)	<50,000	1088 (72.8%)	846 (53.9%)	1934 (63.1%)
	50,000 - <100,000	136 (9.1%)	224 (14.3%)	360 (11.8%)
	100,000 - <200,000	113 (7.6%)	204 (13.0%)	317 (10.3%)
	>=200,000	157 (10.5%)	295 (18.8%)	452 (14.8%)
Baseline CD4+ (cells/mm^3)	N	1494	1546	3040
	Mean	462.90	348.95	404.95
	SD	256.13	210.13	240.67
	Median	411.00	313.00	363.00
	Min	19.00	10.00	10.00
	Max	1831.00	1196.00	1831.00
	100,000 - <200,000	218 (14.6%)	347 (22.1%)	565 (18.4%)
	50,000 - <100,000	142 (9.5%)	294 (18.7%)	436 (14.2%)
	<50,000	27 (1.8%)	104 (6.6%)	131 (4.3%)
	>=200,000	1107 (74.1%)	824 (52.5%)	1931 (63.0%)
Exposure (Days)	N	1494	1569	3063
	Mean	516.32	488.31	501.97

SD	335.64	344.40	340.39
Median	340.00	347.00	342.00

Data Source: Data presented is from the following studies: ARIA (ING117172), ARIES (EPZ108859), ASSERT (CNA109586), ASSURE (EPZ113734), LATTE (LAI116482), LATTE-2 (200056),
SINGLE (ING114467), SPRING-1 (ING112276), SPRING-2 (ING113086), FLAMINGO (ING114915), STRIIVING (201147), ING116070.

Protocol: 207831

Table 1: Demographic and Baseline Characteristics
Summary of Patients Exposed to ABC and DTG or ABC and Non-DTG

Baseline variables		TRIUMEQ (N=1494)	ABC + Non-DTG (N=1569)	TRIUMEQ or ABC + Non-DTG (N=3063)
	Min	1.00	1.00	1.00
	Max	1124.00	1126.00	1126.00
ART Status	Naive	975 (65.3%)	1370 (87.3%)	2345 (76.6%)
	Experienced	519 (34.7%)	199 (12.7%)	718 (23.4%)

Data Source: Data presented is from the following studies: ARIA (ING117172), ARIES (EPZ108859), ASSERT (CNA109586), ASSURE (EPZ113734), LATTE (LAI116482), LATTE-2 (200056),
SINGLE (ING114467), SPRING-1 (ING112276), SPRING-2 (ING113086), FLAMINGO (ING114915), STRIIVING (201147), ING116070.

15.6. Appendix 6: Publications based on the study

Stainsby C, Perger T, Urbaityte R, Oyee J, et. al. Abacavir hypersensitivity reaction reporting rates in a decade of HLA-B*5701 screening as a risk mitigation measure. European AIDS Clinical Society conference, Milan, Italy. 2017; Abstract/Poster: PE12/8.

TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

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

Compound Number:	GI265235, GSK2285967, GSK2619619
Development Phase	IV
Effective Date:	23-03-2017

Subject:	Safety, Abacavir, hypersensitivity reaction, HLA-B*5701 screening
Author(s):	PPD PPD PPD PPD PPD PPD

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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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Chris Stainsby Primary Author/Study Accountable Person	**Date**
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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.

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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