21 March 2013
EMA/332263/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Stribild

International non-proprietary name: ELVITEGRAVIR / cobicistat / EMTRICITABINE / TENOFOVIR DISOPROXIL

Procedure No. EMEA/H/C/002574/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

3TC	lamivudine
AAG	α_1-acid glycoprotein
ABC	abacavir
ADR	adverse drug reaction
AE	adverse event
aGFR	actual glomerular filtration rate
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate, coformulated (Atripla®)
ATV	atazanavir
BID	twice a day (*bis in die*)
BL	baseline
BMD	bone mineral density
BMI	body mass index
BR	background regimen
BUN	blood urea nitrogen
CBV	lamivudine/zidovudine coformulated (Combivir)
CCR5	chemokine receptor type 5
CCSI	Company Core Safety Information
CG	Cockcroft-Gault
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	systemic clearance of the drug after intravenous administration
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
CL_{cr}	creatinine clearance
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
/co	boosted with cobicistat
COBI	cobicistat; previously known as GS-9350
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPI	comparator protease inhibitor
CPK	creatine phosphokinase
CPT	Child-Pugh-Turcotte
CRF	case report form
CSR	clinical study repor

CV	coefficient of variation
CYP	cytochrome P450 enzyme(s)
cysGFR	cystatin C-derived glomerular filtration rate
d4T	stavudine
DAIDS	Division of AIDS (National Institute of Allergy and Infectious Diseases)
ddI	didanosine
DEXA	dual-energy x-ray absorptiometry
DF	disoproxil fumarate
DNA	deoxyribonucleic acid
DRV	darunavir
EC	enteric coated
ECG	electrocardiogram
ECHO	echocardiogram
EE	ethinyl estradiol
EFV	efavirenz
EFV/FTC/TDF	efavirenz/emtricitabine/tenofovir disoproxil fumarate, corformulated (Atripla®)
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
$eGFR_{MDRD}$	estimated glomerular filtration rate calculated using the modified diet in renal disease equation
ERC	External Review Committee
EVG	elvitegravir
EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (QUAD), coformulated
FE_{PO4}	urine fractional excretion of phosphate
FTC	emtricitabine (Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GLSM	geometric least-squares mean
GS-9350	cobicistat
GSS	genotypic sensitivity score
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV, HIV-1	human immunodeficiency virus, type 1
HLGT	high level group term
HLT	high level term
IAS	International Antiviral Society
IC_{xx}	concentration that results in xx% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)

IDV	indinavir
Ig	immunoglobulin (IgG, IgM) INR international normalized ratio
IN	integrase
INSTI	integrase strand-transfer inhibitor ISS Integrated Summary of Safety
ITT	intent-to-treat
IV	intravenous
KM	Kaplan-Meier
LDL	low-density lipoprotein
LPV	lopinavir
LPV/r	lopinavir/ritonavir, coformulated
MATE	multidrug and toxin extrusion protein
m	Module
MDZ	midazolam
M = E	missing = excluded
MedDRA	Medical Dictionary for Regulatory Activities
M = F	missing = failure
M/S = F	missing or antiretroviral therapy switch = failure
NEC	not elsewhere classified
NFV	nelfinavir
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NSAIDs	Nonsteroidal anti-inflammatory drugs
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OATP	organic anion transporting polypeptide
Pgp or MDR1	P-glycoprotein
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PI	protease inhibitor
PK	pharmacokinetic(s)
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PSUR	periodic safety update report
PT	preferred term
Q1, Q3	first quartile, third quartile
QD	once daily
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing the time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
QUAD	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate coformulated
/r	boosted with ritonavir
RAL	raltegravir

RBC	red blood cell
RBC/HPF	red blood cells per high power field
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ class
SQV	saquinavir
STR	single-tablet regimen
T-20	enfuvirtide
TAM	thymidine analog-associated mutation
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TLOVR	time to loss of virologic response
TPV	tipranavir
TSH	thyroid-stimulating hormone
TVD	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US/USA	United States/United States of America
VLDL	very low-density lipoprotein
WBC	white blood cell
ZDV	zidovudine
AUC	area under the plasma concentration-time curve
AUC_{0-last}	area under the plasma/serum/PBMC concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma/serum/PBMC concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the plasma/serum/PBMC concentration versus time curve over the dosing interval
$AUC_{0-\infty}$	partial area under the plasma/serum concentration versus time curve from time 0 to ∞
C_{last}	last observed quantifiable plasma/serum/PBMC concentration of the drug
E_{max}	maximum (pharmacodynamic) effect
C_{max}	maximum observed plasma/serum/PBMC concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
C_{trough}	plasma concentration at the end of the dosing interval
$T_{½}$	estimate of the terminal elimination half-life of the drug in serum/plasma/PBMC, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd. submitted on 24 November 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Stribild, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 May 2011.

The applicant applied for the following indication: Stribild is indicated as a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naïve or who have no known mutations associated with resistance to the individual components of Stribild.

The demonstration of the benefit of the combination elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil as fumarate (tenofovir DF) in HIV-1 infection is based on Week 48 safety and efficacy analysis from 2 randomised, double-blind, controlled Phase 3 studies in treatment-naïve adults (see section 5.1).

The legal basis for this application refers to:

Article 8(3) of Directive No 2001/83/EC

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/125/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substances cobicistat and elvitegravir contained in the above medicinal product to be considered as a new active substances in themselves, as the applicant claims that they are not constituents of a medicinal product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Joseph Emmerich

- The application was received by the EMA on 24 November 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 March 2012 (Annex 2).
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 April 2012.
- During the meeting on 24 May 2012, the CHMP re-adopted a revised consolidated List of Questions. The final consolidated List of Questions was sent to the applicant on 25 May 2012 (Annex 3).
- The applicant requested a Clock stop extension on 1 June 2012 (Annex 4).
- The summary report of the GCP inspection carried out at the following sites, London (UK) and Darlinghurst (Australia), between 27-30 March 2012, 16-20 April 2012 and 23-27 April 2012 was issued on 8 July 2012
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 September 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the consolidated List of Questions to all CHMP members on 29 October 2012 (Annex 5).
- During the CHMP meeting on 15 November 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 December 2012.
- Rapporteurs Assessment report on MAA responses on the List of Outstanding Issues circulated 9 January 2013 (Annex 7).
- Rapporteurs RMP assessment report circulated 16 January 2013 (Annex 8).
- During the CHMP meeting on 17 January 2013, the CHMP agreed 2nd list of outstanding issues to be addressed in writing by the applicant (Annex 9) and endorsed the questions to the SAG.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues

on 23 January 2013.

- Rapporteurs Joint Assessment reports on the MAA's responses to the CHMP 2nd List of Outstanding Issues circulated 4 February 2013 (Annex 10).
- During a meeting of SAG on 6 February 2013, experts were convened to address questions raised by the CHMP (Annex 11).
- Rapporteurs Joint Updated overview circulated 19 February 2013 (Annex 12).
- During the CHMP meeting on 21 February, the CHMP agreed that an oral explanation was no longer required agreed on a 3rd list of outstanding issues to be addressed in writing by the applicant (Annex 13).
- The applicant submitted the responses to the CHMP 3rd List of Outstanding Issues on 28 February 2013.
- Rapporteurs Joint Assessment reports on the MAA's responses to the 3rd CHMP List of Outstanding Issues 7 March 2013 (Annex 14).
- During the meeting on 21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Stribild.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

There are approximately 33 million people worldwide living with HIV-1. HIV-1 infection remains is a life-threatening disease in infected persons who do not receive adequate treatment sufficiently early in the course of the infection and/or are infected with virus that is resistant to anti-retroviral agents of several classes such that an adequate treatment regimen cannot be constructed from approved agents.

Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral (ARV) therapy (HAART). The introduction of HAART was associated with a dramatic decrease in AIDS-related mortality and morbidity in the US and Europe. The goal of ARV therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication. In treatment naïve subjects who have not acquired multi-resistant virus *de novo*, suppression of HIV RNA to < 50 copies/ml has been achieved in ~80% of subjects in clinical studies.

Current treatment guidelines suggest that initial therapy for ARV treatment-naive HIV-1 infected patients should consist of 2 NRTIs/NtRTIs and either an NNRTI—usually efavirenz—a boosted protease inhibitor (PI) or the integrase inhibitor (INSTI) raltegravir (RAL).

- NNRTIs are widely used in the treatment of HIV-1 infection but are associated with safety and tolerability concerns such as hepatotoxicity, central nervous system (CNS) symptoms, rash and/or the risk of teratogenicity.
- Advantages of PI-based regimens include excellent anti-viral activity, a relatively high barrier for development of drug resistance (i.e. requires multiple mutations) and sparing treatment with NNRTIs. However, PIs have the potential for multiple drug interactions and may be associated with metabolic complications such as dyslipidaemia, lipodystrophy and insulin resistance. In addition, they

require co-administration of low-dose RTV to boost exposure through inhibition of CYP3A-mediated metabolism. The use of RTV as a pharmacoenhancer of PIs adds to the pill burden.

- RAL is currently the only INSTI approved for use in adults. It requires twice-daily dosing but it has a better tolerability profile compared to efavirenz and a relatively limited potential for drug-drug-interactions.

In the EU the single treatment regimens (STR) marketed suitable for treatment-naïve subjects are Atripla (emtricitabine [FTC], tenofovir [TDF], efavirenz [EFV]) and Eviplera (FTC/TDF plus the NNRTI rilpivirine) which was recently approved.

2.1.1. About the product

The applicant has developed a fixed drug combination tablet containing three ARVs (FTC/TDF and elvitegravir [EVG; an INSTI]) plus a new pharmacoenhancer cobicistat (COBI), which modifies the PK profile of EVG.

It is proposed that this once daily FDC will provide a useful alternative to existing STRs for the following reasons:

- It does not include a NNRTI, which may have treatment-limiting tolerability issues
- It avoids use of EFV, which is classed as a teratogen so limiting use in women of childbearing potential
- It is the first STR to combine an INSTI with an NRTI backbone
- It provides an alternative for patients who cannot tolerate boosted PIs
- It provides a simplified treatment regimen

Initial proposed indication for use:

Stribild is indicated as a complete regimen for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naïve or who have no known mutations associated with resistance to the individual components of Stribild.

The demonstration of the benefit of the combination elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate (tenofovir DF) in HIV-1 infection is based on Week 48 safety and efficacy analysis from 2 randomised, double-blind, controlled Phase 3 studies in treatment-naïve adults (see section 5.1).

Proposed posology:

The recommended dose of Stribild is one tablet, taken orally, once daily with food.

Since the Stribild contains two active substances that are already approved (alone and as part of three approved FDCs) where applicable the individual assessment reports have concentrated on data for the two new components rather than repeating all the information of relevance that has already been fully assessed and reviewed (pre- and post-approval) by the CHMP. This report reflects this approach.

2.2. Quality aspects

2.2.1. Introduction

Stribild is a fixed dose combination containing two new active substances not previously authorised in the EU -elvitegravir and cobicistat- and two known active substances – emtricitabine and tenofovir.

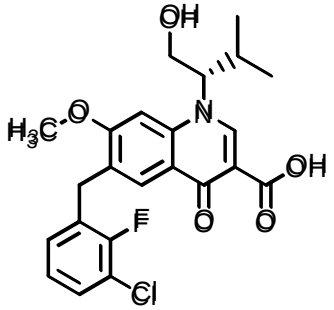
The finished product is presented as film coated tablets, containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 245 mg of tenofovir disoproxil (equivalent to 300 mg of tenofovir disoproxil fumarate or 136 mg of tenofovir). The composition is described in section 6.1 of the SmPC.

The product is available in bottles as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Elvitegravir

Elvitegravir appears as a white to pale yellow crystalline non-hygroscopic powder, sparingly soluble in methanol and ethanol and practically insoluble in water and aqueous solutions at pH 2.0 to 8.3. The chemical name of elvitegravir is 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid, corresponding to the structural formula below:



The molecular formula is $C_{23}H_{23}ClFNO_5$ and its relative molecular mass 447.9 g/mol. Its pKa is 6.6 and the distribution coefficient LogD 4.5 (at pH 6.8). Elvitegravir exhibits polymorphism and appears in three polymorphs. The most thermodynamically stable polymorphic form has been determined and the crystallisation process is designed to consistently deliver this form. It contains a single asymmetric centre at C-11. The absolute configuration was established by single crystal X-ray crystallography and has been determined to be of "S" configuration.

Manufacture

Elvitegravir is manufactured in six well defined synthetic steps using commercially available starting materials. Three sites are involved in the manufacture of elvitegravir. The route of synthesis has been described in sufficient detail and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Information about the formation, presence, origin and fate of impurities during manufacture has been satisfactorily discussed.
Representative batch analysis data provided for all 3 proposed manufacturing sites produced with the proposed synthetic route show that the active substance can be manufactured reproducibly.

Specification

The elvitegravir active substance specification includes tests and limits for appearance (visual inspection), identification (IR, HPLC, UV), water content (Ph. Eur.), assay (HPLC), enantiomeric purity (chiral HPLC), impurities (HPLC), residual solvents (GC), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), polymorphic form (DSC-Ph. Eur.) and Particle size (laser light scattering).

Impurities, including genotoxic impurities, have been evaluated and qualified where necessary. The proposed limits are found to be acceptable from a safety point of view and therefore they are considered justified.
A microbial limit test for the drug substance is not required in accordance with ICH Q6A because the latter steps of the active substance manufacturing process conducted in aqueous organic solvent mixtures and are expected to limit microbial content. In addition, confirmatory testing demonstrated that elvitegravir is moderately to completely inhibitory to microbial growth. Furthermore, data presented in the dossier indicate that no significant bioburden is present.
The analytical methods have been well described and validated according to ICH Q2 (R1) and are suitable to control the quality of the active substance.

Batch analysis data on 23 pilot and commercial scale batches of the active substance manufactured by all three proposed manufacturers have been provided. All 3 sites have manufactured commercial scale batches. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process regardless of the manufacturing site.

Stability

Stability studies have been conducted for four commercial scale batches from the first manufacturer and one batch from the second under ICH long term (25°C±2°C /60±5% RH) and accelerated conditions (40°C±2°C / 75%±5% RH) in the proposed packaging. Results were submitted for up 60 months at long term conditions and for up to 9 months at accelerated conditions.

Long term and accelerated stability samples were tested for appearance, assay, impurity content, and water content. The enantiomeric purity and polymorphic form were tested annually during the long term studies. Enantiomeric purity was determined for 1 batch, at the beginning and end of the accelerated study and polymorphic form was tested at the end of the accelerated study. The analytical methods used are stability indicating.

All parameters remained within the specification limits under both conditions over the duration of study for all four batches. The data show no discernible trends for assay, total impurity content, individual specified impurities, degradation products or any other tested parameter.

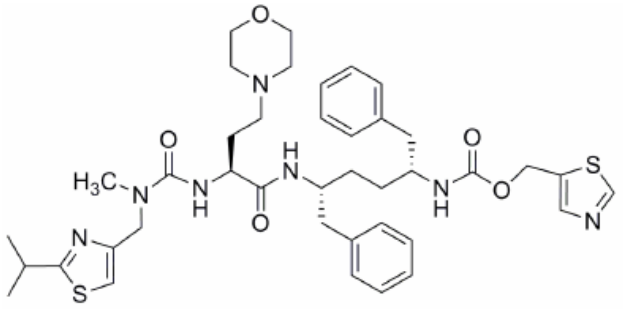
In addition, a photostability study of elvitegravir has been assessed as per the ICH Q1B Guideline on one batch from the second manufacturer. No significant difference was observed between the control sample and exposed sample in appearance, assay, impurity content, polymorphic form and enantiomeric purity. The data indicate that elvitegravir is not sensitive to light.

Based on the presented stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is acceptable.

Cobicistat

The active substance cobicistat is adsorbed on silicon dioxide. Cobicistat appears as a white to pale yellow, very hygroscopic amorphous solid, soluble in 0.1N HCl pH 1.9, sparingly soluble at pH 4.5,

practically insoluble in water and at pH 6.8-8.2, freely soluble in methanol. The chemical name of cobicistat is 1,3-Thiazol-5-ylmethyl [(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl] methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate, corresponding to the structural formula below:



The molecular formula is $C_{40}H_{53}N_7O_5S_2$ and its relative molecular mass 776.0 g/mol. It shows three pKa; 1.8 (thiazole group), 2.5 (alkylthiazole group) and 6.4 (morpholino group). The partition coefficient LogP is 4.3 (at pH 8.5 buffer). No crystal forms have been found. It has three chiral centres and is produced as a single isomer. The stereochemical configuration is defined through the synthetic process and the use of starting material with suitable chirality. Appropriate specifications for these starting materials ensure consistent quality during manufacture of cobicistat.

Cobicistat is an amorphous solid with a low glass transition temperature of 35 ºC. Because of the low glass transition temperature, cobicistat under ambient conditions undergoes moisture and temperature induced phase transition from a foam into a rubber-like material. To increase physical stability of cobicistat it is adsorbed on silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow amorphous powder and as cobicistat is also hygroscopic as determined by dynamic vapor sorption at room temperature. The relatively higher water uptake of cobicistat on silicon dioxide compared to cobicistat is due to the hygroscopic nature of the silicon dioxide carrier. Importantly however and contrary to cobicistat itself, moisture uptake of cobicistat on silicon dioxide is reversible and therefore cobicistat is isolated by adsorption on silicon dioxide to provide a stable solid form, which is suitable for further finished product manufacture.

Manufacture

Three sites are involved in the manufacture of the active substance with one of them involved only in the manufacture of an intermediate. Cobicistat on silicon dioxide is manufactured in four well defined synthetic steps. Details about possible reprocessing have been provided. The route of synthesis has been described in sufficient detail and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Because the actual loading value of cobicistat on silicon dioxide is subject to manufacturing variability, a target loading with an appropriate range was adopted to ensure a robust down-stream manufacturing process.

Both sites have manufactured commercial scale batches of cobicistat on silicon dioxide and many smaller scale batches during the development of the product. The first site has made 9 large scale batches and the second has made 7 large scale batches. Batch analysis data show that the active substance produced by both manufacturers is of similar quality and can be manufactured reproducibly.

Specification

Cobicistat on silicon dioxide specification includes tests and limits for appearance (visual), identification (cobicistat: IR, HPLC, UV, silicon dioxide: chemical reaction), water content (Ph. Eur.), assay (HPLC), enantiomeric purity (chiral HPLC), impurities (HPLC), residual solvents (GC) and heavy metals (Ph. Eur.). No crystal forms have been identified and since the drug substance is produced as an amorphous solid adsorbed onto silicon dioxide, a test for polymorphism is not required as per ICH Q6A.
Cobicistat genotoxic potential has been evaluated in accordance with the recommendations in ICH Q3A. All the identidied impurities are of low concern for genotoxicity, and therefore no further qualification studies were considered necessary. The proposed test and limits are acceptable.
A microbial limit test for the drug substance is not required in accordance with ICH Q6A because the latter steps of the active substance manufacturing process are non-aqueous and been shown to limit microbial content. In addition data presented on several batches during development indicate no significant bioburden is present.
All in-house analytical methods have been validated according to ICH Q2A principles.

Batch analysis data for 9 representative large scale batches from the first site and 7 representative large scale batches from the second manufacturer have been provided. In addition data for (smaller) batches used during development were also provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Two pilot scale and one production scale batch from the first manufacturer and on one full scale batch from the second manufacturer packaged in the proposed container were put on stability testing in accordance with the ICH Q1A (R2) Guideline under long-term conditions at 5 °C for up to 36 months and accelerated at 25 °C/60% RH for up to 36 months. Appearance, water content, assay, impurities and chiral purity have been monitored. The analytical methods used are stability indicating. All physicochemical attributes of cobicistat on silicon dioxide remained within the specification acceptance limits following 36 months of long-term storage at 5 °C and no apparent trend has been observed. A statistical analysis performed for assay, total impurities and the major chiral impurity also demonstrate that there is little change over time. The physicochemical attributes of cobicistat on silicon dioxide remained also within the specification acceptance limits following 36 months of storage at 25 °C/60% RH.

Furthermore, three of the above batches were also tested under 30 °C/75% RH for up to 12 months to evaluate the stability of cobicistat on silicon dioxide at elevated temperatures that may be encountered during shipping and handling. The duration of temperature and humidity excursions is limited to 3 months.

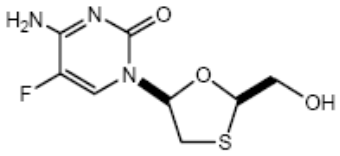
In addition, a photostability study was conducted on cobicistat on silicon dioxide according to ICH Q1B Guideline. The results showed no significant change in appearance, assay, and impurity content following exposure to light. The data indicate that cobicistat on silicon dioxide is not sensitive to light.

Based on the presented stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is acceptable.

Emtricitabine

Emtricitabine appears as a white to off-white non-hygroscopic crystalline powder, freely soluble in methanol and water. The chemical name of emtricitabine is

4-amino-5-fluoro-1-[(2S,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one, corresponding to the structural formula below:



The molecular formula is $C_8H_{10}FN_3O_3S$ and its relative molecular mass 247.24 g/mol. Its pKa is 2.65 and the partition coefficient LogP is -0.43. it has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. Two enantiomeric pairs of diastereomers can exist; cis-(-)-FTC and cis-(+)-FTC, trans-(-)-FTC and trans-(+)-FTC. The synthetic route has been chosen to be stereoselective for the formation of the desired cis-(-) enantiomer, emtricitabine. Three polymorphs of emtricitabine have been observed. However, the most stable thermodynamically form at room temperature, is consistently produced.

Manufacture

Emtricitabine is manufactured by two possible synthetic routes sharing a common first step and followed by two options comprising either by one or two extra steps. The synthesis was described in sufficient detail. The synthetic process results in the stereoselective formation of an intermediate and thus the formation of the desired emtricitabine enantiomer. Four manufacturing sites are involved. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The process has been shown to consistently produce emtricitabine that meets the required quality standards.

Batch analysis data is provided on 18 commercial scale batches produced with the proposed synthetic route from all proposed manufacturers. The data show that the active substance can be manufactured reproducibly by all proposed manufacturers.

Specification

Emtricitabine specification includes tests and limits for appearance (visual), identification (IR, HPLC), Clarity of Solution (visual), water content (Ph. Eur.), enantiomeric purity (chiral HPLC), assay (HPLC), impurities (HPLC), heavy metals (Ph. Eur.), Residue On Ignition (Ph. Eur.), residual solvents (GC) and particle size (Laser Light Scattering). Analytical methods have been validated in accordance with ICH guidelines. The testing and the proposed limits applied, conform to current ICH guidlines and are acceptable from a toxicological and clinical perspective.
Extended testing during development has demonstrated that only a single polymorphic form results from the synthetic process of emtricitabine. Therefore as per ICH Q6A, testing at release is not necessary. Development data demonstrate the absence of indicator organisms and therefore as per ICH Q6 indicate that microbial testing of the drug substance is not required.

Batch analysis data on 13 commercial scale and 5 pilot scale batches of the active substance from all proposed manufacturers were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Ten commercial scale and five pilot scale batches of emtricitabine manufactured using by both synthetic routes and by all four manufacturers packaged in the proposed container were put on stability testing in accordance with the ICH Q1A (R2) Guideline under long-term conditions at 25 ºC/60% RH for up to 36 months. Of the above batches, eight commercial scale and five pilot batches were put under accelerated at 40 ºC/75%RH for up to 6 months. In addition another three batches were put under intermediate 30 ºC/65%RH conditions for up to 12 months. Samples are tested for appearance, impurities and degradation products, water content and for enantiomeric purity by validated stability indicating methods. Stability data for emtricitabine manufactured by both synthetic routes were comparable. All tested parameters remained within the specification limits throughout the tested period for all three stability conditions. In one isolated batch one degradation product exceeded the specification limit at the last time point (36 months). The same degradation product, is observed in emtricitabine stored at accelerated storage. Four batches exceeded the specification limit at 6 months. These data indicate that emtricitabine should not be exposed to elevated temperatures for extended periods of time but poses no quality issue for the active substance.

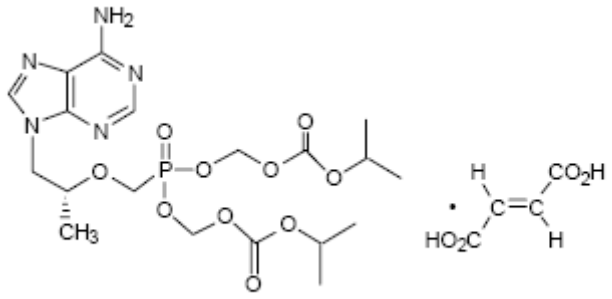
A photostability study was conducted on one batch of emtricitabine. The results showed no significant changes in appearance, purity, and impurity content and indicate that emtricitabine is not sensitive to light.

Based on the long-term stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is considered acceptable.

Tenofovir

The fumarate salt of the disoproxil prodrug of tenofovir is used. Tenofovir disoproxil fumarate (tenofovir DF) appears as a white to off-white, non-hygroscopic, crystalline powder, sparingly soluble in water and phosphate buffer pH 3.6, soluble in 0.1 N HCl, methanol and ethanol.

The chemical name of tenofovir is 9-[(R)-2-[[Bis[(isopropoxycarbonyl)oxy]methoxy]-phosphinyl] methoxy]propyl]adenine fumarate (1:1), corresponding to the structural formula below:



The molecular formula of tenofovir DF is $C_{23}H_{34}N_5O_{14}P$ and its relative molecular mass 635.52 g/mol; the molecular formula of tenofovir is $C_9H_{14}N_5O_4P$ and its relative molecular mass 287.21 g/mol. Its pKa is 3.75 and the partition coefficient LogP is -1.25. It has one chiral centre at C-11 (the C-2 position of the propyl side-chain) and is produced as the R-enantiomer. Two crystal forms of tenofovir DF have been observed. The second crystal form is metastable and rapidly converts to the more stable predominant form in water. However, both forms have identical aqueous solubility and intrinsic dissolution rate. They can be distinguished by either DSC or XRD.

Manufacture

The synthetic process for tenofovir DF consists of four well defined steps. The synthetic process results in the stereoselective formation of an intermediate and thus the formation of the desired tenofovir DF R-enantiomer from a commercially available optically active starting material. The synthetic route is described in sufficient detail. The active substance is manufactured by four manufacturing sites. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The process has been shown able to consistently produce tenofovir DF that meets the required quality standards.

Batch analysis data is provided on 15 representative commercial scale batches produced with the proposed synthetic route from all proposed manufacturers. The data show that the active substance can be manufactured reproducibly by all proposed manufacturers.

Specification

Tenofovir DF specification includes tests and limits for appearance (visual), identification (tenofovir : IR, HPLC, fumaric acid: HPLC), clarity of solution (visual), water content (Ph. Eur.), enantiomeric purity (chiral HPLC), assay (HPLC), fumaric acid content (HPLC), impurities (HPLC), heavy metals (Ph. Eur.), residual solvents (GC) polymorphic form (DSC) and particle size (Laser Light Scattering). Analytical methods have been validated in accordance with ICH guidelines. Tenofovir DF is not amenable to analysis by sulfated ash / residue on ignition due to the variability caused in the testing by the phosphate group. As no inorganic catalysts are used in the synthesis, a visual test for clarity of solution is included to ensure that no foreign matter is present. Development data demonstrated the absence of indicator organisms and therefore as per ICH Q6 indicate that microbial testing of the drug substance is not required. The proposed testing and limits conform to current ICH guidelines and are acceptable from a toxicological and clinical perspective.

Batch analysis data on 15 representative commercial scale batches produced with the proposed synthetic route from all proposed manufacturers have been presented. The results are within the specifications and consistent from batch to batch.

Stability

Three batches from each proposed manufacturing site were placed on long-term stability studies at 5 °C for up to 36 months, and a minimum of one batch from each of the sites was placed on accelerated stability at 25 °C/60% RH for six months in the proposed packaging. An additional three batches from a fourth manufacturer not intended for registrations have been studied as above. Appearance, assay impurities and degradation, enantiomeric purity, water content and polymorphic form were tested using specific, stability-indicating methods.
No apparent change in the tested parameters neither any trend was observed for the twelve commercial batches of tenofovir DF after 36 months of storage at 5 °C and after accelerated storage at 25 °C/60% RH for 6 months.
A photostability study was conducted on one lot of drug substance exposed directly to light in accordance with ICH Q1B guideline. The photostability samples are analysed for appearance, purity, impurity and degradation product profile, enantiomeric purity and water content. The results from these studies indicate that tenofovir DF is not sensitive to light as no significant changes in physicochemical properties were observed.

Based on the long-term stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is considered acceptable.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Stribild is an immediate-release tablet containing elvitegravir 150 mg (EVG), cobicistat 150 mg (COBI), emtricitabine 200 mg (FTC), and tenofovir disoproxil fumarate (TDF) 300 mg (equivalent to 245 mg of tenofovir disoproxil). The fixed-dose combination product containing in a solid oral dosage form was designed in order to provide patient dosing convenience of a single tablet. The degradation pathways of the active substances, their biopharmaceutical performance and the size of the unit dose were also considered for the choice of dosage form for the fixed-dose combination product.

Prototype formulation matrices were evaluated and the results led to the selection of the current quantitative composition. Additionally, the physical separation of EVG and COBI from FTC and TDF using bilayer technology was chosen to reduce potential physicochemical interaction between them. The physical and chemical compatibility between the active substances used in the same layer have been established. Other approaches were also tried but the bilayer tablets proved the most successful from pharmaceutical and manufacture viewpoint. The polymorphism that EVG, FTC and TDF exhibit has been considered during the development. COBI is used adsorbed on silicon dioxide because unlike COBI in itself the moisture uptake for COBI on silicon dioxide is reversible, whereas COBI that has been exposed to high humidity undergoes deliquescence and becomes a rubber-like material that is difficult to process and which does not revert back to its original state. The isolation of COBI on a solid carrier (silicon dioxide) resulted in a switch from an organic solvent COBI solution used in the manufacture of the finished product to a solid COBI on silicon dioxide form. This change allowed the streamlining of the product manufacturing process. As a result of the change, the composition was modified by adjusting the excipients. A pivotal bioequivalence study was performed to evaluate the formulation and process change for the incorporation of the new COBI on silicon dioxide form which indicated that the Phase 3 intended commercial formulation (bilayer tablet, COBI on silicon dioxide), was bioequivalent to the formulation used in the Phase 1 and Phase 2 studies.

The degradation pathways for all the active substances have been studied and considered in the formulation design and development. For the further optimisation of the formulation, previous experience with the two known active substances (FTC and TDF) was taken into account together with new experimental information about the two new substances.

All the excipients used in Stribild formulation are commonly used and meet the standards defined in the current Ph. Eur. monographs, except for the silicon dioxide and the coating material. Both these are tested according to in-house standards, which are based on compendial requirements.

A discriminatory dissolution method has been developed. The interference of the four active substances and their degradation products/ impurities has been considered during the development and validation of the analytical methods.

The product manufacture has been designed to allow for the range of loading levels of COBI on silicon dioxide. Silicon Dioxide has specific use in this formulation apart from typical use as a glidant and it is used to adjust for the variability of COBI loading level on silicon dioxide.
The proposed commercial formulation and manufacturing process were optimised to identify the critical process parameters, critical quality attributes, and to define the manufacturing operating ranges. Design of experiments was used to establish proven acceptable ranges (PARs) and normal acceptable ranges (NORs) operating ranges. PARs and NORs for the elvitegravir tablet compression, and film-coating processes have also been established. Moving inside the PARs would be acceptable without regulatory post approval change assessment. However, it is reminded that in case of excursion of one process

parameter out of its normal operating range, but within the proven acceptable range, the other process parameters should be maintained at their target/ normal operating value.

Adventitious agents

None of the excipients used in the manufacture of Stribild tablets are of human or animal origin. Only lactose is obtained from cow's milk fit for human use. Appropriate BSE/TSE declarations from the manufacturers of excipients have been provided.

Manufacture of the product

The manufacturing process for the tablets involves preparation of two separate blends, granulation tableting and film coating steps.The process optimization studies were conducted on the granulation process tablet compression and film-coating processes.
The process, which is considered a "non-standard", is well described, the critical steps have been identified, suitable in-process controls have been set and holding times for intermediates have been established.
The robustness of the manufacture has been demonstrated by successful process validation of 3 representative batches at the lower end for the proposed batch size range. Process validation will be completed at the high end of the batch size range according to an agreed protocol.

Product specification

The finished product release specifications include appropriate tests for appearance (visual examination), identification (HPLC and TLC), assay (UPLC), uniformity of dosage unit (Ph. Eur.), degradation products (UPLC), water content (Ph. Eur.) and dissolution (Ph. Eur.).

The drug product is not tested for microbial purity, because the active substances inhibit microbial growth and sufficient data has been provided in this respect as required by the relevant Ph. Eur. monograph. Appropriate dissolution acceptance criteria for each of the active ingredients in the tablets were determined by evaluating development and clinical batches produced during manufacturing. Analytical procedures have been validated according to ICH Q2A guidelines.

Batch analysis results are submitted for 4 commercial scale and 4 smaller batches used throughout development. The batch analysis data are within the set specification limits and show that the Stribild tablets can be manufactured reproducibly.

Stability of the product

Four commercial scale and one smaller batch in the proposed packaging were placed on stability according to ICH guidelines under the following conditions: long term 25°C ±2°C / 60% ±5% RH, intermediate 30°C ±2°C / 75% ±5%RH and accelerated 40°C ±2°C / 75% ±5% RH. Results were provided for up to 36 months in long term and intermediate conditions and for 6 months in accelerated. The drug product remained within the acceptance limits of the specification for appearance, strength, degradation product content, dissolution, and water content following 36 months of long-term storage. Analytical methods used were validated and stability indicating. No elvitegravir-related degradation products were observed. The degradation products observed for the other three substances were as expected and were within the limits for the 36 month period. The stability profile in intermediate conditions was comparable to the long term.

There was no significant change in the dissolution profiles upon storage for elvitegravir, cobicistat, emtricitabine and tenofovir DF. The water content also remained within the limits and no change in product appearance was observed for all four primary stability lots.
Under accelerated conditions no significant changes were observed on all the stability attributes after six months including dissolution, water content and degradation products.
Photostability of the tablets has been assessed per the ICH Q1B, Guideline. The assay and degradation product content were not significantly different between the light and dark control samples. No changes in appearance, dissolution, and water content were observed following exposure to light. The results of the study indicate that Stribild tablets are not sensitive to light.
Additional stress studies under extreme temperature and humidity conditions were performed at 50 °C/ambient humidity and at 25°C/80% RH for six weeks. To assess in-use stability, the tablets were also stored in open containers at 25°C/60% RH and 30°C/75% RH for six weeks. The stability data acquired at the long-term storage conditions remained within the specified acceptance criteria and supported the proposed shelf-life.

The overall stability results support the proposed shelf life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Stribild is a complex formulation containing four different active substances.
Information on development, manufacture and control of each of the active substances has been presented in a satisfactory manner.
Development of the drug product has presented a number of challenges arising from the particular characteristics of the individual active substances and most importantly the need to ensure a physically and chemically stable form of cobicistat and to avoid interactions between the four drug substances.
The choice of formulation, of excipients and the manufacturing process has been extensively justified.
The degradation pathways of the four active substances have been sufficiently studied and taken into account in the design of the finished product. Possible interference during analysis testing has been also addressed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive non-clinical toxicology program has been previously undertaken in support of the registration of FTC and TDF. For EVG and COBI, the toxicology package included repeated-dose oral

toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), dogs (up to 39 weeks), *in vitro* and *in vivo* genotoxicity studies; 2-year oral carcinogenicity studies in mice and rats; and a full developmental and reproductive toxicity program.

The pivotal toxicology and the majority of the safety pharmacology studies conducted by the applicant were reported to be GLP compliant. The safety studies that were not conducted to GLP were conducted to an appropriate scientific standard.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamic effect of cobicistat (COBI) is inhibition of human CYP3A enzymes, whereby the IC_{50} value for inhibition of human hepatic microsomal midazolam 1'-hydroxylase activity is 0.15 µM. The inhibition of CYP3A enzymes in human hepatocytes was time-dependent and co-factor (NADPH)-dependent). Elvitegravir (EVG) inhibited DNA strand-transfer with an IC_{50} value of 8.8 nM and inhibited laboratory strains and various clinical isolates of HIV-1 with an EC_{50} of 0.38 nM. Emtricitabine (FTC) is a nucleoside analogue of cytidine. Tenofovir disoproxil fumarate (TDF) is converted *in vivo* to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Both FTC and tenofovir act as inhibitors of HIV reverse transcriptase.

Secondary pharmacodynamics studies

Elvitegravir did not inhibit the activity of human topoisomerase I and II enzymes, cellular enzymes that display analogous activities to the viral integrase activity. The previously approved anti-virals, FTC and TDF had a high selectivity for HIV reverse transcriptase and were very weak inhibitors of mammalian DNA polymerases α, β, δ, ε, and mitochondrial DNA polymerase γ.

Elvitegravir, COBI, FTC, and TDF demonstrated low cytotoxicity in a variety of human cell types. Nucleoside reverse transcriptase inhibitors carry a class labelling for mitochondrial toxicity; however, both FTC and TDF have shown a low potential for mitochondrial toxicity in long term toxicity studies. The potential for mitochondrial toxicity of EVG was considered low based on assessment of the mitochondrial DNA levels in HepG2 liver cells and the potential for mitochondrial toxicity by COBI is also considered to be low. As EVG and COBI are not anticipated to significantly increase the exposure of FTC and TDF, the potential for mitochondrial toxicity with the EVG/COBI/FTC/TDFD combination is low.

Elvitegravir, FTC, and TDF exhibited no pharmacologically significant affinity at the secondary targets tested, while significant binding to the hCav1.2 L-type calcium channel (IC_{50} 6 µM), hERG potassium channel (IC_{50} 1.8 µM), and the hNav1.5 sodium channel site-2 (IC_{50} 86.5 µM) was observed with COBI. The effective concentrations for binding to these targets were ≥20-fold higher than that proposed in humans following administration of COBI at 150 mg (assuming 6.3% unbound drug).

Safety Pharmacology Programme

EVG, FTC, and TDF had little effect on vital organ systems in safety pharmacology studies. Cobicistat showed the potential to decrease LV function and prolong the PR interval in the isolated rabbit heart at concentrations approximately 11-fold higher than those observed clinically; these effects are likely due to the observed interaction with cardiac calcium channels. No significant changes in ECG parameters or LV function were observed clinically; hence, the potential of COBI to decrease LV function and prolong PR is considered to be low. Given the favourable safety pharmacology profiles of EVG, FTC, and TDF,

combination of these 3 agents with COBI is not expected to exacerbate the potential for minor cardiovascular effects with COBI.

2.3.3. Pharmacokinetics

A series of method validation, absorption, distribution, metabolism, excretion and pharmacokinetic drug interaction studies have been conducted. Modest to high absorption was observed in animals following oral administration of EVG, COBI, FTC and TDF. Studies in the dog demonstrated that generally comparable exposures for each of the 4 components can be achieved through co-formulation, relative to co-administration of the individual clinical formulations. With respect to the new active substances, EVG showed moderate oral bioavailability in the rat and dog (with values similar in fasted and non-fasted animals), while the bioavailability of COBI was moderate in the rat and low in the dog in monkey (due to high first pass metabolism in these species).

Following oral administration, all 4 components were widely distributed and it was noted that for both EVG and COBI, drug-related material was largely excluded from the brain and the eye. Although plasma protein binding of EVG is high, the binding is very low for FTC and TFV, and moderate for COBI; hence, interactions via binding displacement are not anticipated. An *in vivo* study whereby [^{14}C]EVG was co-administered with RTV, revealed no change in the tissue distribution of EVG, and no increase in CNS penetration of EVG. Hence, the potential for drug interactions, within the 4 drug combination, that would affect drug distribution is considered to be low.

Elvitegravir is largely eliminated by oxidative metabolism by CYP3A (the major route) and by glucuronidation (minor route) by UGT1A1 and 1A3. When administered with a CYP3A inhibitor, such as COBI, oxidative metabolism is blocked and the resulting bioavailability and half-life of EVG are compatible with once-daily dosing. In the rat and dog, M1 (GS-9202, p-hydroxylated- EVG) was identified as the most abundant metabolite, followed by M4 (GS-9200, EVG acyl glucuronide) and M7 (JTP-74488, M1 glucuronide); however the parent compound, EVG was the most abundant component circulating in plasma.

Cobicistat is a potent time-dependent and co-factor-dependent inhibitor of human CYP3A enzymes, in contrast to its effect in non-clinical species, whereby the clearance of COBI is high due to a lack of self-inhibition of metabolism. The primary routes of metabolism of COBI are oxidation by CYP3A (major) and CYP2D6 (minor) enzymes and COBI was extensively metabolized in all species examined, including humans. The parent compound, COBI was the major component in plasma. Metabolites M21, M26, and M31 were identified in mouse, rat, dog, and human samples *in vitro*, and were later identified in the excreta from these species. M31 [GS-9612 (oxidation of isopropylthiazole), E3], was identified as the most abundant metabolite in the mouse, rat, and dog. One other primary metabolite, M39, was also identified in all species *in vivo*. Other metabolites arise from secondary metabolism, due to combinations of these primary pathways, and from other minor primary metabolites. There were no unique or major (> 10%) human metabolites.

The intended pharmacokinetic drug interaction of inhibition of the CYP3A dependent metabolism of EVG by COBI has been studied extensively *in vitro* and in humans *in vivo*. In the rat, following co-administration with COBI at 30 mg/kg/day, exposures to EVG (AUC) were increased in males (when compared to that observed when EVG was administered alone) on Day 1. The effect was less pronounced in females due to the lower contribution of CYP3A to EVG metabolism.

Non-clinical and clinical data suggest that COBI is a relatively selective inhibitor and has a low potential to be an inducer in man. The metabolites of COBI are weaker inhibitors of CYP3A compared to COBI and due to their low systemic concentrations should not contribute to the primary pharmacodynamic effect of CYP3A inhibition. Neither FTC nor TDF interact with drug metabolizing enzymes as substrates, inhibitors,

or inducers and that suggests that metabolic drug interactions between these agents and EVG or COBI are unlikely.

EVG and COBI were identified as inhibitors of OATP1B1 (IC_{50} value 3.5 µM) and OATP1B3 (IC_{50} values 1.88 µM), and were subsequently identified as substrates of the hepatic transporters *in vitro*. The data presented do not suggest significant clinical implications with respect to the exposures of the Stribild components. However, when the two agents were co-administered with the OATP substrate, rosuvastatin, modest increase in rosuvastatin exposure was observed.

Emtricitabine did not undergo extensive first pass or systemic metabolism, and was eliminated primarily by renal excretion of unchanged drug. The total body clearance of FTC exceeded the glomerular filtration rate, suggesting the drug is actively secreted by renal tubules into the urine. Renal excretion was the primary systemic route of elimination of TFV in all non-clinical species tested. Since FTC and TFV are almost exclusively eliminated by renal excretion, while very little EVG or COBI is excreted in the urine; it is considered that the potential for interactions between the compounds during excretion is low.

Cobicistat and EVG are weak inhibitors of intestinal efflux transporters; however, high concentrations of COBI in the intestinal lumen, which are achievable briefly during absorption, may inhibit P-gp and result in a modest increase in TFV exposure (as seen with RTV-boosted protease inhibitors and Stribild). Cobicistat inhibits the renal efflux transporter, novel organic cation transporter 1 (OCTN1; IC_{50} 2.49 µM) at concentrations that are within range of the total C_{max} (1.57 µM). Cobicistat is also an *in vitro* inhibitor of the renal transporters, OCT2 (IC_{50} 14.4 µM) and MATE1 (IC_{50} 1.87 µM), which have been shown to transport creatinine and are thought to play a role in the active secretion of creatinine by the kidney (in addition to the majority of creatinine which is renally excreted by passive glomerular filtration). In a subsequent study EVG was also shown to inhibit OCT2 (IC_{50} >20 µM) and MATE1 (IC_{50} 2 µM). Inhibition of OCT2 and/or MATE1, and thus inhibition of active secretion of creatinine by the kidney, provides a plausible mechanistic explanation for the reduction in creatinine clearance seen during COBI dosing, in the absence of changes of true GFR. It was noted that Stribild did not have a more pronounced effect on MATE1 than COBI alone.

In accordance with the Guideline on the Investigation of Drug Interactions, the effects on additional transporter systems have been performed. A detailed overview of the potential pharmacokinetic interactions between the constituents suggests that aside from the interactions listed previously, the potential for clinically relevant interactions at the level of CYP enzymes or any of the remaining transporter systems are low.

2.3.4. Toxicology

Single dose toxicity

Acute toxicity studies conducted using the oral route with EVG didn't induce mortality in animals even at very high doses (up to 2000 mg/kg). Emesis was described in dogs after oral administration that wasn't observed after IV injection. Hypoactivity was described in mice receiving 300 mg/kg COBI PO. No signs of toxicity were described with FTC in rats at doses up to 4000 mg/kg PO. Renal toxicity since 90 mg/kg was observed in dogs treated with TDF.

Repeat dose toxicity

The repeated-dose studies demonstrate that EVG is well tolerated for up to 6 months in the rat and 9 months in the dog at doses producing systemic exposure levels in animals 2.3- to 36-fold greater than

those in patients treated with the recommended clinical dose. No adverse target-organ toxicity was observed in single- or repeated-dose studies with EVG.

Treatment-related effects included changes in cecum weights, dilation of the cecum, and the presence of lipid vacuoles in the lamina propria of the upper small intestines of rats and dogs. In these species, changes in the cecum were not accompanied by any histological changes or gastrointestinal (GI) adverse events. Similar changes in the cecum have been reported with antibacterial quinolones which affect the GI microflora. Elvitegravir has a quinolone moiety and was confirmed to have antibacterial activity in the reverse mutation assay. Although the activity was much weaker than that of the antibacterial quinolones, the changes in the cecum were considered to be due to the anti-bacterial activity of high local concentrations of EVG in the GI tract.

The incidence and severity of lipid vacuoles in the upper small intestines did not increase with repeated dosing of EVG, which was questioned by the CHMP as the 13-week rat study suggested otherwise. However, it was evident that there was no evidence of toxicity or any adverse tissue reactions associated with these vacuoles. The vacuolization is considered related to the high local EVG concentrations to which the GI epithelium was exposed. These effects were not considered adverse and in most cases, these minor effects were slowly reversible after a recovery period. It is noted that this finding occurs at exposures similar and in excess to those observed clinically. However, in the 2-year rat carcinogenicity study there were no notable findings in the upper small intestine, further suggesting that the presence of the vacuoles was not adverse or of toxicological significance.

Target organs identified for COBI were the liver (mouse, rat, and dog) and thyroid (rat). Slight, non-adverse hematological changes were noted in rats and slight clinical chemistry changes were observed in mice, rats, and dogs, with urinalysis changes noted primarily at high doses in rats and dogs. In rats, the thyroid changes are considered rodent-specific, secondary to microsomal enzyme induction and thyroid hormone imbalance, and it is unlikely that COBI presents a risk to the human thyroid. Liver changes in mice, rats, and dogs included microsomal enzyme induction, increased weights, and hepatocellular hypertrophy and/or vacuolation. All effects appeared to be completely reversible after a 1- or 3-month recovery period and were considered to be adaptive responses. Urinalysis changes (higher urine volume, lower urine specific gravity, increases in electrolyte excretion) showed no progression after long term dosing, were not associated with remarkable serum chemistry or histopathological correlates, and were reversible. Other potential toxicities related to COBI that were observed in non-clinical studies include PR interval prolongation in the 4-week dog toxicity study and decreases in left ventricular (LV) function in isolated rabbit hearts.

Combination toxicity studies of COBI with EVG did not result in unexpected or additive toxicity.

For the currently authorised compounds: emtricitabine has an established clinical safety profile with no significant toxicities observed. The only toxicity observed in chronic animal studies with FTC was mild, reversible anaemia in mice and minor decreases in erythrocyte counts/increases in mean corpuscular haemoglobin in monkeys at large multiples of clinical exposure (137-fold in mice; 21-fold in monkeys); therefore, these haematological findings are not considered relevant to clinical use and in theory, should not cause an overlapping toxicity with COBI that produced minimal decreases (< 10%) in red blood cell parameters in rats at the maximum doses tested.

For tenofovir disoproxil fumarate (TDF), the principal target organs of toxicity following oral administration were the kidney (karyomegaly, tubular degeneration), bone, and GI tract (in rodents). These correlate with the known clinical toxicities of TDF (renal and bone toxicity). It is noted that cobicistat was associated with urinalysis and urine chemistry changes (increased urine volume; decreased urine specific gravity; increased electrolyte excretions) at high doses in rats and dogs. However, these changes showed no progression after long-term dosing, were reversible, were not

associated with remarkable clinical chemistry changes, including serum creatinine and BUN, and were without morphological evidence of kidney damage.

GI toxicity is dose limiting in rodents for TDF, and was due to high local concentrations. For EVG, changes in the cecum and upper small intestine in rats and dogs were due to high local concentrations and were not considered adverse. It is noted that in some instances, erosion of the stomach has been reported following repeated administration of COBI. However, these findings were not observed in the pivotal studies or in the 2-year carcinogenicity studies; hence the potential for additive effects on the gastrointestinal tract is considered to be low.

Cobicistat, EVG, and FTC have not shown any potential for bone toxicity in chronic rat and dog toxicity studies; thus the non-clinical data do not predict any exacerbation of any TDF effects on bone.

Genotoxicity

Of the 4 compounds, only TDF was genotoxic (mouse lymphoma cell assay and UDS assay). Although EVG showed an equivocal effect in an *in vitro* chromosome aberration study, it was negative in 2 *in vivo* micronucleus studies and is unlikely to have the potential to induce chromosome aberrations *in vivo*. The combination of FTC and TDF in a mouse lymphoma cell assay did not exacerbate the genotoxic potential of TDF. Given the findings presented, the EVG/COBI/FTC/TDF combination is should not alter the genotoxicity profile of the individual agents.

Carcinogenicity

Elvitegravir, FTC and TDF have all demonstrated low carcinogenic potential in conventional 2-year studies. COBI was not genotoxic and in the mouse, COBI was not carcinogenic at exposures that were 7-to 16-fold higher than those observed clinically. In the rat, following repeated oral administration for a minimum of 97 weeks at 10, 25, and 50 mg/kg/day (males) and 5, 15, and 30 mg/kg/day (females), COBI caused an increased incidence of combined thyroid follicular cell adenoma and carcinomas at exposures (AUC) that were lower than that observed clinically. It is acknowledged that the thyroid and liver changes are considered adaptive changes, secondary to hepatic microsomal enzyme induction due to activation of PXR. Given that this extent of activation of PXR and CYP3A does not occur at clinically relevant concentrations in humans, COBI is not considered to pose a carcinogenic risk in man.

Reproduction toxicity

Elvitegravir, COBI, FTC, and TDF were not teratogenic reproductive and developmental toxicity studies. However, TDF reduced the viability index and weight of pups in peri and –post natal toxicity studies at maternally toxic doses. In addition, cobicistat at 125 mg/kg/day increased in post implantation loss and decreased foetal weights also at maternally toxic doses.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant has conducted a full environmental risk assessment and the results are summarised in the tables below.

For the adsorption-desorption study, the K_d and K_{OC} values for EVG exceed the trigger values. Hence the applicant has agreed to progress to Phase IIb of the assessment. An environmental risk assessment for the terrestrial compartment including an OECD 307, OECD 216, OECD 208, OECD 207 and a Collembolan reproduction test (ISO 11267) will be performed by the applicant. During the studies performed to evaluate transformation in aquatic sediment systems, as sediment shifting of the drug substance (which

is a new active substance) was demonstrated (sediment shifting > 10%) with both EVG and COBI, the effects on sediment organisms will be investigated further. In addition, the Applicant has agreed to conduct a tailored environmental risk assessment for tenofovir, including an adsorption/desorption study (OECD 106), transformation studies in aquatic sediment systems (OECD 308) and an Early-Life Stage Toxicity Test (OECD 210). Transformation products ≥10% will be fully characterized. These additional studies will be provided by Q2 2015.

Table 1. Summary of main study results on EVG

Substance (INN/Invented Name): EVG					
CAS-number (if available):					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD117	3.39-4.33			Not > 4.5; not PBT.
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	For Fpen (1%): 0.75 For Fpen (with from data Etonie): 0.0085	µg/l			Then > 0.01 µg/l
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	Koc soil: 25500-10400L/Kg Kd sludge: 10400L/Kg			But Koc of EVG is very high and above the limit of 10000L/Kg (EMEA/CHMP/4447/00). EVG has a good adsorption on soils and sludge.
Ready Biodegradability Test	OECD 301	Not readily biodegradable (28d: 0-2.5% mineralization)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	>10% fixed in sediment from Day 7 System DT50 6-53 days Water DT50 2-3 days Sediment DT50 (degradation) >100 days No metabolites			EVG is highly localised in the sediment (with more 10% found after 7 days).
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae Growth Inhibition *Pseudokirchneriella subcapitata*)	OECD 201	NOEC	162	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	390	µg/L	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	206	µg/L	
Activated Sludge	OECD 209	NOEC	≥ 500	mg/L	
Phase IIb Studies :					
Bioaccumulation	OECD 305	BCF	<10		The reports are not complete.

Table 2. Summary of main study results on COBI

Substance (INN/Invented Name): COBI			
CAS-number (if available):			
PBT screening		Result	Conclusion

Bioaccumulation potential- log K_{ow}	OECD122	3.05-4.10			Not > 4.5; not PBT.
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	For Fpen (1%): 0.75 For Fpen (with from data Etonie): 0.0085	µg/l			Then > 0.01 µg/l
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	Koc soil: 3624-9012L/Kg Koc sludge: 830-1287L/Kg			No high adsorption with COBI.
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	>10% fixed in sediment from Day 7 DT50 (dissipation) > 30 days DT50 (degradation) >30 days No metabolites			COBI is highly localisated in the sediment (with more 10% found after 7 days).
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae Growth Inhibition *Pseudokirchneriella subcapitata*)	OECD 201	NOEC	29.3	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	17.5	mg/L	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	4.84	mg/L	
Activated Sludge	OECD 209	NOEC	≥ 1000	mg/L	
Phase IIb Studies :					
Bioaccumulation	OECD 305	BCF	<2		The reports are not complete.

Table 3. Summary of main study results on FTC

Substance (INN/Invented Name): FTC					
CAS-number (if available):					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD122	-0.694-0.670			Not > 4.5; not PBT.
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	For Fpen (1%): 1 For Fpen (with from data Etonie): 0.11	µg/l			Then > 0.01 µg/l
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	Koc sludge: 12.9L/Kg			No high adsorption with FTC.
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	>10% fixed in sediment from Day 7 DT50 (dissipation) 36-151 days DT50 (degradation) >100 days No metabolites			FTC is highly localisated in the sediment (with more 10% found after 7 days).
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae Growth Inhibition *Pseudokirchneriella subcapitata*)	OECD 201	NOEC	110	mg/ L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	110	mg/ L	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	6.10	mg/ L	
Activated Sludge	OECD 209	NOEC	≥ 1000	mg/ L	
Phase IIb Studies :					
Bioaccumulation	OECD 305	BCF			

Table 4. Summary of main study results on TDF

Substance (INN/Invented Name): TDF					
CAS-number (if available):					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD122	0.992-1.18			Not > 4.5; not PBT.
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	For Fpen (1%): 1.5 For Fpen (with from data Etonie): 0.17	µg/l			Then > 0.01 µg/l
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	Koc soil: 18L/Kg			No high adsorption with TDF.
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	>10% fixed in sediment from Day 7 DT50 (dissipation) 0.5-2.24 days DT50 (degradation) >100 days No metabolites			TDF is highly localisated in the sediment (with more 10% found after 7 days).
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae Growth Inhibition *Pseudokirchneriella subcapitata*)	OECD 201	NOEC	14	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	13	mg/L	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	1.9	mg/L	
Activated Sludge	OECD 209	NOEC	600	mg/L	
Phase IIb Studies :					
Bioaccumulation	OECD 305	BCF			

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed by Q2 2015:

- Update the environmental risk assessment to clarify the effects of EVG on the terrestrial compartment, the effects of EVG and COBI on sediment dwelling organisms, the transformation products of tenofovir disoproxil fumarate and the effects of tenofovir on the environment.

2.3.6. Discussion on non-clinical aspects

The primary pharmacology and pharmacodynamic drug-drug interaction package for the anti-viral agents EVG, FTC and TDF are considered adequate and is further discussed in clinical pharmacology. No serious concerns rise from the studies on secondary pharmacodynamic effects. The safety pharmacology data support the effective and safe use of these 4 agents together in combination for treatment of HIV-1.

PK data showed that generally comparable exposures for each of the 4 components can be achieved through co-formulation and that the potential for drug interactions, within the 4 drug combination, that would affect drug distribution is considered to be low.

Elvitegravir is largely eliminated by oxidative metabolism by CYP3A (the major route) and by glucuronidation (minor route) by UGT1A1 and 1A3. *Cobicistat* is a potent time-dependent and co-factor-dependent inhibitor of human CYP3A enzymes, in contrast to its effect in non-clinical species, whereby the clearance of COBI is high due to a lack of self-inhibition of metabolism. The primary routes of metabolism of COBI are oxidation by CYP3A (major) and CYP2D6 (minor) enzymes. The pharmacokinetic drug interaction of inhibition of the CYP3A dependent metabolism of EVG by COBI is the intended effect of COBI. COBI is a relatively selective inhibitor of CYP3A and has a low potential to be an inducer in man. The potential for interactions between the compounds during excretion is considered to be low. Cobicistat and EVG are weak inhibitors of intestinal efflux transporters. Cobicistat also inhibits the renal efflux transporter, novel organic cation transporter 1 (OCTN1) at concentrations that are within range of the total C_{max}. Cobicistat is also an *in vitro* inhibitor of the renal transporters, OCT2 and MATE1. Inhibition of OCT2 and/or MATE1, and thus inhibition of active secretion of creatinine by the kidney, provides a plausible mechanistic explanation for the reduction in creatinine clearance seen during COBI dosing, in the absence of changes of true GFR. When EVG and COBI were co-administered with an OATP substrate, rosuvastatin, modest increase in rosuvastatin exposure was observed.

Aside from the identified potential interactions, the potential for clinically relevant interactions at the level of CYP enzymes or any of the remaining transporter systems is considered to be low. In addition, as indicated in the Risk Management Plan, further studies to confirm the potential for inhibition of UGT enzymes are being performed by the Applicant and the results are to be provided to the CHMP. The potential for pharmacokinetic interactions between the constituents and other concomitant medicinal products is summarized in Section 4.5 of the SmPC.

No adverse target-organ toxicity was observed in single- or repeated-dose studies with EVG. The observed EVG treatment-related effects of changes in cecum weights, dilation of the cecum, and the presence of lipid vacuoles were found not to be of toxicological significance.

Target organs identified for COBI were the liver (mouse, rat, and dog) and thyroid (rat). The thyroid changes In rats were considered rodent-specific, and it is unlikely that COBI presents a risk to the human thyroid. Liver changes in mice, rats, and dogs appeared to be completely reversible after a 1- or 3-month recovery period and were considered to be adaptive responses. Other potential toxicities related to COBI that were observed in non-clinical studies include PR interval prolongation in the 4-week dog toxicity study and decreases in left ventricular (LV) function in isolated rabbit hearts.

Potential toxicities related to COBI observed in the non-clinical studies (decreases in LV function, urinalysis and urine chemistry changes, immunosuppressive effects [lower anti-KLH IgG antibody titers] in female rats, and adaptive liver and thyroid changes), have not been observed in Phase 1 and 2 clinical studies conducted to date with COBI or with the EVG/COBI/FTC/TDF STR. Cobicistat has the potential to prolong the PR interval; a modest, dosing-related increase in PR interval observed in the thorough QT study which was not considered to be clinically significant.

For the currently authorised compounds: emtricitabine has an established clinical safety profile with no significant toxicities observed. For tenofovir disoproxil fumarate (TDF), the principal target organs of toxicity following oral administration were the kidney (karyomegaly, tubular degeneration), bone, and GI tract (in rodents). These correlate with the known clinical toxicities of TDF (renal and bone toxicity).

It has been suggested that there is little potential for exacerbation of the observed toxicity, when all 4 components of Stribild are co-administered, as the components do not appear to have overlapping toxicity profiles.

Although, the non-clinical data presented do not currently suggest a potential for exaggerated renal toxicity with Stribild, COBI and EVG is associated with inhibition of human renal transporters OCT2, MRP4, and MATE2-K (COBI only). Moreover there is evidence of increased renal toxicity with Stribild in man. Preliminary data suggest that FTC, COBI and EVG do not affect the cytotoxicity of TFV in renal proximal tubule cells and that COBI has no effect on TFV accumulation in isolated renal cortical tissue. In line with the Risk Management plan, the Applicant is in the process of conducting additional studies in order to elucidate the mechanism for the renal toxicity observed with the 4 components of Stribild.

The CHMP noted that EVG possesses a quinolone moiety within its structure and consequently possesses some antibiotic properties as demonstrated in the Ames test. It is unlikely that the antibacterial properties of EVG would have a major impact on the risk-benefit for Stribild. However, the Applicant has been recommended to conduct additional studies to determine the EVG MIC for a number of common bacteria in the human gut and assess MICs in light of its estimated intra-colonic concentrations. The interpretation of the results will need to be measured against the lack of evidence that any effect of EVG on gut flora that may occur has any clinical consequences.

Given the findings presented, the EVG/COBI/FTC/TDF combination is should not alter the genotoxicity profile of the individual agents. Elvitegravir, FTC and TDF have all demonstrated low carcinogenic potential in conventional 2-year studies and COBI is not considered to pose a carcinogenic risk in man.

Although, the potential for the EVG/COBI/FTC/TDF combination to have additive effects on the foetus is considered to be low, the observed effects on foetal weight and viability are captured within Section 5.3 of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

Overall, there are no major objections on the non-clinical aspects to the approval of this application. The outstanding issues are minor and do not preclude recommendation for granting a Marketing Authorisation.

The CHMP considers the following non-clinical measures necessary post-authorisation, which are included in the Risk Management Plan:

- In vitro studies to assess the potential for EVG to inhibit UGT1A1, UGT1A3 and UGT2B7 (by Q2 2013).
- Studies to investigate the possible mechanisms that could lead to an additive or synergistic toxic effect of COBI + TDF on renal tubular function and/or a decrease in the aGFR during Stribild therapy (by Q3 2013)

In addition the CHMP recommends the Applicant to conduct the following measures post-authorisation to elucidate potential concerns regarding the antibacterial properties and regarding the environmental risk assessment:

- Additional studies to investigate the effects of EVG on aerobic and anaerobic species found in the gut and to compare these with estimated intra-colonic concentrations of EVG (recommended by Q1 2014).
- An updated environmental risk assessment which clarifies the effects of EVG on the terrestrial compartment, the effects of EVG and COBI on sediment dwelling organisms, the transformation products of tenofovir disoproxil fumarate and the effects of tenofovir on the environment (recommended by Q2 2015).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

There was an extensive assessment of the pharmacokinetics of the two new active substances – the integrase inhibitor elvitegravir (EVG) and the pharmacokinetic enhancer cobicistat (COBI) – and some studies with Stribild itself. The most important studies for the application are summarised below.

Table 5.

PK and DDI	
EVG	XAX1-1 safety and PK of EVG after single oral administration.
	XAX1-2 safety and PK of EVG after single oral administration of solid dispersion formulation of EVG.
	GS-US-183-0152 steady-state PK; confirmed dose of EVG/r in HIV-1 infected ARV-experienced adolescents.
	GS-US-183-0126 mass-balance study of EVG/r.
	GS-US-183-0103 evaluated PK of EVG, FTC or TFV on co-administration of EVG/r and TVD
	GS-US-183-0111 multiple-dose DDI EVG/r and didanosine (ddI) or d4T.
	GS-US-183-0112 multiple-dose DDI EVG/r and etravirine.
	GS-US-183-0115 multiple-dose DDI EVG/r and abacavir (ABC) sulfate.
	GS-US-183-0118 multiple-dose DDI EVG/r and maraviroc.
	GS-US-183-0120 multiple-dose DDI EVG/r and darunavir (DRV)/r.
	GS-US-183-0123 multiple-dose DDI EVG/r and fosamprenavir (FPV)/r.
	GS-US-183-0125 multiple-dose DDI EVG and rifabutin.
	GS-US-183-0147 multiple-dose DDI EVG and ATV.
	GS-US-183-0102 EVG 100 mg after single and multiple oral dosing +/- RTV 100 mg.
	GS-US-183-0113 dose response of RTV on CYP3A activity and EVG PK.
	GS-US-183-0146 effect of a second, potent CYP3A (and UGT1A1) inhibitor (ketoconazole) on boosted EVG.
	GS-US-183-0119 effect of acid-reducing agents on EVG.
	GS-US-183-0106 and -0108 effect of ATV/r on boosted EVG.
	GS-US-183-0116 multiple-dose DDI EVG/r and LPV/r.
COBI	GS-US-216-0116 2 formulations of COBI tablets and PK of EVG tablets administered with COBI tablets.
	GS-US-216-0110 relative bioavailability and PK of ATV co-administered with COBI versus RTV.
	GS-US-216-0115 relative bioavailability and PK of DRV co-administered with COBI versus RTV.
	GS-US-216-0119 twice-daily COBI alone; DRV and TPV administered twice-daily with COBI or RTV.
	GS-US-201-0101 GS-8374 administered in combination with COBI.
	GS-US-216-0111 mass-balance study of COBI.
	GS-US-216-0112 effect COBI on selected P450 enzymes and Pgp or MDR1
	GS-US-216-0101 dose-ranging study that evaluated the safety, tolerability, and PK/PD of COBI.
	GS-US-216-0113 evaluated the PK, safety, and tolerability of COBI in healthy volunteers.

EVG and COBI	GS-US-201-0104 evaluated the PK of EVG and COBI when co-administered with DRV.
	GS-US-216-0123 evaluated unboosted ATV, rosuvastatin and dose-reduced rifabutin on EVG and COBI.
	GS-US-216-0120 and -0122 evaluated the effect of acid-reducing agents on EVG and EVG/COBI.
STRIBILD	GS-US-236-0106 evaluated the drug-drug interaction of the STRIBILD and hormonal contraceptives.
Special Populations	
EVG and COBI	GS-US-183-0133 evaluated the PK of EVG/COBI in subjects with moderate hepatic impairment.
	GS-US-216-0124 evaluated the PK of EVG/COBI in subjects with varying degrees of renal impairment.
Food Effect	
STRIBILD	GS-US-236-0105 effect of food on EVG, COBI, FTC, and TFV when administered as the STRIBILD.
Biopharmaceutics	
EVG	GS-US-183-0140 multiple-dose relative bioavailability of a test formulation of EVG/r.
	GS-US-183-0121 relative bioavailability of various formulations of EVG/r.
STRIBILD	GS-US-236-0101 bioavailability of EVG boosted with COBI, FTC and TFV administered as the STRIBILD. GS-US-236-0110 bioavailability of new vs. original STR formulations.

During the procedure the applicant completed an additional DDI study between TDF and COBI (GS-US-216-0134) and data were reported from two studies ongoing at the time of submission as follows:

Table 6.

GS-US-216-0125	Phase 1 study evaluating the drug interaction potential between once-daily cobicistat-boosted elvitegravir and methadone or buprenorphine/naloxone.	November 2012.
GS-US-236-0120	Phase 1 multiple-dose pharmacokinetic switch study of cobicistat-boosted elvitegravir administered as QUAD following treatment with efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®).	Completed. Study report available Q2 2012.

- Stribild is presented for use as a bilayer tablet – one layer contains EVG/COBI and one FTC/TDF.
- The EVG/COBI layer was developed in accordance with the planned standalone tablet formulations and involved changes over time. In study GS-US-236-0101 COBI 150 mg administered as part of Stribild was found to boost EVG exposure to levels similar to those obtained with EVG/r. This formulation was used in the Phase 2 study GS-US-236-0104.
- Subsequently the isolation of COBI on a solid carrier resulted in a switch from an ethanolic solution to a solid form (i.e. COBI on silicon dioxide) in the manufacturing process. Study GS-US-236-0110 compared this proposed commercial formulation (used in Phase 3 studies GS-US-236-0102 and -0103) with the original formulation.

Elvitegravir

The bioanalytical method involved SPE from human plasma and LC-MS/MS with positive ionisation. Initially, calibration curves ranged from 1 (LLQ) to 1000 ng/mL. The fully validated bioanalytical method gave calibration curves from 20-10,000 ng/mL. A similar assay method applied to urine samples gave calibration curves that ranged from 32.5 (LLQ) to 1300 ng/mL.

COBI

The method involved SPE followed by LC-MS/MS with positive ionisation. Initial calibration ranged from 5 (LLQ) to 1000 or 2500 ng/mL. In a later version the range was 10-5000 ng/mL. The range for GS-8374 was 20-10000 ng/mL and for GS-9612 was 5-2500 ng/mL while that for GS-341842 and GS-342006 was 5-5000 ng/mL.

Bioavailability

EVG

XAX1-1 evaluated single unboosted doses from 100 mg to 800 mg (using 50 mg or 200 mg tablets) in fasted Japanese males. C_{max} and AUC_{inf} of EVG and M4 increased in a less than dose-proportional manner with dose proportionality constants β of 0.723 and 0.789, respectively, and 95% CIs for both parameters that did not include 1. The plasma exposures (AUC_{inf}) of M4 were < 10% of EVG. **XAX1-2** was of similar design but evaluated 50 - 400 mg doses as 50 mg solid dispersion tablets the EVG dose proportionality constant β was 1.043 for C_{max} and 1.103 for $AUC_{inf.}$ Plasma exposures (AUC_{inf}) of M4 were < 10% of EVG across all doses.

GS-US-183-0102 evaluated the PK of EVG 100 mg (2 x 50 mg) BID without (Days 1-10) and with ritonavir (RTV) 100 mg BID (Days 11-20) when taken in the fed state. Without RTV the EVG steady-state mean AUC_{tau} was ~ 20% lower vs. a single dose (AUC_{inf}), indicating modest auto-induction of its metabolism. With RTV there was a significant increase in systemic exposures with high trough concentrations, greater than predicted steady-state AUC and a longer median elimination half-life (T1/2) (9.5 vs. 3.5 hours). The applicant concluded that administration with RTV improved oral bioavailability due to decreased first-pass metabolism and reduced systemic clearance.

A further study (GS-US-183-0113) evaluated co-administration of RTV doses from 20-200 mg once daily with 125 mg EVG once daily for 10 days with dosing in the fed state. Midazolam (MDZ) 1 mg intravenous was also given in the afternoon on day 1, 11 and 21. RTV resulted in increases in C_{max}, AUC_{tau} and C_{tau} of EVG that were less than RTV-dose proportional. The apparent clearance of EVG decreased and t1/2 increased as the RTV dose increased with a plateau around 100 mg suggesting that near maximal inhibition of CYP3A was attained at 50 -100 mg RTV.

Plasma levels of GS-9202 (M1) and 1′-OH MDZ were BLLQ at most time points. GS-9200 (M4) was < 10% of the corresponding EVG exposures with a ratio that was unaffected by the RTV dose. Most subjects had no measurable M4 by 12 h post-dose. The applicant concluded that increasing doses of RTV did not affect the formation or elimination of M4 such that linear PK was maintained.

There were greater than dose proportional increases in RTV C_{max}, AUC_{tau} and C_{tau}. The dose-response curve ED50 for hepatic CYP3A4 (as assessed using intravenous MDZ) was 12.2 mg.

COBI

GS-US-216-0101 (50 - 200 mg) and GS-US-216-0113 (300 - 400 mg), each with administration in the fed state, showed that the bioavailability of COBI increased with dose before reaching a plateau ≥ 200 mg and also increased with multiple vs. single dose administrations. The data were consistent with its metabolic auto-inhibition properties.

In GS-US-216-0101 peak COBI concentrations were mostly observed ~ 4 to 4.5 hours post-dose. Increases in COBI AUC_{inf} were ~ 6.8-fold and ~ 5.1-fold, respectively, for doubling of doses from 50 to 100 mg and from 100 to 200 mg.

Table 7.

COBI Plasma PK Parameter	COBI 50 mg	COBI 100 mg	COBI 200 mg
Single Dose	**(N = 12)**	**(N = 15)**	**(N = 15)**
C_{max} (ng/mL)	61.6 (57.2)	342.6 (34.6)	1200.1 (30.1)
AUC_{0-last} (ng•h/mL)	228.9 (71.8)	1610.8 (49.0)	8111.1 (40.0)
AUC_{inf} (ng•h/mL)	242.9 (69.5)	1650.7 (48.3)	8422.0 (41.4)
C_{last} (ng/mL)	6.8 (27.4)	10.7 (51.2)	45.7 (70.1)
T_{max} (h)	3.26 (2.53, 4.25)	4.00 (3.50, 4.50)	4.00 (3.50, 4.50)
$T_{½}$ (h)	1.41 (0.98, 1.78)	2.68 (2.31, 2.95)	4.17 (3.32, 5.07)
CL/F (mL/h)	435,292.1 (92.0)	77,125.2 (58.9)	29,097.6 (53.3)
Multiple Dose	**(N = 12)**	**(N = 11)**	**(N = 12)**
C_{max} (ng/mL)	170.0 (70.1)	563.3 (30.7)	1854.8 (28.0)
AUC_{tau} (ng•h/mL)	827.0 (81.6)	3435.8 (34.3)	16,108.3 (34.3)
C_{tau} (ng/mL)	0.4 (346.4)	4.9 (87.0)	126.6 (74.9)
T_{max} (h)	4.50 (3.50, 4.50)	4.50 (4.50, 4.53)	4.50 (4.50, 4.50)
$T_{½}$ (h)	2.19 (1.34, 2.48)	3.12 (2.55, 3.36)	5.20 (4.12, 6.10)
CL_{ss}/F (mL/h)	154,288.3 (106.9)	33,190.3 (43.6)	13,952.5 (38.4)

In **GS-US-216-0113** on dosing at 300 mg or 400 mg once daily for 7 days (with 100 mg tablets) COBI exhibited nonlinear PK with respect to time and dose. Single-dose escalation from 300 to 400 mg resulted in statistically significant decreases in CL/F and corresponding increases in AUC and C_{max}, without changes in T1/2. Comparison of 300 mg data revealed a large decrease in CL/F and increases in T1/2, AUC and C_{max} with multiple doses, indicative of changes in COBI bioavailability, systemic clearance or both with time.

EVG plus COBI

Cohort 2 of GS-US-216-0116 (see below) received multiple dosing as follows:

- Treatment C: EVG 150 mg + COBI 150 mg F2 every morning for 10 consecutive days
- Treatment D: EVG 150 mg + RTV 100 mg every morning for 10 consecutive days

Bioequivalence was shown for EVG when boosted with the F2 COBI tablet (EVG/COBI) vs. EVG/rtv.

Bioequivalence

EVG

GS-US-183-0140 compared the 125 mg tablet used in the Phase II EVG study (GS-US-183-0105) with the 150 mg F2 tablet intended for commercial use that was administered in the Phase III EVG study (GS-US-183-0145). Each formulation was administered with 100 mg RTV every morning within 5 minutes of a meal for 10 days. The results met the BE criteria (AUC_{tau}, C_{max} and C_{tau}). The comparisons of rtv exposures also fell within the bounds of 80% to 125%.

Table 8. Single- and Multiple Dose (Once Daily) PK of EVG Administered as EVG/r Using the Phase 2 (125 mg) or Phase 3 (150 mg Formulations in Healthy Subjects)

EVG PK Parameter	EVG/r Day 1 (N = 12)		EVG/r Day 10 (N = 24)	
	125/100 mg	150/100 mg	125/100 mg	150/100 mg
AUC_{inf} or AUC_{tau} (ng•h/mL)	20,800 (59)	20,000 (56)	20,600 (36)	22,100 (32)
C_{max} (ng/mL)	1440 (53)	1410 (50)	2030 (39)	2130 (38)
C_{24} (ng/mL)	361 (67)	349 (62)	408 (51)	440 (48)
T_{max} (h)	4.0 (3.5, 8.0)	4.3 (4.0, 5.0)	4.0 (3.0, 5.0)	4.0 (2.0, 6.0)
$T_{1/2}$ (h)	11 (6.9, 14)	11 (7.3, 14)	8.9 (6.1, 12)	9.1 (6.0, 14)

AUC and C_{max} were comparable between single-dose (AUC_{inf}) and multiple-dose (AUC_{tau}) administration of EVG/r, indicating substantial inhibition of EVG metabolism/first-pass by RTV. Elvitegravir C24 was ~ 26% higher following multiple-dose administration (349 vs. 440 ng/mL), consistent with the development of mechanism-based inhibition of CYP3A by RTV and consequent reduction in EVG systemic clearance as well as progression to steady-state conditions.

COBI

GS-US-216-0116 compared the Phase III formulation (150 mg F2) with the Phase II version (F1 150 mg) after dosing Cohort 1 for 10 days. The 90% CIs around the GMRs for COBI AUC_{tau}, C_{tau}, and C_{max} showed bioequivalence between the formulations. Bioequivalence was also shown for MDZ and 1-OH MDZ exposures, indicating comparable inhibition of CYP3A by the two COBI formulations.

Stribild

GS-US-236-0101 evaluated the relative bioavailability of tablets containing EVG 150 mg, FTC 200 mg, TDF 300 mg plus COBI at either 100 mg or 150 mg vs. EVG/rtv 150/100 mg and vs. FTC 200 mg + TDF 300 mg. All dosing was once daily in the fed state for 10 days. The table below summarises the results.

- EVG with COBI 100 mg was bioequivalent to EVG/r as assessed by EVG AUC_{tau} and C_{max} but 37% lower as assessed by C_{tau} estimate
- EVG exposure was modestly higher for Stribild containing COBI 150 mg vs. 100 mg such that the upper bound of the 90% CI of AUC_{tau} exceeded the criteria by 1%. EVG trough concentrations (C_{tau}) were 9% higher than with EVG/r when the COBI dose was 150 mg, resulting in high IQ_{95} values (C_{trough}/IC_{95} [protein-binding adjusted]).
- The AUC_{tau}, C_{max} and C_{tau} values for COBI increased in a greater than proportional manner to dose. The COBI metabolite GS-341842 (E5) was undetectable at most time points while the GS-342006 (E1) metabolite was present at very low concentrations (< 1.5% of parent exposure by AUC) following administration of the Stribild. Mean plasma exposure (AUC) of GS-364751 (E3) was < 3% of COBI exposure at the 150 mg dose.

Table 9.

Plasma PK Parameter	Mean (%CV)		GLSM Ratio (%) (90% CI)
	Test (N = 42)	Reference (N = 42)	
EVG	**QUAD STR (COBI 100 mg)**	**EVG/r**	
AUC_{tau} (ng•h/mL)	21,102.1 (25.4)	22,514.3 (23.4)	93.4 (89.3, 97.8)
C_{max} (ng/mL)	2246.6 (26.3)	2498.0 (32.1)	91.8 (86.4, 97.5)
C_{tau} (ng/mL)	282.3 (60.4)	408.5 (40.5)	63.2 (56.6, 70.7)
EVG	**QUAD STR (COBI 150 mg)**	**EVG/r**	
AUC_{tau} (ng•h/mL)	26,986.9 (29.4)	22,514.3 (23.4)	117.7 (110.1, 125.9)
C_{max} (ng/mL)	2660.5 (27.6)	2498.0 (32.1)	108.1 (100.3, 116.4)
C_{tau} (ng/mL)	489.8 (52.9)	408.5 (40.5)	109.9 (95.3, 126.7)
TFV	**QUAD STR (COBI 150 mg)**	**FTC + TDF**	
AUC_{tau} (ng•h/mL)	3011.8 (20.4)	2552.6 (22.6)	118.0 (114.1, 122.1)
C_{max} (ng/mL)	331.5 (28.9)	251.8 (24.9)	130.0 (122.2, 138.3)
C_{tau} (ng/mL)	64.7 (26.0)	52.0 (25.4)	123.7 (119.0, 128.6)
FTC	**QUAD STR (COBI 150 mg)**	**FTC + TDF**	
AUC_{tau} (ng•h/mL)	11,526.9 (19.4)	9326.7 (22.1)	126.8 (114.5, 140.4)
C_{max} (ng/mL)	1858.9 (22.5)	1603.5 (26.1)	121.0 (107.1, 136.7)
C_{tau} (ng/mL)	100.5 (26.8)	80.1 (25.9)	126.3 (117.6, 135.8)
COBI	**QUAD STR (COBI 150 mg)**	**QUAD STR (COBI 100 mg)**	
AUC_{tau} (ng•h/mL)	10,405 (35.2)	5153.5 (31.7)	195.4 (177.1, 215.6)
C_{max} (ng/mL)	1566.1 (29.7)	855.4 (27.6)	179.4 (165.0, 195.2)
C_{tau} (ng/mL)	22.7 (107.2)	7.6 (124.4)	234.5 (210.6, 261.2)
RTV		**EVG/r**	
AUC_{tau} (ng•h/mL)		5746.5 (38.4)	
C_{max} (ng/mL)	—	1033.1 (47.8)	—
C_{tau} (ng/mL)		37.6 (52.2)	

- Tenofovir AUC_{tau} met the bioequivalence criterion. The TFV C_{max} and C_{tau} were slightly higher after administration of the Stribild vs. FTC + TDF but comparable with TFV exposures reported when TDF was co-administered with a PI/r. Higher TFV exposures with Stribild were attributed to the effect of COBI on P-glycoprotein (Pgp or MDR1) transporter in the gut. Emtricitabine AUC_{tau}, C_{max}, and C_{tau} were modestly higher with Stribild.

GS-US-236-0110 compared Stribild F2 used in Phase III and intended for the market with the F1 tablet used in the Phase 2 study GS-US-236-0104. The F2 tablet is 15% smaller in size and employs the updated mode of manufacture of COBI. The third group received FTC 200 mg + TDF 300 mg co-administered (not Truvada). Dosing was daily for 10 days within 5 minutes of a meal.

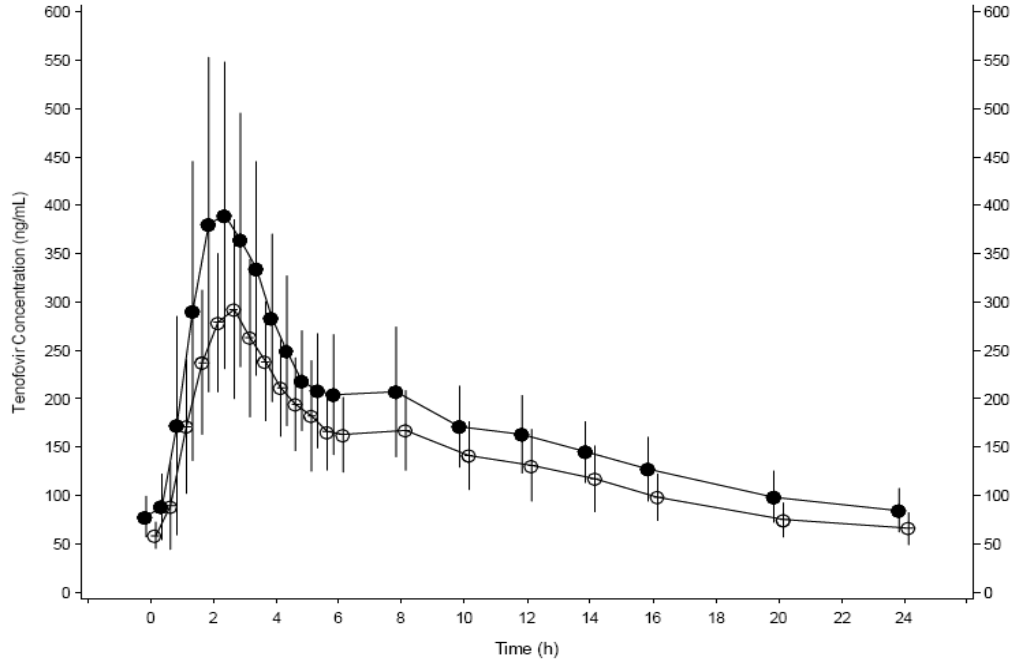
- EVG and COBI exposures showed bioequivalence between formulations.
- Emtricitabine exposure was bioequivalent when administered as a component of the F2 relative to administration of FTC + TDF.

- TFV exposures were higher (26% for AUC; there was no change in t1/2) with the F2 relative to administration of FTC + TDF but the applicant considered that exposures were clinically comparable between Stribild and Truvada.

Table 10.

Tenofovir PK Parameter	Geometric Least Squares Means		Geometric Least Squares Mean Ratio (%)	90% Confidence Interval
	FDC Formulation 2 (Treatment A)	Emtricitabine + Tenofovir DF (Treatment C)		
n	37	37		
AUC_{tau} (ng•h/mL)	3952.08	3136.81	125.99	122.61, 129.46
C_{max} (ng/mL)	464.70	308.95	150.41	142.90, 158.32
C_{tau} (ng/mL)	81.13	63.32	128.13	122.68, 133.81

Figure 1. GS-US-236-0110: Mean (SD) Plasma Concentration – Time Profiles by Treatment (Analysis Set: Tenofovir PK)



● = STR Formulation 2 (Multiple Dose)
○ = Emtricitabine + Tenofovir DF (Multiple Dose)

The applicant concluded that exposures to the components of the F2 formulation were appropriate and this (intended commercial) formulation was used in Phase 3 studies (GS-US-236-0102 and -0103).

Influence of food

Stribild

GS-US-236-0105 evaluated the effect of food (fasted, light and high-fat meal) when the F1 tablet (EVG 150 mg, COBI 150 mg, FTC 200 mg, TDF 300 mg) was administered once daily for 15 days.

- COBI AUC_{inf}, AUC_{last} and C_{max} met bioequivalence criteria for light meal vs. fasted conditions. There were decreases from 17% to 27% with a high-calorie/high-fat meal vs. the fasted state or vs. a light meal but the differences were not considered to affect the ability of COBI to boost EVG exposure.
- The maximum increases in EVG exposure vs. fasted state (AUC_{inf} 87%, AUC_{last} 91% and C_{max} 56%) were seen following a high-calorie/high-fat meal. Modest increases in EVG exposure (AUC_{inf} 34%, AUC_{last} 36%, and C_{max} 22%) occurred with a light meal vs. fasted state.
- Emtricitabine PK was not affected by food.
- The AUC TFV increased by about 23-25% in the fed state regardless of the type of meal. C_{max} increased by 20% after a light meal vs. fasted administration but this was not observed after a high fat/high calorie meal.

Table 11.

Treatment Condition N=24	TFV PK Parameters[a]		
	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)	AUC_{last} (ng•h/mL)
HC/HF Meal GLSM	319.39	3083.60	2724.93
Light Meal GLSM	370.76	3094.48	2726.58
Fasted GLSM	308.90	2505.63	2178.74
HC/HF Meal vs. Fasted GLSM ratio (90% CI), %	103.39 (89.38, 119.60)	123.07 (117.08, 129.36)	125.07 (119.09, 131.35)
Light Meal vs. Fasted GLSM ratio (90% CI), %	120.02 (103.76, 138.84)	123.50 (117.50, 129.81)	125.14 (119.16, 131.42)
HC/HF Meal vs. Light Meal GLSM ratio (90% CI), %	86.14 (74.47, 99.65)	99.65 (94.80, 104.74)	99.94 (95.16, 104.95)

Excretion

EVG

In the mass balance study (GS-US-183-0126), using RTV (100 mg)-boosted [14C]EVG (50 mg total dose) in the fed state, the T1/2 of the administered radioactivity from pooled plasma samples was similar to that observed for EVG (9.64 vs. 9.59 hours). The combined faecal and urinary recovery accounted for 101% of the administered radioactive dose, which was almost all in faeces. The radioactivity in faeces was mainly due to EVG and GS-9202. The applicant considered that EVG in faeces (30.8%) was likely a combination of unabsorbed drug, biliary secretion of EVG itself and biliary secretion of GS-9200 converted back to EVG by the β-glucuronidases in the intestinal microflora. Renal elimination accounted for 6.7% of the administered dose, mostly as the glucuronide of EVG or its hydroxylation products (M7, M19, and M20).

COBI

In the mass balance study GS-US-216-0111 after a 150 mg dose of [14C]COBI on day 7 following 150 mg daily for 6 days, 86.2% of the dose was recovered in faeces, consistent with hepatobiliary excretion, primarily as parent drug or metabolites M21 (GS-9454 or E1) or M31 (GS-9612, or E3). In most subjects, plasma radioactivity was undetectable beyond 32 h. COBI was the major species in the faeces (27%), followed by the oxidative metabolites - E3 (14%; hydroxylation of isopropyl thiazole) and E1 (5.5%; carbamate cleavage) – and others in trace amounts. Only 8.2% of the administered dose was recovered

in urine, primarily as unchanged parent drug and with low levels of metabolites M21 and M31. COBI displayed both dose- and time-dependent changes in apparent clearance (CL/F), consistent with the properties of a mechanism-based inhibitor.

In GS-US-126-0101 COBI exhibited nonlinear PK with respect to dose and time. Single-dose escalation from 50 mg to 100 mg and from 100 mg to 200 mg resulted in dramatic decreases in COBI CL/F. Similarly, apparent clearance of COBI at steady state (CLss/F) was reduced with increasing dose levels (ratios were 33.49% and 42.48%, respectively). Lower apparent clearances were observed following multiple doses at all dose levels. Ratios (single vs. multiple doses) were 312%, 219% and 199% for 50, 100 and 200 mg doses, respectively.

Metabolism

EVG

In the mass balance study with EVG/rtv (as described above) the predominant circulating species in plasma was EVG (~ 94% of radioactivity). All observed metabolites, including several minor metabolites, constituted < 10% relative systemic exposure (AUC_{tau}) to EVG. In-vitro studies indicated that biotransformation of EVG is primarily via CYP-mediated aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation. Following unboosted administration there are two primary metabolites (essentially virologically inactive):

- M1 (GS-9202) is produced by CYP3A4 and its formation is almost completely inhibited by RTV or COBI (typically BLLQ 20 ng/mL)
- M4 (GS-9200) is produced by UGT1A1/3, which becomes the predominant route of metabolism in the boosted state. The AUCtau of GS-9200 (M4) is typically < 10% of that for EVG and is unaffected by boosting.

COBI

In the mass balance study COBI represented 98.6% of the circulating radioactivity in plasma. In-vitro studies showed that COBI is extensively metabolised via CYP3A (major) and CYP2D6 (minor) mediated oxidation, with no evidence of direct Phase 2 metabolism. Primary metabolites include isopropyl oxidation (M31, GS-9612), cleavage at the N-methylurea (M26, GS-341842), cleavage of the carbamate (M21, GS-9454) and cleavage and deethylation of the morpholine (M39). CYP3A can catalyse all reactions, while CYP2D6 contributes to the generation of M31. Mean plasma exposures of M31 were < 3% of COBI exposure (AUC) after a single 150 mg dose or multiple doses of Stribild.

Distribution

EVG

In equilibrium dialysis studies EVG was ~98% to 99% bound to human plasma proteins regardless of concentration, with preferential binding to albumin over AAG. In GS-US-183-0126 the blood-to-plasma ratio of total 14C-radioactivity was time-independent and ~ 0.73, indicating that EVG and its metabolites are predominantly distributed to plasma relative to the cellular components of the blood.

COBI

In equilibrium dialysis studies COBI was ~97% to 98% bound to human plasma proteins regardless of concentration. When [14C] COBI (150 mg COBI dose) was administered on the last day of a multiple-dose period (150 mg once daily for 6 days) in healthy subjects (GS-US-216-0111) the blood-to-plasma ratio of total 14C-radioactivity was time-independent and ~ 0.5, indicating that COBI is excluded from the cellular components of the blood.

Elimination

Dose proportionality and time dependencies

EVG

Likely due to solubility-limited dissolution, doubling the dose from 125 mg F2 to 250 mg resulted in a ~ 40% increase in mean EVG trough concentrations. Administration of EVG/r 300/100 mg in HIV-1 infected subjects gave ~ 17% increase in EVG trough concentrations vs. 150/100 mg.

COBI

COBI exhibits non-linear increases in systemic exposure following single-dose (164-fold higher AUC_{inf} over an 8-fold dose range) and multiple-dose administration (47-fold higher AUC_{tau} over a 6-fold dose range). Also, COBI exhibits dose and time dependent changes in CL/F.

Intra- and inter-individual variability

The CV% values were comparable between the Stribild F1 and F2 formulations and were mostly in the range 20-30% for AUC and C_{max}. In GS-US-236-0105 using the F1 formulation the CV% values for AUC and C_{max} EVG were generally smaller after administration in the fed vs. fasting state and smallest on dosing with the high fat and high calorie meal. This trend in CV% was not observed or was small and inconsistent for COBI, FTC and TFV. The mean %CV values after multiple-dose administration of Stribild are shown below for HIV-1 infected subjects and healthy subjects.

Table 12. Mean (%CV) EVG, COBI, FTC, and TVF PK Parameters in HIV-1 Infected Subjects and Healthy Subjects

Study No.	PK Parameter (N)	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
QUAD STR				
HIV-1 Infected Subjects				
GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104	EVG (N = 419) [a]	23,000 (33)	1730 (23)	451 (58)
	COBI (N = 415) [a]	8920 (32)	1200 (17)	33.4 (179)
	FTC (N = 62) [b]	12,700 (35) [c]	1880 (27)	142 (170) [c]
	TFV (N = 419) [a]	3200 (28)	320 (22)	72.7 (46)
Healthy Subjects				
GS-US-236-0101 and GS-US-236-0110	EVG (N = 78)	24,900 (30)	2320 (31)	498 (47)
	COBI (N = 78)	10,800 (32)	1550 (28)	34.1 (101) [d]
	FTC (N = 79)	12,000 (20)	1890 (20)	108 (28)
	TFV (N = 79)	3510 (27)	404 (36)	73.8 (30)
COBI				
HIV-1 Infected Subjects				
GS-US-216-0105 and GS-US-216-0114 [e]	COBI (N = 68)	10,900 (35)	1220 (23)	68.2 (110)
Healthy Subjects				
GS-US-216-0110	COBI (N = 35)	11,300 (24)	1380 (19)	61.6 (94)
TRUVADA® Fixed-Dose Combination				
Healthy Subjects				
GS-US-183-0103	FTC (N = 24)	9770 (19)	1680 (32)	84.8 (26)
	TFV (N = 24)	2880 (27)	310 (24)	60.0 (31)
GS-US-299-0101 [f]	FTC (N = 16)	9580 (10)	1830 (21)	70.5 (24)
	TFV (N = 16)	2890 (16)	323 (28)	55.2 (19)
ATRIPLA® STR				
Healthy Subjects				
GS-US-236-0120 [g]	FTC (N = 30)	10,600 (21)	2050 (24)	68.9 (29)
	TFV (N = 30)	2280 (19)	314 (25)	45.9 (21)
GS-US-248-0127 [f,h]	FTC (N = 13)	10,200 (14)	1810 (20)	61.6 (24)
	TFV (N = 13)	2280 (16)	308 (26)	45.2 (19)
EMTRIVA®				
{20490}	FTC (N = 20)	10,000 (31)	1800 (40)	90 (—)

Study No.	PK Parameter (N)	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
		VIREAD®		
HIV-1 Infected Subjects				
GS-99-907 [i]	TFV (N = 7)	3300 (31)	327 (18)	—
Healthy Subjects				
GS-00-914 [j]	TFV (N = 37)	2710 (18)	335 (24)	—

—, data not available/not reported

Data are mean (%CV) and are shown to 3 significant digits, except where indicated.

a All the QUAD STR-treated subjects in GS-US-236-0103 and GS-US-236-0104 and all the QUAD STR-treated subjects who participated in the PK substudy in GS-US-236-0102 were included (based on population PK analysis).

b All the QUAD STR-treated subjects who participated in the PK substudy in GS-US-236-0102, GS-US-236-0103, or GS-US-236-0104 were included.

c n = 61. AUC_{tau} and C_{tau} were not calculated for Subject 2191-7159 for any analyte because concentration values were missing for some postdose time points.

d n = 76

e The model-based COBI PK parameters were available for 68 subjects in the ATV/co+TVD treatment group (n = 46 in Study GS-US-216-0105 and n = 22 in Study GS-US-216-0114).

f Preliminary data; study ongoing

g Administered once daily in the morning under fasting conditions

h Administered once daily in the evening under fasting conditions

i Administered once daily for 48 weeks under fed conditions.

j Administered as a single dose under fed conditions.

Note the derivation of parameters for HIV-infected subjects and the additional data for COBI as described in footnotes. The applicant concluded that inter-subject variability (% CV) for EVG AUC, C_{max} and C_{tau}, and for the AUC and C_{max} for the other three active substances (COBI, FTC and TFV) following administration of Stribild or COBI was comparable between HIV-1 infected subjects and healthy subjects. The variability in FTC and TFV exposures following administration of TVD (fed) or ATR (fasted) were comparable to those observed following Stribild administration and to those reported for FTC and TDF.

Pharmacokinetics in target population

Intensive sampling data were obtained with Stribild in Phase 2 (GS-US-236-0104) and Phase 3 (GS-US-236-0102, GS-US-236-0103) studies and sparse sampling data were obtained in Phase 3 studies. In the population PK analysis the COBI-boosted EVG exposure parameters were analysed across studies and compared between healthy subjects and HIV-infected subjects treated in Phase 2 and 3 studies. Based on actual data the applicant considered that EVG exposures were comparable across studies in HIV-infected subjects who received Stribild.

Table 13.

EVG	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
GS-US-236-0102 (N = 23)	17,400 (39)	1470 (31)	267 (70)
GS-US-236-0103 (N = 350)	23,600 (31)	1760 (22)	472 (53)
GS-US-236-0104 (N = 46)	21,100 (37)	1650 (23)	388 (83)

A two-compartment PK model with first-order absorption rate constant and absorption lag time provided a good description of EVG PK in healthy subjects and HIV infected patients. The EVG AUC_{tau}, C_{max} and C_{tau} were comparable between HIV-1 infected subjects and healthy subjects.

Table 14.

EVG	AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
Population PK[a] (N = 419)	23,000 (33)	1730 (23)	451 (58)
Healthy Subjects (N = 36)	22,500 (27)	1920 (24)	508 (41)

In HIV-1 infected subjects treated with Stribild COBI exposures were comparable across studies.

Table 15.

COBI	AUC_{tau} [a, b] (ng•h/mL)	C_{max} [c] (ng/mL)	C_{tau} [a, d, e] (ng/mL)
HIV-1 infected Subjects (N = 62)	8300 (46)	1140 (36)	49.1 (260)

In addition, targeted plasma trough concentrations of COBI were assessed throughout 48 weeks of dosing in GS-US-236-0104 and GS-US-236-0103. In the Phase 3 study the means were mostly in the range 40-70% but the CV% estimates around these trough values were very large. The cross-study comparison between HIV-1 infected subjects (Phase 2 and 3 studies) and healthy subjects (GS-US-236-0110) following multiple-dose administration of Stribild showed that COBI AUC_{tau} and C_{max} were ~ 25% lower while Tmax and T1/2 were comparable in HIV-1 infected subjects compared with healthy subjects. The applicant stated that the reasons for the observed differences are unclear.

In the population PK analyses for EVG, COBI exposure was not associated with differences in EVG exposure at the 150 mg dose.

Treatment with Stribild gave exposures to FTC and TFV in HIV-infected subjects that were considered to be comparable with those observed in healthy subjects in GS-US-236-0110. Mean TFV exposures upon multiple-dose administration of Stribild were higher (25%–30%) compared with historical data for TDF. This was attributed to the inhibitory effect of COBI on Pgp (MDR1)-mediated secretory (efflux) transport of TDF in the intestine (see further below). The relative increases in TFV exposure were in the range of values observed when TDF is co-administered with a PI/r, such as LPV/r, DRV/r and ATV/r with increases in TFV exposure of 32%, ~ 22% and ~37%, respectively.

Table 16. Steady-State EVG, COBI, FTC, and TFV PK after Once-Daily Administration of the QUAD STR in HIV-1 Infected Subjects (GS-US-236-0102, GS-US-236-0103, GS-US-236-0104 Population PK-[EVG] of Intensive PK Substudies-Derived [COBI, FTC, TFV])

	N	AUC_{tau} [a] (ng•h/mL)	N	C_{max} (ng/mL)	N	C_{tau} (ng/mL)
EVG[b]	419	23,000 (33)	419	1730 (23)	419	451 (58)
COBI[c]	61	8300 (46)	62	1140 (36)	53	49.1 (260)[d]
FTC[c]	61	12,700 (35)	62	1880 (27)	61	142 (170)
TFV[c]	61	4360 (51)	62	450 (36)	61	98.7 (85)

Data are mean (%CV) and are shown to 3 significant digits.

a AUC_{tau} and C_{tau} were not calculated for Subject 2191-7159 for any analyte because concentration values were missing for some postdose time points.

b Population PK data was used for EVG PK parameters

c Data for all the QUAD STR-treated subjects who participated in the PK substudy in GS-US-236-0102, GS-US-236-0103, or GS-US-236-0104

d Missing C_{tau} (except for Subject 2191-7159) was due to values below the limit of quantitation and was excluded from this analysis.

Impaired renal function

GS-US-216-0124 evaluated the PK of *EVG and COBI* in subjects with severe renal impairment (eGFR < 30 mL/min) not on dialysis vs. matched controls (eGFR ≥ 90 mL/min). The actual mean eGFRCG values at baseline were 23.5 mL/min and 97.2 mL/min. EVG 150 mg and COBI 150 mg were co-administered (using 150 mg tablets of each) once daily in the fed state for 7 days.

EVG AUC_{tau}, C_{max}, and C_{tau} were modestly lower (by 25%, 33% and 31%, respectively) in subjects with severe renal impairment vs. controls. However, it was also noted that EVG exposure on Day 7 among subjects with normal renal function was substantially higher than in previous clinical studies with EVG/COBI co-administered at these doses. The applicant considered that the differences were not clinically relevant. The EVG mean (SD) % free fraction on Day 7 was 1.42 (0.17) in the renally impaired subjects and 1.16 (0.16) in the matched controls.

COBI AUC_{tau}, C_{max}, and C_{tau} were modestly higher (by 25%, 22% and 13%, respectively) in subjects with severe renal impairment but the applicant considered that the differences were not clinically relevant. The COBI mean (SD) % free fraction on Day 7 was 2.47 (0.62) in the renally impaired subjects and 2.49 (0.29) in the matched controls.

On Day 7 of co-administration eGFRCG was 10.5% lower vs. baseline among subjects with severe renal impairment and 8.4% lower among controls. Similar results were obtained were obtained using eGFRMDRD. Values returned to baseline levels by Day 14. The decreases in eGFR were attributed to inhibition of proximal tubular secretion of creatinine by COBI (see also GS-US-126-0121 below).

Impaired hepatic function

GS-US-183-0133 evaluated the PK of *EVG and COBI* in subjects with moderate hepatic impairment (CPT B; actual scores were 7-9) and healthy controls. EVG 150 mg and COBI 150 mg were co-administered (using 150 mg tablets of each) once daily in the fed state for 10 days followed by an 11-day follow-up. Mean creatinine clearance was estimated at 98.7 ml/min and 116.8 ml/min in respective groups.

The steady-state AUC_{tau}, C_{tau} and C_{max} of EVG were 35%, 80% and 41% higher, respectively, in subjects with moderate hepatic impairment but the applicant considered the differences were not clinically relevant. The mean (SD) % free fraction EVG was 1.15 (0.14) in the control group and 1.22 (0.23) in the CPT B group, indicating the lack of effect of hepatic impairment on EVG protein binding.

The AUC_{tau} and C_{max} of COBI were generally comparable in subjects with moderate hepatic impairment relative to normal matched control subjects. C_{tau} was higher (GLSM 208%) in the presence of moderate hepatic impairment. The mean (SD) % free fraction COBI was 2.71 [0.56] in the control group and 3.23 [0.63] in the CPT B group.

Interactions

In vitro data – including data added during the procedure

EVG

- EVG showed no detectable inhibition of human hepatic microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 activity and only weak inhibition of CYP3A.
- The effect of EVG on the activities of CYP2B6 and CYP2C8 showed no detectable inhibition of either enzyme (IC_{50} > 25 µM).
- The K_m value for glucuronidation of EVG (to M4, GS 9200) by human hepatic microsomal fraction is 21 µM. The Ki value for inhibition of UGT1A1 and UGT1A3 is expected to match this. Formal determination of EVG inhibition of UGT1A1 and UGT1A3 and the assessment of the potential for inhibition of UGT2B7 is ongoing.

- Formation of GS-9200 (M4) was extensively inhibited by ATV, a selective UGT1A1 inhibitor.
- At clinically relevant concentrations EVG is a weak inducer of CYP3A activity. This effect is countered by COBI and so it is unlikely to cause DDIs due to induction of other CYPs.
- EVG plasma exposures are maximally boosted by COBI. No further increases in EVG exposures are anticipated in the presence of other CYP3A inhibitors.
- EVG showed modest transport by Pgp with <3-fold increase in the efflux ratio in Pgp over-expressing cells vs. wild type cells. The EVG efflux ratio decreased in the presence of the Pgp inhibitor cyclosporin A (CsA; 10 µM). Co-administration with inhibitors or inducers of MDR1 is not expected to affect EVG plasma levels.
- EVG showed modest transport by BCRP with <3-fold increase in the efflux ratio in BCRP over-expressing cells vs. wild type cells. The EVG efflux ratio decreased in the presence of the BCRP inhibitor Ko134 (10 µM).
- EVG showed weak dose-dependent inhibition of Pgp (IC50 = 70 µM) and BCRP (IC50 = 89 µM). Inhibition constants for EVG and COBI suggest the potential for modest intestinal DDIs to occur during the absorption process when co-administered with Pgp and BCRP substrates and no potential for inhibition once in the systemic circulation.
- The rate of EVG uptake in OATP1B1 and OATP1B3 transfected cells increased by 3.8 and 2.1 fold, respectively, vs. wild-type cells. Rates of uptake of EVG decreased in the presence of the OATP inhibitor rifampicin.
- EVG is a weak inhibitor of human OATP1B1 and an inhibitor of human OATP1B3 (IC50 0.44 µM).
- EVG did not influence MRP2-mediated oestradiol 17β-glucuronide transport at 20 µM.
- EVG showed weak inhibition of OCT2 (31% inhibition at 20 µM) and inhibited MATE1 with an IC50 of 2.0 µM.
- EVG did not markedly inhibit OAT1, OAT3 or MRP4 at the highest concentrations tested (IC50 > 20 µM). In light of the PK of EVG, inhibition of OAT1 and OAT3 would not be expected to be important but an effect on MRP4 could be relevant.
- EVG showed weak or no inhibition of OCT1 and BSEP.
- Chelating of EVG via binding to pharmacophore binding can occur with high concentrations of divalent and trivalent cations, as found in some antacid preparations.

COBI

- COBI is expected to substantially increase exposure to drugs whose bioavailability and elimination are affected by CYP3A enzymes. COBI is a more specific CYP3A inhibitor than ritonavir.
- COBI is expected to weakly-modestly increase exposures of substrates of CYP2D6.
- CYP3A inducers are expected to lower COBI (and consequently EVG) exposure while strong inhibitors of CYP3A enzymes may increase COBI exposures.
- Neither recombinant human CYP2B6 nor CYP2C8 metabolised COBI to a significant extent
- COBI shows high intestinal permeability primarily via passive transcellular diffusion and does not undergo active efflux (secretory) transport.
- COBI was found to be a substrate for Pgp based on observations of increased efflux ratios in Pgp over-expressing cells and decreased efflux in the presence of CsA.
- Based on increased efflux ratio in BCRP over-expressing cells and decrease in efflux ratio in the presence of Ko134, COBI was found to be a substrate for BCRP.

- COBI is a weak inhibitor of Pgp and BCRP (IC50 values of 36 µM and 59 µM). Inhibition constants suggest the potential for modest intestinal DDIs to occur during the absorption process when co-administered with Pgp and BCRP substrates and no potential for inhibition once in the systemic circulation. High concentrations of COBI in the intestinal lumen during absorption can increase systemic TFV exposure due to inhibition of Pgp-dependent efflux of TDF.
- COBI is transported by OATP1B1 and OATP1B3. The rate of COBI uptake in OATP1B1 and OATP1B3 transfected cells increased by 14.6 and 5.3 fold, respectively, vs. wild-type cells. Rates of uptake of COBI decreased in the presence of the OATP inhibitor rifampicin.
- COBI is expected to weakly-modestly increase exposures of OATP1B1/3 substrates.
- COBI was shown to not inhibit transport of model substrates by OAT1 and OAT3 at up to 100 µM and to weakly inhibit MRP4 (IC50 20.7 µM).
- COBI IC50 values for OCT2 and MATE1 were 14.4 and 1.87 µM, respectively. COBI is expected to weakly-modestly increase exposures of substrates of MATE1. For example, inhibition of cationic transporters by COBI may cause slight increases in circulating FTC levels by partially inhibiting the active tubular secretion component of its renal clearance.
- COBI inhibited OCT1 and BSEP with calculated IC50 values of 14.7 and 6.5 µM, respectively. RTV inhibited BSEP with IC50 of 1.8 µM and reached 49% of inhibition of OCT1 at 20 µM. COBI inhibition constants for OCT1 and BSEP were in excess of the total C_{max} (1.4 µM; not taking into account protein binding) observed with STB.
- COBI exerted weak inhibition of MRP2 (IC_{50} >71 µm).

Additional data come from the next 3 studies.

The active tubular secretion of TFV is mediated by a low affinity and high capacity anionic transport pathway including OAT1, OAT3 and MRP4. The following studies provided relevant results:

PC-236-2008 assessed the effect of COBI vs. RTV on the active transport of TFV by OAT1 (SLC22A6) and OAT3 (SLC22A8) expressed in basolateral membrane of renal proximal tubules. COBI up to 15 µM showed no inhibitory effect on the active transport of TFV mediated by two genetic variants of OAT1 while RTV showed weak inhibition (10% and 30% inhibition at 5 and 15 µM). The OAT3-mediated transport of TFV was more sensitive to inhibition by COBI and RTV with IC50 values of 6.6 and 4.8 µM, respectively. These inhibitory effects occurred only at concentrations exceeding human C_{max} so COBI has a low potential to affect the active renal tubular uptake of tenofovir or other OAT1 and OAT3 substrates *in vivo*.

PC-236-2009 assessed the potential for COBI to affect the MRP4-mediated cellular efflux of TFV vs. RTV. In the absence of serum, COBI and RTV inhibited TFV efflux by MRP4 with IC50 values of 8 and 12 µM, respectively, while adding 10% bovine serum significantly reduced the effects (45% and 19% inhibition at 20 µM, respectively). No effects on MRP4 were observed in 100% human serum at concentrations far exceeding C_{max} so COBI and RTV were considered weak inhibitors of MRP4.

PC-236-2007 assessed the effect of COBI vs. RTV on the accumulation of TFV in fresh human renal cortex tissue. Tissue slices were incubated with 1.2 µM TFV and increasing concentrations of COBI and RTV (1.5, 5 and 15 µM). At 15 µM COBI (substantially above C_{max}) the TFV uptake was reduced by approximately 20% following incubation for 60 minutes. RTV 5 and 15 µM concentrations reduced the TFV accumulation by 38% and 43%, respectively, but showed minimal effects at the clinically relevant concentration of 1.5 µM.

FTC and TFV (note TFV and not TDF)

- TFV and FTC were not found to be substrates for Pgp (< 2-fold increase in efflux ratios in Pgp over-expressing cells and no effect of CsA).

- TFV and FTC were not substrates for BCRP (< 2-fold increase in efflux ratio and no observed decrease in efflux in the presence of Ko134).
- FTC and TFV showed no dose-dependent inhibition of Pgp and BCRP.
- FTC did not influence MRP2-mediated oestradiol 17β-glucuronide transport at 100 µM. TFV did not inhibit MRP2 and the effect of TDF is under evaluation.
- FTC and TFV showed ≤ 20% inhibition of OCT2 and MATE1 at the highest tested concentrations (100 and 300 µM, respectively).
- FTC did not show marked dose dependent inhibition of OATP1B1 and OATP1B3 up to 100 µM. TFV showed weak dose dependent inhibition of OATP1B1 and OATP1B3 (37% and 32%, respectively, at 100 µM).
- Combined results suggest the potential for Stribild to modestly increase co-administered OATP1B1 and OATP1B3 substrates due to net inhibition of these transporters (see also the EVG and COBI results above).
- FTC and TFV showed weak or no inhibition of OCT1 and BSEP.

In vivo

The applicant performed a large number of DDI studies with each of EVG and COBI, a limited number with EVG/COBI and one with Stribild. Many of these studies involved co-administration of EVG with, or evaluated the effects of COBI on, other HIV agents so the findings are not directly relevant to this application for Stribild since it will not be given with additional ARVs. However, some of the findings have implications for other agents handled by similar mechanisms that could require co-administration with Stribild and the main results are provided in the clinical assessment report.

Data from other DDI studies that are of interest were as follows:

EVG

- GS-US-183-0119 evaluated the effects of administering EVG/rtv 50/100 mg after food but also 2 or 4 h before or after Mg/Al-containing antacid and at 2 h after 40 mg omeprazole under steady state conditions. Dosing EVG/rtv with a 4 h interval before/after antacid and at 2 h after a dose of omeprazole there was no significant affect on EVG exposures. Use of a 2 h interval with respect to antacid gave 90% CI around ratios that did not span zero in any case but the applicant concluded that a 2 h interval would be satisfactory. Co-administration of omeprazole with EVG/r did not affect the PK of EVG. RTV PK was not affected by antacid or omeprazole.

Table 17.

EVG Plasma PK Parameter	C_{max} (ng/mL)	AUC_{tau} (ng•h/mL)	C_{tau} (ng/mL)
EVG/r Alone (N = 48)	928.7 (31.2)	10,666.7 (28.3)	211.4 (39.9)
EVG/r 4 h after Antacid (N = 8)	928.9 (12.8)	11,507.2 (19.6)	258.7 (31.3)
GLSM ratio (%) (90% CI)	94.75 (83.90, 107.00)	95.82 (88.29, 103.99)	104.30 (93.39, 116.50)
EVG/r 4 h before Antacid (N = 10)	892.7 (50.1)	9056.8 (44.8)	181.4 (65.4)
GLSM ratio (%) (90% CI)	98.32 (88.16, 109.65)	98.20 (91.26, 105.66)	99.98 (90.14, 110.90)
EVG/r 2 h after Antacid (N = 11)	699.6 (17.5)	8584.6 (19.0)	181.2 (32.6)
GLSM ratio (%) (90% CI)	82.23 (74.10, 91.26)	84.76 (79.04, 90.90)	90.44 (82.29, 99.39)
EVG/r 2 h before Antacid (N = 10)	758.6 (15.5)	9427.0 (12.4)	179.7 (20.0)
GLSM ratio (%) (90% CI)	78.86 (70.71, 87.95)	80.30 (74.63, 86.40)	80.48 (72.90, 88.85)
EVG/r + Omeprazole (N = 9)	798.7 (20.0)	9756.0 (19.1)	201.6 (44.2)
GLSM ratio (%) (90% CI)	92.64 (82.59, 103.91)	98.59 (91.27, 106.50)	94.02 (84.71, 104.36)

- GS-US-183-0125 evaluated co-administration of EVG/rtv 300/100 mg once daily with rifabutin 150 mg every other day, using a rifabutin 300 mg every other day control group.

Table 18.

Plasma PK Parameter	Mean (%CV)		GLSM Ratio (%) (90% CI)
	Test[a]	Reference[b]	
EVG	**(N = 19)**	**(N = 19)**	
AUC_{tau} (ng•h/mL)	31,760.1 (24.5)	33,452.5 (24.8)	95.6 (89.7, 101.9)
C_{max} (ng/mL)	2698.3 (22.6)	2947.6 (20.4)	91.9 (84.2, 100.4)
C_{tau} (ng/mL)	605.1 (55.4)	613.8 (40.2)	94.3 (81.9, 108.5)
RTV	**(N = 19)**	**(N = 19)**	
AUC_{tau} (ng•h/mL)	6664.4 (42.1)	5178.2 (32.5)	124.5 (109.1, 142.0)
C_{max} (ng/mL)	860.3 (35.9)	697.2 (30.0)	120.5 (101.0, 143.7)
C_{tau} (ng/mL)	59.4 (89.3)	43.9 (62.4)	112.7 (85.4, 148.7)
Rifabutin	**(N = 18)**	**(N = 18)**	
AUC_{tau} (ng•h/mL)	6238.3 (27.9)	6637.3 (26.8)	93.7 (85.6, 102.6)
C_{max} (ng/mL)	372.8 (31.8)	402.7 (31.2)	91.7 (82.7, 101.6)
C_{tau} (ng/mL)	63.2 (45.3)	53.0 (33.2)	115.9 (102.3, 131.3)
25-O-Desacetyl Rifabutin	**(N = 18)**	**(N = 18)**	
AUC_{tau} (ng•h/mL)	4066.8 (18.6)	468.0 (53.5)	951.1 (809.5, 1117.5)
C_{max} (ng/mL)	144.2 (24.9)	29.1 (52.2)	539.7 (466.1, 624.8)
C_{tau} (ng/mL)	56.9 (22.3)	3.1 (63.4)	1936.0 (1584.5, 2365.3)
Total Antimycobacterial Activity	12.20	8.14	150.0 (137.8, 163.2)

EVG/r and 150 mg rifabutin resulted in equivalent exposures vs. EVG/rtv alone and 300 mg rifabutin alone but 25-O-desacetyl rifabutin AUC0−48, C_{max} and C_{tau} increased by 9.5-, 5.4- and 19.4-fold, respectively, on co-administration. The total antimycobacterial activity (calculated from total µM rifabutin plus 25-O-desacetyl rifabutin) was increased by 50% during co-administration. RTV AUC_{tau} was not affected by rifabutin but C_{max} and C_{tau} were increased by ~ 21% and ~ 13%, respectively.

- GS-US-183-0146 assessed co-administration of EVG/rtv 150/100 mg once daily with ketoconazole (KTZ) 200 mg twice daily. Midazolam 5 mg orally was also administered pre-dosing, with EVG/rtv alone and at the end of co-administration. KTZ resulted in increases in EVG concentrations as shown below. There was also a decrease in the M4:EVG AUC_{tau} ratio on concurrent administration with KTZ. The applicant considered the effects reflected inhibition of UGT1A1 by KTZ.

Table 19.

Plasma PK Parameter (N = 18)	Mean (%CV)		GLSM Ratio (%) (90% CI)[a]
	EVG/r + KTZ	EVG/r	
EVG			
C_{max} (ng/mL)	2450.7 (52.8)	1985.4 (24.6)	117.3 (103.8, 132.6)
AUC_{tau} (ng•h/mL)	34,817.6 (50.0)	22,389.9 (23.9)	148.3 (136.2, 161.6)
C_{tau} (ng/mL)	900.1 (62.1)	511.4 (32.3)	166.7 (148.2, 187.5)
$T_{1/2}$ (h)	12.6 (9.4, 16.6)	11.8 (10.2, 13.9)	104.0 (87.5, 123.6)

Co-administration of MDZ and EVG/r resulted in increased MDZ AUC_{inf}, C_{max} and C_{last} with slight additional increases in AUC_{inf} and C_{last} when KTZ was added. Co-administration with EVG/r resulted in significant decreases in 1′-OH MDZ exposure but there were increases on addition of KTZ.

COBI

GS-US-216-0134 was reported during the procedure, at which time it was ongoing. This is a randomized, open-label, single-centre, multiple-dose, crossover study to evaluate the PK and safety of COBI (150 mg; A) and TFV (300 mg TDF; C) following multiple-dose administrations of each agent given alone or together (B) once daily for 7 days in healthy adult subjects. All dosing was after a standard meal. An interim report presented preliminary results after all subjects completed 2 dosing regimens over 19 days and 7 days of follow up. Two-thirds of the 46 treated subjects were male and 45 completed study drug.

COBI exposures were unaffected by co-administration of TDF and the mean plasma profiles were almost super-imposable.

Table 20. GS-US-216-0134: Statistical Comparison of Single-and Multiple- Dose Pharmacokinetic Parameters for Test Versus Reference Treatments (Cobicistat PK Analysis Set)

COBI PK Parameter	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Single Dose				
COBI+TDF (Test) vs. COBI (Reference)	n = 32	n = 32	—	—
AUC_{inf} (ng•h/mL)	7193.57	6680.25	107.68	(100.43,115.46)
AUC_{last} (ng•h/mL)	7030.88	6546.49	107.40	(100.11,115.21)
C_{max} (ng/mL)	1144.40	1087.41	105.24	(98.25,112.73)
Multiple Dose				
COBI+TDF (Test) vs. COBI (Reference)	n = 31	n = 31	—	—
AUC_{tau} (ng•h/mL)	14791.33	14750.87	100.27	(94.73,106.14)
C_{max} (ng/mL)	1879.04	1873.59	100.29	(95.38,105.45)
C_{tau} (ng/mL)	83.56	78.25	106.78	(94.13,121.13)

Consistent with the known inhibitory effect of COBI on Pgp-mediated intestinal efflux of TDF, the TFV C_{max} and secondarily the AUC were higher (51% for C_{max} and 23% for AUC_{tau}) upon single- or multiple-dose administration of COBI+TDF vs. TDF alone.
This finding was consistent with previous data with Stribild where TFV C_{max} and AUC_{tau} were 50% and 26% higher vs. TDF alone (GS-US-236-0110). However, the TFV exposures on co-administration with COBI were in the range of historical data for TDF when dosed with other Pgp-inhibitors, including RPV, RTV or PI/r (ATV, DRV and LPV).

Figure 2. GS-US-216-0134: Mean (SD) Multiple-Dose Plasma Concentration-Time Pfofiles (Semi-Logarithmic Scale; Tenofovir PK Analysis Set)

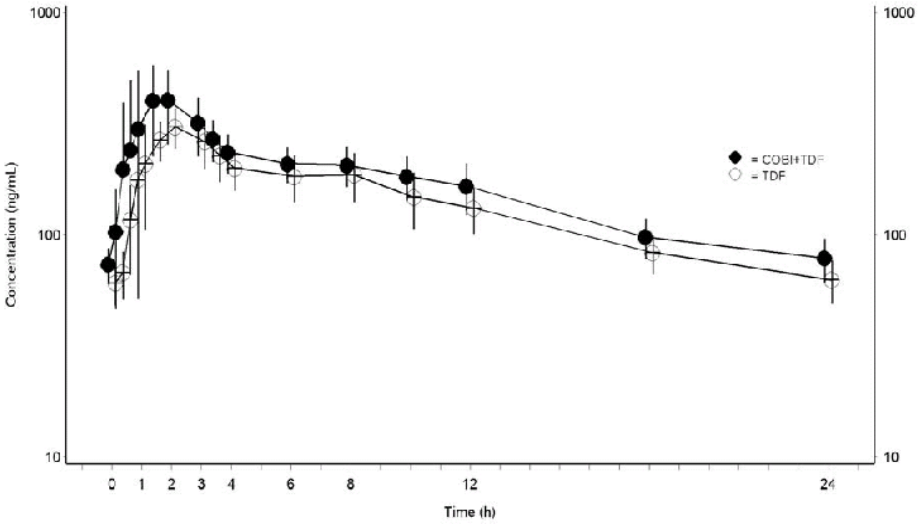


Table 21. GS-US-216-0134: Summary Statistics for Multiple-Dose Pharmacokinetic Parameters (Tenofovir PK Analysis Set).

TFV Multiple Dose PK Parameter	TDF (n = 14)	COBI+TDF (n = 13)
AUC_{tau} (ng•h/mL), Mean (%CV)	3330.6 (17.6)	4088.0 (17.8)
C_{max} (ng/mL), Mean (%CV)	337.9 (16.5)	529.6 (37.1)
C_{tau} (ng/mL), Mean (%CV)	62.6 (21.3)	78.6 (22.0)
T_{max} (h), Median (Q1, Q3)	2.00 (1.50, 2.00)	1.50 (1.50, 2.00)
$T_{½}$ (h), Median (Q1, Q3)	10.96 (9.68, 11.87)	10.87 (9.39, 12.55)

Table 22. GS-US-216-0134: Statistical Comparison of Single- and Multiple-Dose Pharmacokinetic Parameters for Test Versus Reference Treatments (Tenofovir PK Analysis Set).

TFV PK Parameter	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Single Dose				
COBI+TDF (Test) vs. TDF (Reference)	n = 13	n = 13	—	—
AUC_{inf} (ng•h/mL)	3374.30	3053.72	110.50	(103.60,117.86)
AUC_{last} (ng•h/mL)	2612.22	2448.08	106.70	(96.61,117.85)
C_{max} (ng/mL)	455.11	320.13	142.16	(122.59,164.86)
Multiple Dose				
COBI+TDF (Test) vs. TDF (Reference)	n = 13	n = 13	—	—
AUC_{tau} (ng•h/mL)	4028.57	3281.69	122.76	(115.91,130.01)
C_{max} (ng/mL)	505.13	326.23	154.84	(134.80,177.86)
C_{tau} (ng/mL)	76.95	61.38	125.37	(115.66,135.90)

Following multiple-dose administrations the renal clearance of TFV was slightly lower with COBI+TDF vs. TDF alone. This was driven by similar urinary recoveries of TFV in the urine but higher AUC values. Assessment of urinary recovery with multiple doses of study drug is confounded, as the absolute absorption and elimination of a dose of study drug is not assessed.

Table 23. GS-US-216-0134: Summary Statistics for Urinary Pharmacokinetic Parameters (Tenofovir PK analysis set).

	TDF (n = 14)	COBI+TDF (n = 13)
Amount excreted (µg), Mean (%CV)	43590.2 (20.4)	43696.1 (19.1)
CL_{renal} (mL/min), Mean (%CV)	220.9 (19.4)	182.6 (22.9)

The TFV plasma concentration-time terminal phase profiles were parallel between the two treatments and accordingly, TFV T1/2 estimates were similar between treatments for both the single- and multiple-dose comparisons of COBI+TDF vs. TDF alone. The applicant concluded that the interaction between COBI and TDF is at the intestinal level and that COBI does not affect the elimination of TFV. In the DDI study of COBI and the Pgp substrate digoxin the C_{max} of digoxin was increased ~40%, which is comparable to the change observed in TFV C_{max} described above. In addition, in-vitro transport studies have confirmed that TDF is a substrate of intestinal Pgp and undergoes secretory transport and COBI is a Pgp inhibitor at concentrations observed in the intestine during absorption. Moreover, in-vitro data demonstrate minimal to no effect of COBI on renal transporters involved in TFV excretion in the urine.

Grade 1 serum creatinine abnormalities occurred in 2 subjects during co-administration and in one during COBI. Grade 1 urine protein abnormalities occurred in 1 subject during the COBI treatment phase and 1 subject during the TDF treatment phase. No graded abnormalities in phosphorus or urine glucose occurred. The median baseline value for serum creatinine was 0.9 mg/dL during COBI+TDF, COBI, and TDF treatment phases, and slight increases (0.1 mg/dL) were seen as early as Day 2 of COBI+TDF and COBI alone. The median baseline eGFRCG values were between 110 and 120 mL/min. Decreases in eGFRCG were seen as early as Day 2 of COBI+TDF (median change at post-dose Day 2 of -10.5 mL/min) and COBI (median change at post-dose Day 2 of -9.0 mL/min) with improvements observed after dosing was discontinued. In the TDF treatment phase smaller decreases occurred.

Related to this study, the applicant explored the possible reasons for the increased plasma levels of TFV when give with COBI as follows:

TDF (but not TFV) is a substrate for Pgp. Inhibition of intestinal Pgp results in modest changes in TFV exposure when given with inhibitors or inducers of Pgp, including RTV, COBI and RPV. The basis for drug

interactions between RTV-boosted HIV-1 PIs and TDF has been ascribed to inhibition of Pgp-mediated intestinal efflux of TDF. The data are consistent with the interaction between COBI and TDF having the same basis. The magnitude of increase in TFV exposure when administered with COBI is comparable to that observed with other Pgp inhibitors, such as RTV and RPV. Additionally, there was no change in TFV plasma half-life when it was given as a component of the Stribild vs. TDF alone, which is consistent with an effect on bioavailability and not on systemic clearance.

Tenofovir DF is not considered to be transported by MRP2 or BCRP so it is not affected by inhibition of these transporters or by any pharmacogenomics-driven effects on their functionality. The COBI IC50 for inhibition of MRP2 is 71 μM. COBI is not considered to inhibit renal MRP2 since the ratio for C_{max}/IC50 is 0.02 (i.e. 1.5 μM / 71 μM), which is well below the 0.1 threshold for interaction potential. However, COBI could inhibit intestinal MRP2 at concentrations theoretically achievable in the intestinal lumen following a 150 mg oral dose.

The participation of transporters in the renal excretion of TFV has been well-characterized in vitro and involves uptake by OAT1 and OAT3 and efflux by MRP4. COBI showed no inhibition of OAT1 and OAT3 (IC50 values exceeded 100 μM). Based on a COBI IC50 for MRP4 transport of 20.7 μM and plasma unbound C_{max} of 90 nM this level of inhibition is not considered to be pharmacologically relevant. EVG did not markedly inhibit OAT1, OAT3 or MRP4 at the highest concentrations tested (IC50 > 20 μM).

GS-US-216-0112 was designed to evaluate the effects of COBI on CYP2D6 and 2B6 and on Pgp. Subjects were enrolled into one of 3 cohorts to receive the following oral treatments in the fed state:

Cohort 1 (CYP2D6)	A: Desipramine 50 mg as a single dose in the morning
	B: COBI 150 mg once daily for 10 days + desipramine 50 mg on the 10th day
Cohort 2 (Pgp)	C: Digoxin 0.5 mg as a single dose in the morning
	D: COBI 150 mg once daily for 10 days + digoxin 0.5 mg on the 10th day
Cohort 3 (CYP2B6)	E: EFV 600 mg as a single dose in the morning
	F: COBI 150 mg once daily for 10 days + EFV 600 mg on the 10th day

Co-administration of desipramine with COBI resulted in increases in desipramine C_{max}, AUC_{inf} and AUC_{0-last}. Digoxin C_{max} and AUC_{0-last} increased but AUC_{inf} remained unchanged with co-administration. EFV C_{max} decreased but $AUC_{0-last/inf}$ remained unchanged with co-administration.

Table 24.

Plasma PK Parameter	Mean (%CV)		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Desipramine: Desipramine 50 mg + COBI 150 mg (Test) versus Desipramine 50 mg (Reference) (n = 8)				
AUC_{inf} (ng•h/mL)	1205.0 (64.7)	752.0 (83.3)[a]	165.41	135.76, 201.54
AUC_{0-last} (ng•h/mL)	970.4 (51.2)	650.9 (66.3)	157.52	134.88, 183.95
C_{max} (ng/mL)	33.2 (28.2)	27.9 (43.6)	124.31	107.54, 143.68
Digoxin: Digoxin 0.5 mg + COBI 150 mg (Test) versus Digoxin 0.5 mg (Reference) (n = 22)				
AUC_{inf} (ng•h/mL)	34.7 (26.6)[b]	31.9 (24.1)[c]	107.73	99.58, 116.55
AUC_{0-last} (ng•h/mL)	26.5 (28.1)	22.0 (28.2)	119.60	109.98, 130.06
C_{max} (ng/mL)	2.5 (32.3)	1.7 (24.9)	140.95	128.52, 154.58
EFV: EFV 600 mg + COBI 150 mg (Test) versus EFV 600 mg (Reference) (n = 17, all evaluable)				
AUC_{inf} (ng•h/mL)	150,254.8 (27.2)	161,453.8 (25.5)	92.88	89.22, 96.69
AUC_{0-last} (ng•h/mL)	129,806.8 (29.1)	139,120.4 (26.2)	92.84	89.70, 96.09
C_{max} (ng/mL)	3866.4 (20.6)	4400.2 (14.4)	86.62	79.59, 94.27
EFV: EFV 600 mg + COBI 150 mg (Test) versus EFV 600 mg (Reference) (n = 16, excluding outlier)				
AUC_{inf} (ng•h/mL)	149,452.1 (28.2)	161,369.5 (26.3)	92.43	88.59, 96.44
AUC_{0-last} (ng•h/mL)	129,900.2 (30.0)	139,615.9 (27.0)	92.53	89.20, 95.98
C_{max} (ng/mL)	3929.3 (19.8)	4329.2 (13.4)	89.45	83.30, 96.05
COBI: Desipramine 50 mg + COBI 150 mg (n = 9)				
AUC_{tau} (ng•h/mL)	17,850.4 (25.5)	—	—	—
C_{tau} (ng/mL)	146.1 (63.5)	—	—	—
C_{max} (ng/mL)	1905.3 (16.2)	—	—	—
COBI: Digoxin 0.5 mg + COBI 150 mg (n = 22)				
AUC_{tau} (ng•h/mL)	15,637.7 (30.6)	—	—	—
C_{tau} (ng/mL)	116.2 (75.1)	—	—	—
C_{max} (ng/mL)	1816.5 (22.1)	—	—	—
COBI: EFV 600 mg + COBI 150 mg (n = 17)				
AUC_{tau} (ng•h/mL)	14,784.4 (32.5)	—	—	—
C_{tau} (ng/mL)	103.8 (87.9)	—	—	—
C_{max} (ng/mL)	1692.5 (19.9)	—	—	—

Co-administration of COBI and desipramine resulted in CYP2D6 inhibition (58% and 65% increases in AUC_{0-last} and AUC_{inf}, respectively, and 24% increase in C_{max}). A small reduction in the C_{max} of EFV was observed upon co-administration with COBI. In addition, the applicant considered that co-administration with digoxin may have resulted in transient inhibition of gut Pgp as evidenced by an increase in digoxin C_{max}. These changes were not considered to require dose modifications or to necessitate additional DDI studies with substrates of CYP2D6, CYP2B6 or Pgp.

In GS-US-216-0101 MDZ 5 mg (oral syrup) was administered orally on Days 0 and 14.

Table 25.

MDZ Plasma PK Parameter	MDZ Alone (N = 60)	MDZ + COBI 50 mg (N = 12)	MDZ + COBI 100 mg (N = 11)	MDZ + COBI 200 mg (N = 12)	MDZ + RTV 100 mg (N = 9)
C_{max} (ng/mL)	14.5 (28.5)	45.3 (26.6)	55.0 (17.5)	56.0 (20.7)	58.5 (16.4)
AUC_{0-last} (ng•h/mL)	58.0 (29.2)	493.2 (34.1)	665.3 (17.8)	690.1 (16.2)	729.4 (22.9)
AUC_{inf} (ng•h/mL)	64.1 (33.3)	626.0 (49.9)	855.7 (18.2)	1219.6 (26.6)[a]	1526.3 (42.8)
C_{last} (ng/mL)	0.6 (69.0)	7.4 (70.6)	11.8 (26.9)	16.9 (25.4)	18.9 (40.2)
T_{max} (h)	1.00 (1.00, 2.00)	1.75 (1.27, 3.75)	4.00 (2.50, 4.52)	2.25 (1.75, 4.25)	3.00 (2.00, 4.00)
$T_{½}$ (h)	5.23 (3.85, 6.89)	8.89 (6.35, 10.89)	11.23 (8.24, 12.92)	19.35 (11.34, 28.22)[a]	25.79 (16.37, 35.10)
T_{last} (h)	16.00 (16.00, 16.00)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)
CL/F (mL/h)	87,336.1 (35.4)	9660.6 (41.8)	6019.8 (17.9)	4351.4 (24.3)[a]	3935.5 (45.4)

COBI 200 mg and RTV 100 mg exhibited similar inhibition of MDZ CL/F (−94.8% and −95.6%, respectively) and gave 19.2- and 22.5-fold increases in MDZ AUC (vs. MDZ alone). The lower COBI dose (100 mg) achieved slightly less inhibition of MDZ CL/F (−92.7% vs. MDZ alone).

EVG + COBI

GS-US-216-0120 evaluated co-administration of EVG/COBI 150/150 mg with omeprazole or famotidine over 8 days using different timings of administrations. Omeprazole and famotidine did not affect PK EVG or COBI when dosing was separated by 12 h. When omeprazole was given 2 h before EVG/COBI there was no appreciable effect on PK COBI. Plasma levels of EVG increased slightly with 90% CI for C_{max} and C_{tau} that exceeded the upper limit but the AUC ratio was 110 [102, 119]. GS-US-216-0122 then evaluated EVG/COBI 150/150 mg co-administered with famotidine 40 mg once daily and showed no significant effects on PK EVG or COBI.

GS-US-216-0123 evaluated once daily dosing of EVG/COBI as follows:

- EVG/COBI 150/150 mg with/without a single dose of rosuvastatin 10 mg. Rosuvastatin did not affect PK EVG.
- EVG/COBI 85/150 with/without ATV 300 mg vs. ATV/rtv 300/100 mg. Co-administration with ATV did not affect the EVG AUC_{tau} while C_{max} was modestly lower (~ 15%) and C_{tau} was higher than observed with EVG/COBI 150/150 mg alone (see also GS-US-183-0106)
- EVG/COBI 150/150 mg with/without rifabutin 150 mg every other day vs. rifabutin 300 mg once daily taken alone. On co-administration the EVG C_{max} was unchanged but the AUC_{tau} was modestly (~ 20%) lower and C_{tau} markedly (~ 63%) lower vs. EVG/COBI given alone.
    - COBI exposures were generally comparable across treatments, but substantially lower at 18 and 24 h following co-administration with rifabutin with a lower t1/2.
    - The RTV AUC_{tau} and C_{max} values (10,947 ng•h/mL and 2191 ng/mL, respectively) were comparable to values observed with ATV/r dosing in GS-US-183-0106 and GS-US-183-0108.
    - Rosuvastatin C_{max} and AUC were greater (89% and 38%, respectively) following EVG/co plus ROS administration, but the overall concentration-time profile (and t1/2) was similar relative to ROS dosing alone. The applicant considered that this interaction did not require dose adjustment.

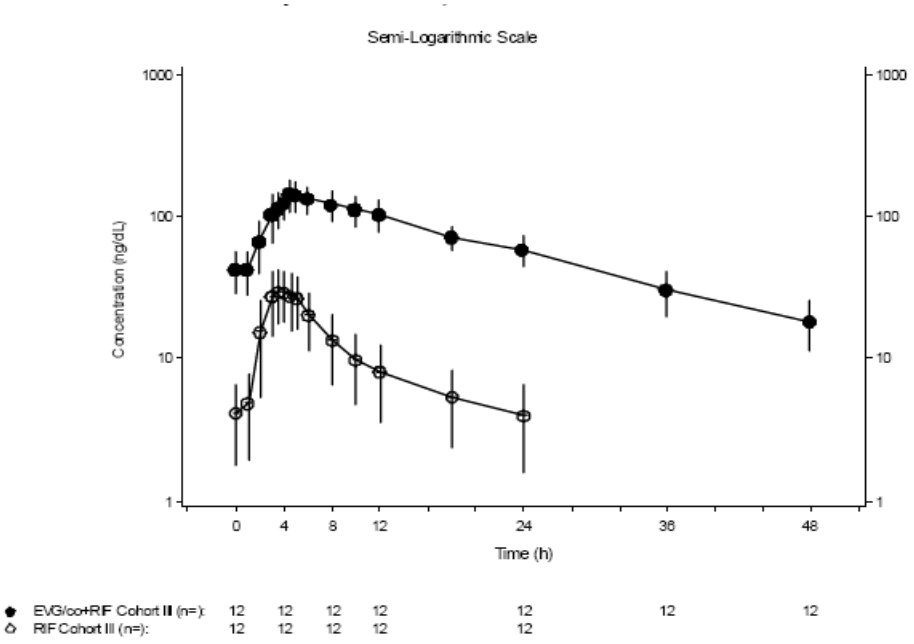
Table 26.

ROS PK Parameter	Geometric Least Squares Means		Geometric Least Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
EVG/co + ROS (Test) vs ROS (Ref) in Cohort I	N=10	N=10		
AUC_{inf} (ng•h/mL)	34.99	25.36	137.98	113.83, 167.25
C_{max} (ng/mL)	4.46	2.35	189.31	148.19, 241.84
C_{last} (ng/mL)	0.14	0.10	143.10	108.22, 189.22

- The ATV AUC_{tau} was lower (10-12%) when given with EVG/COBI vs. ATV/rtv. C_{max} was ~ 21-24% lower and C_{tau} was ~ 20-35% lower, although C_{tau} was well above the DHHS recommended target (140 ng/mL) in all subjects.
- The AUC_{tau}, C_{max} and C_{tau} rifabutin were comparable between the EVG/COBI + rifabutin 150 mg dose and 300 mg given alone. The median T½ was 11.7 h when rifabutin was given alone but was 28.6 h following concomitant administration.

  Co-administration with EVG/COBI resulted in large increases in AUC_{tau}, C_{max} and C_{tau} of 25-O-desacetylrifabutin vs. rifabutin alone. [The AUC_{tau} of 25-O-desacetylrifabutin after administration alone was doubled for the comparison because of the different dosing frequencies]. The applicant estimated that antimycobacterial activity was unaffected by co-administration (ratio 120.9 [107, 136]).

Figure 3. GS-US-216-0123: Mean (SD) 25-*O*-desacetylrifabutin Plasma Concentration – Time Profiles (Analysis Set: 25-*O*-desacetylrifabutin PK).



GS-US-216-0125 was provided during the procedure. It evaluated the drug interaction potential between once-daily EVG/co and methadone or buprenorphine/naloxone (BUP/NLX). Eligible subjects were assigned to a cohort based on their chronic regimen for opioid use (i.e. Cohort 1–methadone; Cohort 2-BUP/NLX) and received their dose with and without EVG 150 mg + COBI 150 mg once daily in the morning with a light meal.

R-methadone plasma concentrations were slightly higher following co-administration with EVG/co while S-methadone plasma concentrations were more closely comparable across treatments. However, the 90% CI around the GLSMs for R- and S-forms fell within 80, 125% for both AUC and C_{max}.

Table 27. GS-US-216-0125: Statistical Comparison of Methadone Pharmacokinetic Parameters for Test Versus Reference Treatments (Analysis Set: Methadone PK).

PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
R-Methadone EVG/co + Methadone (Test) vs Methadone (Reference), (N = 11)				
AUC_{tau} (ng•h/mL)	5822.95	5442.79	106.98	(96.06, 119.16)
C_{max} (ng/mL)	315.17	310.78	101.41	(90.75, 113.32)
C_{tau} (ng/mL)	210.43	191.30	110.00	(94.84, 127.58)
S-Methadone EVG/co + Methadone (Test) vs Methadone (Reference), (N = 11)				
AUC_{tau} (ng•h/mL)	6617.31	6606.32	100.17	(89.38,112.26)
C_{max} (ng/mL)	406.11	423.37	95.92	(86.62,106.23)
C_{tau} (ng/mL)	211.99	207.46	102.19	(89.24,117.01)

Inhibition of CYP3A4 by COBI would not be expected to significantly influence methadone exposures and the comparable exposures of both methadone enantiomers observed in the presence or absence of EVG/co confirm there is no inductive effect on CYP2B6 and/or CYP2C19. The totality of the data indicates the lack of effect on methadone PK and/or PD by EVG/co.

The primary comparison for BUP was co-administration vs. dosing alone, with each subject serving as their own control. BUP exposures were higher following co-administration with EVG/co. BUP T1/2 could not be reliably estimated due to limited sampling duration relative to the T1/2 of 24-42 h).

Plasma concentrations of norBUP were also higher following co-administration with EVG/co while Tmax values were comparable. The norBUP T1/2 could not be reliably estimated due to limited sampling duration relative to the T1/2 of norBUP (~44 hours).

Table 28. GS-US-216-0125: Statistical Comparison of BUP Pharmacokinetic Parameters for Test Versus Reference Treatments (Analysis Set: BUP PK).

BUP PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
EVG/co + BUP/NLX (Test) vs BUP/NLX (Reference), (N = 17)				
AUC_{tau} (ng•h/mL)	83.80	61.95	135.26	(118.25,154.72)
C_{max} (ng/mL)	8.43	7.55	111.69	(97.94,127.36)
C_{tau} (ng/mL)	2.08	1.25	166.28	(143.14,193.17)

Table 29. GS-US-216-0125: Statistical Comparison of norBUP Pharmacokinetic Parameters for Test Versus Reference Treatments (Analysis Set: norBUP PK).

norBUP PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
EVG/co + BUP/NLX (Test) vs BUP/NLX (Reference), (N = 17)				
AUC_{tau} (ng•h/mL)	125.48	88.09	142.45	(121.60,166.88)
C_{max} (ng/mL)	7.06	5.71	123.71	(102.67,149.05)
C_{tau} (ng/mL)	4.87	3.10	156.89	(130.66,188.39)

NLX plasma concentrations were slightly higher when given as BUP/NLX alone vs. co-administration with EVG/co. Consistent with the short T1/2, plasma concentrations of NLX in both treatments were BLQ at 24 hours post-dose.

Table 30. GS-US-216-0125: Statistical Comparison of NLX Parameters for Test Versus Reference Treatments (Analysis Set: NLX PK).

NLX PK Parameter	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test Treatment	Reference Treatment		
EVG/co + BUP/NLX (Test) vs BUP/NLX (Reference), (N = 17)				
AUC_{tau} (ng•h/mL)	0.299	0.418	71.57	(58.65,87.33)
C_{max} (ng/mL)	0.135	0.188	72.13	(61.44,84.67)

Inhibition of CYP3A4 by COBI gave a modest increase in the BUP and norBUP (~2% as potent as parent compound), which is in line with the change expected when CYP3A does not have a predominant role in drug elimination. The BUP and norBUP exposures observed following BUP/NLX administration alone were in the range of historical data.

The reasons for the decrease in NLX exposures, which show intersubject variability, are unclear. The range of NLX exposures across both treatments were comparable with those reported on dosing with BUP/NLX alone or in combination with ARVs. The totality of the data indicates there is no clinically relevant influence of EVG/co administration on the PK or PD of BUP/NLX. This is consistent with previous ARV-opioid DDI studies where a modest change in drug levels is not accompanied by a measurable change in pharmacodynamic endpoint (BUP/NLX + RTV resulted in a 57% and 33% increase AUC for BUP and norBUP, respectively, versus BUP/NLX alone, with no change in PD).

EVG plasma concentrations were comparable on co-administration with each opioid and were in the range of historical data with EVG/co or Stribild (mean [%CV] EVG AUC_{tau}: 18,695.8 [35.1] ng*h/mL GS-US-216-0123; and 22,485.9 [26.7] ng*h/mL GS-US-236-0110).

COBI PK parameters were also comparable between treatments and in the range of historical data with EVG/co or Stribild (mean [%CV] COBI AUC_{tau}: 10,389.4 [38.6] ng*h/mL GS-US-216-0123; and 11,288.2 [28.5] ng*h/mL GS-US-236-0110).

Opioid PD was assessed using the standardized tests SOWS, OOWS, COWS, and OOAS daily prior to the morning dosing. The resulting scores observed were minimal in all treatments relative to the overall test score range. The clinical significance and relevance of the change from baseline in PD scores and the resulting conclusions on PD-related changes was primarily based on investigator assessments of patients and associated clinical judgement, including the individual signs and symptoms that contributed to the total score. Accordingly, the values present a descriptive summary of the PD scores, which indicate

minimal to no change in these values upon co-administration of opioids with EVG/co vs. opioid dosing alone. In each Cohort these data indicate no meaningful changes in the opioid pharmacodynamics and a lack of relevant withdrawal and overdose symptoms. No subjects experienced withdrawal or overdose symptoms.

Stribild

GS-US-236-0106 was conducted with Stribild and an oral contraceptive containing norgestimate and ethinyl oestradiol (0.025 mg). Co-administration was for 9 days in subjects at least in the second dosing cycle and resulted in creases in norelgestromin AUC_{tau}, C_{max} and C_{tau} but decreases in ethinyl oestradiol AUC_{tau} and C_{tau}. EVG and COBI levels were in the expected range.

Serum progesterone remained unchanged while FSH decreased to a similar extent and LH showed a larger decrease on co-administration. The applicant concluded that doses of < 0.25 mg ethinyl oestradiol should not be used in conjunction with Stribild.

GS-US-236-0120 was provided during the procedure. This was an open-label study to evaluate the PK of COBI-boosted EVG administered as Stribild before and after treatment with Atripla (ATR) in 32 healthy subjects. A subpopulation of 8 healthy subjects had a genetic polymorphism in CYP2B6 associated with decreased CYP2B6 metabolic activity and reduced efavirenz (EFV) clearance. Eligible subjects received the following:

- Period 1: Stribild once daily (Days 1-7) within 5 minutes of completion of a standard meal
- Period 2: ATR once daily (Days 15-28) in the fasting state
- Period 3: Stribild once daily (Days 29-62) within 5 minutes of completion of a standard meal

There was a 7-day washout between Periods 1 and 2 but not between Periods 2 and 3.

EVG and COBI reference exposures (Day 7) were similar to those reported from previous studies with Stribild (GS-US-236-0101 and GS-US-236-0110).

Following administration of Stribild after switching from treatment with ATR, EVG exposures for 29 PK evaluable subjects were lower with 90% CI around GLSMs that fell outside of 70% to 143% at 1 (D35) and 2 weeks (D42) post-switch vs. Day 7 pre-switch.

Table 31. GS-US-236-0120: Summary Statistics for Elvitegravir Pharmacokinetic Parameters (Analysis Set, Elvitegravir PK).

EVG PK Parameter	QUAD Day 7 (N = 29)	QUAD Day 35 (N = 29)	QUAD Day 42 (N = 29)
AUC_{tau} (ng•h/mL), Mean (%CV)	22064.1 (26.1)	14312.9 (35.5)	15782.0 (30.4)
C_{max} (ng/mL), Mean (%CV)	2021.0 (31.2)	1717.7 (45.1)	1821.4 (37.3)
C_{tau} (ng/mL), Mean (%CV)	435.9 (38.0)	153.5 (69.4)	210.2 (50.6)
T_{max} (h), Median (Q1, Q3)	4.50 (4.00, 4.50)	4.50 (4.00, 4.50)	4.50 (4.00, 4.50)
$t_{½}$ (h), Median (Q1, Q3)	9.66 (8.66, 10.75)	6.48 (4.15, 7.21)	7.11 (5.81, 8.68)

%CV, percent of coefficient of variation; Q1, first quartile; Q3, third quartile

EVG PK Parameter	Test Mean (%CV) N = 29	Reference Mean (%CV) N = 29	GLSM Ratio (Test/Reference) (%)	90% Confidence Interval
QUAD (Day 35) (Test) vs. QUAD (Day 7) (Reference)				
AUC_{tau} (ng•h/mL)	14312.9 (35.5)	22064.1 (26.1)	63.10	59.81, 66.57
C_{max} (ng/mL)	1717.7 (45.1)	2021.0 (31.2)	81.50	76.00, 87.39
C_{tau} (ng/mL)	153.5 (69.4)	435.9 (38.0)	32.82	28.26, 38.13
QUAD (Day 42) (Test) vs. QUAD (Day 7) (Reference)				
AUC_{tau} (ng•h/mL)	15782.0 (30.4)	22064.1 (26.1)	70.84	67.15, 74.73
C_{max} (ng/mL)	1821.4 (37.3)	2021.0 (31.2)	88.70	82.72, 95.12
C_{tau} (ng/mL)	210.2 (50.6)	435.9 (38.0)	44.53	38.56, 51.42

The data from the CYP2B6 poor metabolizers were used to evaluate the effect on EVG and COBI of the higher levels of EFV that occurred at the time of switching from ATR to Stribild. These CYP2B6 poor metabolizers displayed lower EVG exposures (AUC_{tau}) at Day 7 but the difference was even greater at 1 and 2 weeks post-switch (39% and 29% lower, respectively) compared with non-poor metabolizers.

Table 32. GS-US-236-0120: Summary Statistics for Elvitegravir Pharmacokinetic Parameters (Analysis Set, Elvitegravir PK CYP2B6 Poor and Nonpoor Metabolizers).

EVG PK Parameter	QUAD Day 7	QUAD Day 35	QUAD Day 42
CYP2B6 Poor Metabolizers of EFV (N = 7)			
AUC_{tau} (ng•h/mL), Mean (%CV)	18343.1 (25.4)	9631.1 (30.5)	12107.0 (25.2)
C_{max} (ng/mL), Mean (%CV)	1719.4 (30.1)	1332.2 (38.4)	1553.0 (36.4)
C_{tau} (ng/mL), Mean (%CV)	340.1 (40.6)	38.8 (110.2)	97.9 (53.6)
T_{max} (h), Median (Q1, Q3)	4.00 (4.00, 4.50)	4.00 (4.00, 4.00)	4.00 (4.00, 4.50)
$t_{½}$ (h), Median (Q1, Q3)	8.60 (7.83, 12.92)	3.46 (2.80, 4.81)	5.51 (4.22, 6.25)
Nonpoor Metabolizers of EFV (N = 22)			
AUC_{tau} (ng•h/mL), Mean (%CV)	23248.0 (24.3)	15802.5 (29.9)	16951.3 (27.7)
C_{max} (ng/mL), Mean (%CV)	2117.0 (30.4)	1840.4 (44.2)	1906.8 (36.8)
C_{tau} (ng/mL), Mean (%CV)	466.4 (35.3)	190.0 (49.5)	245.9 (38.0)
T_{max} (h), Median (Q1, Q3)	4.50 (4.00, 4.50)	4.50 (4.00, 4.50)	4.50 (4.00, 4.50)
$t_{½}$ (h), Median (Q1, Q3)	9.68 (9.10, 10.64)	6.90 (5.87, 8.07)	7.80 (6.76, 8.79)

%CV, percent of coefficient of variation; Q1, first quartile; Q3, third quartile

All subjects (including the CYP2B6 poor metabolizers) had EVG trough concentrations above the protein-binding adjusted IC95 (44.5 ng/mL) at 2 weeks post-switch. Percentages of all 29 subjects below the IC95 at 3, 5, 7, 10 and 12 days post-switch were 48%, 31%, 17%, 10% and 10%, respectively. In the subset of CYP2B6 poor metabolizers the percentages below the IC95 at 3, 5, 7, 10 and 12 days post-switch were 100%, 86%, 57%, 43% and 43%, respectively.

The mean EVG trough concentration for all 29 subjects was ~3-fold and ~5-fold greater than the IC95 at 1 week and 2 weeks post-switch, respectively, and 7 to 8-fold above the IC95 at 5 weeks post-switch.

Exposures (AUC_{tau}) of GS-9200, the glucuronidated metabolite of EVG, were higher (46.64% and 37.03% on Days 35 and 42, respectively, vs. Day 7) post-switch. Concentrations of the primary hydroxylated metabolite GS-9202 were BLLQ.

The GLSM ratio of COBI exposure parameters (AUC_{tau} and C_{max}) and 90% CIs were within 70% to 143% by 1 week post-switch vs. reference levels on Day 7. The COBI C_{tau} was 35% lower at 2 weeks post-switch.

Table 33. GS-US-236-0120: Statistical Comparison of Cobicistat Pharmacokinetic Parameters for Test Versus Reference Treatments (Analysis Set, Cobicistat PK).

COBI PK Parameter	GLSM		GLSM Ratio (Test/Reference) (%)	90% Confidence Interval
	Test (N = 29)	Reference (N = 29)		
QUAD (Day 35) (Test) vs. QUAD (Day 7) (Reference)				
AUC_{tau} (ng•h/mL)	9027.11	11294.49	79.92	74.57, 85.67
C_{max} (ng/mL)	1340.48	1508.37	88.87	84.14, 93.86
C_{tau} (ng/mL)	15.86	30.62	51.80	45.48, 59.01
QUAD (Day 42) (Test) vs. QUAD (Day 7) (Reference)				
AUC_{tau} (ng•h/mL)	10033.66	11294.49	88.84	82.88, 95.22
C_{max} (ng/mL)	1436.66	1508.37	95.25	90.18, 100.60
C_{tau} (ng/mL)	19.91	30.62	65.02	57.52, 73.50

Treatment with ATR for 2 weeks is stated to have resulted in EFV levels consistent with the dose described in the Sustiva US prescribing information. CYP2B6 poor metabolizers displayed higher EFV AUC_{tau} and C_{max} compared with non poor metabolizers (125% and 91% higher, respectively).

Table 34.

EFV PK Parameter	ATR Day 28
All Subjects (N = 30)	
AUC_{tau} (ng•h/mL), Mean (%CV)	65571.1 (53.9)
C_{max} (ng/mL), Mean (%CV)	3811.3 (44.1)
CYP2B6 Poor Metabolizers of EFV (N = 8)	
AUC_{tau} (ng•h/mL), Mean (%CV)	110752.0 (30.2)
C_{max} (ng/mL), Mean (%CV)	5857.1 (30.4)
C_{tau} (ng/mL), Mean (%CV)	4046.4 (31.1)
Nonpoor Metabolizers of EFV (N = 22)	
AUC_{tau} (ng•h/mL), Mean (%CV)	49141.7 (34.8)
C_{max} (ng/mL), Mean (%CV)	3067.4 (26.8)
C_{tau} (ng/mL), Mean (%CV)	1611.3 (44.4)

Following the final ATR dose (Day 28) in all subjects completing the study the EFV trough concentration was above the suggested MEC of 1000 ng/mL for 3 days post-switch from ATR to Stribild. Mean EFV trough concentration in all subjects was above the protein-binding adjusted IC90 (10 ng/mL) through 3-5 weeks post-switch. All CYP2B6 poor metabolizers had EFV trough concentration levels above the IC90 through 4 weeks post-switch, while 4/7 had EFV trough concentration levels above IC90 through 5 weeks post-switch.

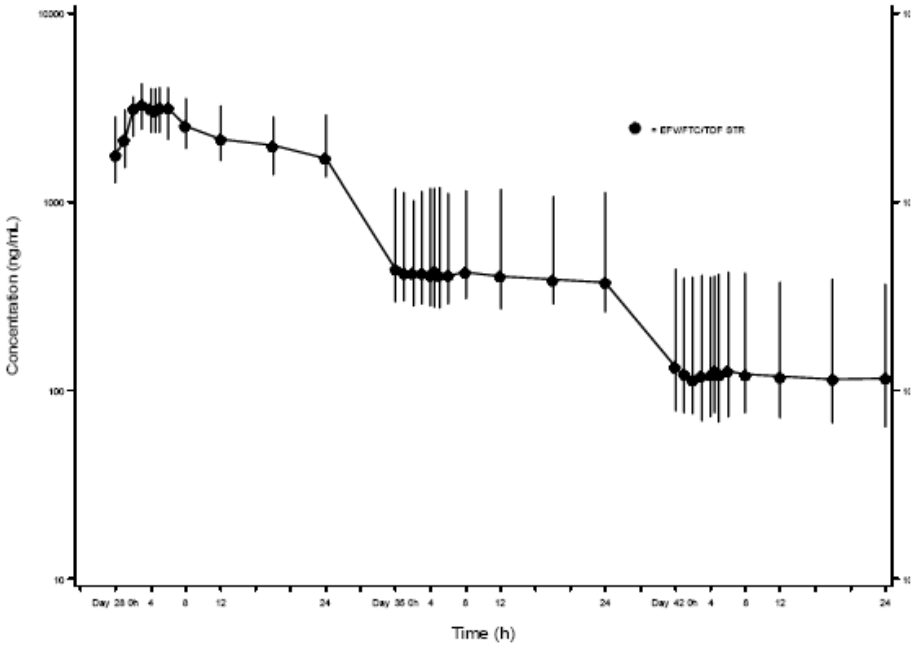
The table below shows the troughs according to CYP2B6 status and the figure shows the EFV plasma levels for all subjects on days 28, 35 and 42 of the study.

Table 35. GS-US-236-0120: Summary Statistics of Efavirenz Trough Concentrations (ng/mL) (Analysis Set, Efavirenz PK CYP2B6 Poor and Nonpoor Metabolizers)

	Day 29	Day 31	Day 33	Day 36	Day 38	Day 40	Day 43	Day 46	Day 49	Day 56	Day 63
CYP2B6 Poor Metabolizers of EFV											
N	8	8	7	7	7	7	7	7	7	7	7
EFV C_{trough} (ng/mL), Mean (%CV)	4046.4 (31.1)	3026.1 (33.9)	1966.0 (28.6)	1302.7 (29.8)	962.0 (31.8)	698.7 (49.0)	476.4 (59.4)	312.1 (76.1)	200.0 (98.8)	89.0 (131.2)	36.8 (174.3)
Nonpoor Metabolizers of EFV (N = 22)											
EFV C_{trough} (ng/mL), Mean (%CV)	1611.3 (44.4)	1014.4 (59.4)	676.4 (70.8)	431.4 (86.4)	328.1 (95.5)	226.2 (98.8)	145.8 (111.5)	100.5 (120.6)	66.9 (140.5)	29.3 (182.4)	11.7 (219.1)

%CV, percent of coefficient of variation; C_{trough}, trough concentration

Figure 4. GS-US-236-0120: Mean (SD) Efavirenz Plasma Concentration – Time Profiles (Semi-Logarithmic Scale; Analysis Set, Efavirenz PK).



FTC plasma exposures following treatment with Stribild were described as being comparable before and after ATR treatment.

TFV plasma concentrations were described as comparable at 1 and 2 weeks post-switch vs. TFV levels on Day 7, while TFV levels were lower following administration of ATR vs. Stribild.

Table 36. GS-US-236-0120: Summary Statistics for Tenofovir Pharmacokinetic Parameters (Analysis Set, Tenofovir PK).

TFV PK Parameter	QUAD Day 7 (N = 31)	ATR Day 28 (N = 30)	QUAD Day 35 (N = 29)	QUAD Day 42 (N = 29)
AUC_{tau} (ng•h/mL), Mean (%CV)	3937.8 (20.3)	2276.3 (18.9)	3519.8 (24.0)	3467.4 (23.4)
C_{max} (ng/mL), Mean (%CV)	441.9 (24.1)	314.4 (24.9)	403.3 (35.3)	383.3 (29.2)
C_{tau} (ng/mL), Mean (%CV)	79.1 (25.0)	45.9 (21.0)	72.5 (28.6)	71.3 (25.7)
T_{max} (h), Median (Q1, Q3)	2.00 (1.00, 2.00)	1.00 (1.00, 1.00)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)
$t_{½}$ (h), Median (Q1, Q3)	14.40 (12.74, 15.86)	15.06 (12.64, 17.37)	14.55 (13.86, 16.05)	14.70 (13.19, 15.45)

The applicant's conclusions from this study (note they are based on the applicant's pre-defined acceptance criteria of 90% CI within 70-143%) were as follows:

- At 1 and 2 weeks after switching from ATR to Stribild the mean EVG exposures for all subjects were lower, which is likely due to induction of CYP3A4 and UGT1A1 by EFV.
- CYP2B6 poor metabolizers displayed lower EVG AUC_{tau} at 1 and 2 weeks post-switch (39% and 29% lower, respectively), compared with nonpoor metabolizers.
- All subjects had EVG trough concentrations > protein-binding adjusted IC95 (44.5 ng/mL) at 2 weeks post-switch. Percentages below the IC95 at 3 and 12 days post-switch were 48% and 10%, respectively. Mean EVG trough concentration increased from ~3-fold and ~5-fold greater than the IC95 at 1 week and 2 weeks post-switch, respectively, to 7 to 8-fold above the IC95 at 5 weeks post-switch.
- The AUC_{tau} of GS-9200 was higher (46.64% and 37.03% on Days 35 and 42, respectively) post-switch.
- CYP2B6 poor metabolizers displayed higher EFV AUC_{tau} and C_{max} as compared with nonpoor metabolizers (125% and 91% higher, respectively). The EFV trough concentration was above the MEC (1000 ng/mL) for 3 days post-switch and above the protein-binding adjusted IC90 (10 ng/mL) through 3 weeks post-switch.
- Post-switch COBI exposures were comparable except that C_{tau} was lower (GMR on Day 42: 65.02 [57.52, 73.50]).
- FTC and TFV were comparable when Stribild was given before and after ATR.

Overall, the study subject population, including a limited numbers of CYP2B6 poor metabolizers, displayed exposures of EFV and/or EVG in a range associated with antiviral activity through 5 weeks post-switch from ATR to Stribild.

Comment on pharmacokinetics

The applicant conducted a comprehensive investigation of the PK of the two new active substances (EVG and COBI) contained in Stribild when administered alone, together and as part of the Stribild film-coated tablet. The PK data obtained with the F1 and F2 Stribild tablets were relatively limited but are critically important. There are data from HIV-infected subjects enrolled into Phase 2 and 3 studies and comparisons with data obtained in healthy subjects.

EVG showed auto-induction of metabolism when administered without RTV or COBI. With 100 mg RTV or with 150 mg COBI there appeared to be maximal inhibition of CYP3A4-mediated metabolism. The large increase in exposure to EVG on co-administration with RTV was attributed to improved oral bioavailability due to decreased first pass metabolism and to reduced systemic clearance. The formation of the M4 glucuronide metabolite was not affected by RTV or COBI. On co-administration with RTV 100 mg the EVG 125 mg tablet was bioequivalent to the 150 mg final formulation (F2) tablet. Stribild incorporates 150 mg F2 EVG.

The EVG C24 was ~ 26% higher following multiple-dose administration of the F2 formulation (349 vs. 440 ng/mL), consistent with the development of mechanism-based inhibition of CYP3A by RTV and consequent reduction in EVG systemic clearance as well as progression to steady-state conditions.

The bioavailability of COBI increased with dose and with multiple vs. single dose administrations. The greater than dose-proportional increases in AUC were consistent with its metabolic auto-inhibition properties. The large decreases in CL/F and increases in T1/2, AUC and C_{max} with multiple doses were considered to reflect changes in COBI bioavailability, systemic clearance or both with time. The F1 and F2 formulations were bioequivalent. Stribild incorporates 150 mg F2 COBI, reflecting the data obtained in GS-US-236-0101 in which Stribild containing COBI 150 mg gave a slightly higher EVG plasma exposure (AUC and trough) vs. COBI 100 mg.

Based on the food effect study GS-US-236-0105, Stribild was administered with food in Phase 2/3 studies to achieve desired exposures of EVG that maintain high inhibitory quotient. The SmPC also recommends administration with food (unspecified). It is pertinent to note the different effects of a high fat/kcal meal compared to a light meal on EVG, COBI and TFV in GS-US-326-0105. The exact dosing conditions in the Phase 2/3 studies are not known.

Data from healthy subjects and from HIV-infected subjects have demonstrated that plasma exposures to TFV and FTC when TDF and FTC are given with COBI are higher compared to FTC + TDF co-administration and to TDF given alone. The applicant demonstrated that the data were comparable with TFV exposure when TDF was co-administered with a PI/r in prior studies and attributed the higher TFV exposures to the effect of COBI on handling of TDF by Pgp (MDR1) in the gut. Additional transporter studies were performed to demonstrate that neither COBI nor EVG is likely to have an important effect on the three transporters that are involved in the renal elimination of TFV.

COBI administration is associated with a decrease in the estimated CL_{cr} due to inhibition of tubular secretion of creatinine via its effect on MATE1.

Stribild will not be used in severe renal impairment because the dose-interval adjustment that is required for FTC and TDF in patients with CL_{cr} < 50 mL/min cannot be achieved with the FDC. Stribild has not been studied in patients with severe hepatic impairment.

Given the results of the DDI studies (e.g. EVG/rtv 200/100 mg plus ATV/rtv 300/100 mg) it is possible that EVG levels could be affected by UGT1A1/1A3 polymorphisms. A PK study of EVG in subjects with UGT1A1*28/*28 genotype administered STB to obtain information on EVG exposure in patients with UGT1A1 polymorphism associated with decreased activity of UGT1A1 is included in the RMP and expected by Q2 2015.

Based on the DDI profile of EVG and COBI the applicant has concluded that Stribild must not be co-administered with drugs with narrow therapeutic ranges that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with severe and/or life-threatening events. In addition, Stribild should not be given with potent CYP3A inducers, as these could decrease plasma levels of COBI, and hence reduce EVG plasma concentrations with the attendant risk of a clinically important negative effect on efficacy.

In GS-US0216-0112 the digoxin C_{max} and AUC0−last increased but AUC_{inf} remained unchanged when 0.5 mg was given on day 10 of COBI 150 mg daily compared with 0.5 mg digoxin alone. The applicant considered that although COBI is regarded as a weak inhibitor of Pgp it is highly soluble so it may achieve transient inhibition of gut Pgp during its absorption and increase digoxin C_{max} without having a marked effect on its AUC. If this finding is extrapolated to other orally administered Pgp substrates then the concern would be for co-administration with those agents for which the pharmacodynamic effect and/or the safety profile are in some way influenced by C_{max}.

The additional data provided from GS-US-236-0120 raise a real potential that prolonged sub-efficacious EVG levels could occur at least in CYP2B6 poor metabolizers if they are switched from ATR to Stribild, which may occur reasonably often in routine use.

The applicant's conclusion regarding the most likely explanation for the effect of Stribild on ethinyl oestradiol being mediated by CYP2C9 induction is plausible. It is expected that the effect of Stribild on CYP2C9 would be comparable to that of RTV when it is used to boost PIs.

The SmPC carries several contraindications for use with other medicinal products along with warnings and an extensive Section 4.5 of the SmPC. There are also several additional studies of relevance to drug-drug interaction potential ongoing or planned/requested, which are reflected in the RMP.

2.4.3. Pharmacodynamics

Mechanism of action

EVG specifically inhibits HIV-1 integrase strand-transfer activity and the integration of viral DNA into host cell chromosomal DNA in cell culture.

COBI is a structural analogue of RTV but it is devoid of anti-HIV activity (HIV protease IC50 > 30 µM; vs. 0.6 nM for ritonavir). The role of COBI in the Stribild is to enhance the PK profile of EVG by means of its ability to inhibit CYP3A4 and so prevent conversion of EVG to its major metabolite (M1).

Primary and Secondary pharmacology

Primary pharmacology

EVG

- EVG inhibited DNA strand-transfer with an IC50 value of 8.8 nM. It inhibited laboratory strains and various clinical isolates (wild-type and NRTI, NNRTI, and PI drug-resistant strains) of HIV-1 with an EC50 of 0.38 nM (range, 0.02 to 1.3 nM) in human PBMCs. Activity was shown against multiple subtypes (Group M: A, B, C, D, E, F, G and Group O) of HIV-1 and against HIV-2.
- The EC95 value in the presence of HSA and AAG was 100 nM (44.8 ng/mL) in HIV-1 infected human PBMC cultures, representing an 80-fold loss in antiviral activity.
- In-vitro ARV combination studies showed additive to synergistic interactions with the NRTIs FTC and TFV (as well as others tested), with NNRTIs (EFV, nevirapine and etravirine) and with a range of PIs. In-vitro assays with T-20, RAL and maraviroc also demonstrated additive to synergistic interactions.
- The in-vitro ARV activity of EVG was not altered by the presence of COBI.
- Combination of EVG, TFV and FTC was synergistic.
- EVG selected for 3 primary resistance mutations in HIV-1 integrase - T66I/A/K, E92Q/G or Q148R – *in vitro*. These confer 15-, 36- and 109-fold reduced susceptibility, respectively.

- Additional secondary IN mutations selected by EVG were H51Y, F121Y, S147G, S153Y, E157Q and R263K. These mutations further decreased susceptibility to EVG when they occurred in addition to T66I or E92Q mutations.
- Elvitegravir did not inhibit replication of HBV or HCV *in vitro*.
- There were no measurable changes in the content of mtDNA and therefore the potential for mitochondrial toxicity is considered low.
- In MT-2 cells the M4 (GS-9200) and M1 (GS-9202) metabolites showed HIV-1 antiviral activity that was 6.7- and 9.3-fold lower than EVG. Other experiments also showed that the M1 and M4 metabolites are markedly less active (M1: 5- to 18-fold and M4: 10- to 38-fold in antiviral activity assays) than EVG. From these data and the low plasma levels observed on co-administration with COBI M1 and M4 are not considered to contribute to the antiviral activity of EVG. GS-9200 and GS-9202 selected EVG-associated resistance mutations and have similar resistance profiles as EVG.

Stribild

- Anti-HIV activity of EVG + FTC + TFV and these with a 25 μM COBI overlay showed synergy. The anti-HIV-1 activity of EVG with FTC, TFV and FTC+TFV was found to be additive to synergistic in multiple in-vitro assay systems. In-vitro combination studies showed that EVG, FTC and TFV have additive to synergistic anti-HIV-1 activity with NRTIs, NNRTIs, PIs, enfuvirtide, maraviroc and RAL.

In an integrated analysis of 1479 ARV-naive subjects receiving the Stribild in the three pivotal studies (GS-US-236-0104, -0102 and -0103) resistance analyses were performed for HIV-1 isolated from 53 subjects (27 in the Stribild group) who were virological failures or had > 400 copies/mL at Week 48 or when discontinued. There were 13/749 (1.7%) in the Stribild group with virus that had developed primary (INSTI-R) or NRTI resistance (NRTI-R) mutations and phenotypic resistance to one or more components of the Stribild.

Important findings in the Stribild group were:

- The most common mutations were T66I, E92Q, Q148R and N155H in the IN gene and RT M184V/I, with or without K65R, in the RT gene. Secondary IN mutations that developed in a single case in addition to a primary INSTI mutation were H51Y, L68V, G140C, S153A and E157Q.
- Within the Stribild group, viruses that developed genotypic resistance to EVG (n = 11) showed a mean of 67-fold reduced susceptibility vs. wild-type. All viruses that developed resistance to EVG also showed reduced susceptibility to RAL (mean 7.9-fold).
- In addition, 27/749 subjects had viruses with the K103N substitution in RT at baseline but none developed resistance to a component of the Stribild. The presence of K103N at baseline did not predispose subjects to failure on the Stribild or ATV/r + TVD.
- Additional analyses found no impact of HIV-1 subtype on response or development of resistance.
- Subjects with viruses that developed mutations had a trend for higher baseline viral load and lower CD4 cell counts than the overall study population.
- A trend for lower replication capacity was found in viruses that developed resistance to a component of the Stribild compared to baseline.
- In the ATR group, 18 viruses were analysed for resistance development (18 of 375 subjects, 4.8%). Eight subjects (8 of 375 subjects, 2.1%) in the ATR group developed RT resistance to one or more components of ATR and most commonly consisted of K103N with or without M184V/I and K65R.

Secondary pharmacology

QTc and other cardiac studies

GS-US-183-0128 evaluated the effect of steady-state ritonavir-boosted EVG plasma levels on QTc using a two-part parallel study design because of the numbers of days (10) needed to achieve steady state. All treatments were administered orally under fed conditions. In Part 1 the subjects received placebo or moxifloxacin 400 mg as a single dose in the morning on Day 1. In Part 2 the subjects received EVG/rtv 125/100 mg on Days 6−15 or EVG/rtv 250/ 100 mg on Days 6−15 or placebo on these days.

Moxifloxacin showed the expected positive control effect with a difference in QTcF vs. placebo that was generally between 5 and 10 ms and with an upper limit of the 90% CI > 10 ms at multiple time points. For the QTcF change from baseline in Part 2 of the study the upper limits of the 2-sided 90% CI for the difference in LSMs (EVG/r vs. placebo) were all < 10 ms. Actual differences in LSMs were < 5 ms at all time points for both EVG/r groups. Consistent results were obtained from similar analyses conducted for QTcB, QTcI and QTcN. The categorical analyses were unremarkable. The linear correlations between QTcF, QTcB, QTcN and QTcI and plasma concentrations of EVG and GS-9200 were very weak.

GS-US-216-0107 was a cross-over study that evaluated the effect of 250 mg and 400 mg COBI, each administered once in the fed state on QTc, vs. placebo and moxifloxacin 400 mg at weekly intervals. The plasma levels of COBI actually achieved exceeded the predicted values. Assay sensitivity was established based on the differences between controls. COBI did not show prolongation of the QTcF interval. The upper bounds of the 2-sided 90% CIs were < 10 ms at all time points after dosing with similar findings applied to QTcN and QTcI and a single instance of QTcB at 10.1 ms at 12 hours at the supra-therapeutic dose. Categorical analyses of QT data were unremarkable. There was a modest increase in PR interval between 3 and 5 h post-dose. The largest baseline-adjusted treatment mean difference in PR interval between the therapeutic or supra-therapeutic doses and placebo was +9.6 ms and +20.2 ms, respectively, both at 3.5 hours after dosing. In all but 5 subjects the absolute PR interval was ≤ 210 ms.

As part of the COBI bioequivalence study GS-US-216-0116 (see 2.1.3 for details) ECGs and echocardiograms were obtained from Cohort 1 subjects at baseline and once between days 14-19 of dosing at 150 mg COBI daily at 3.5-6 h post-dose. All subjects had normal absolute PR (< 210 msec) and QTcF (< 450 msec) intervals. The ECHO assessments showed that the three measures of left ventricular function were normal. Nonparametric comparisons of the mean change from baseline showed an increase in left ventricular end-systolic volume (3.72 mL, p = 0.017) that was not considered to be clinically significant.

Renal effect studies

GS-US-126-0121 was conducted following Phase II studies with COBI in which decreases in eGFR calculated using the Cockcroft-Gault method (eGFRCG) occurred within the first few weeks of dosing. The study evaluated the effect of COBI and RTV in normal function or mild/moderate renal impairment based on eGFRCG and MDRD, CLiohexol (actual GFR; aGFR) and measured GFR (mGFR) using 24-hour urinary output and serum creatinine concentration.

In Cohort 1 parallel groups of healthy subjects were randomised (1:1:1) to receive one of the following for 7 days once daily after a standardised meal:

• COBI: COBI 150 mg + RTV 100 mg placebo (Treatment 1)

• RTV: RTV 100 mg + COBI 150 mg placebo (Treatment 2)

• Placebo: COBI 150 mg placebo + RTV 100 mg placebo (Treatment 3)

In Cohort 2 subjects with mild/moderate renal impairment (eGFRCG 50−79 mL/min at screening) received COBI 150 mg dosed as above. On day 7 higher COBI exposures (AUC_{tau}, C_{max}, and C_{tau}) were observed in Cohort 2 subjects.

Table 37.

COBI PK Parameter	GLSM		GLSM Ratio (%) (90% CI)
	Test Cohort 2 (N = 18)	Reference Cohort 1 (N = 12)	
AUC_{tau} (ng•h/mL)	19,104.61	13,962.97	136.82 (107.78, 173.69)
C_{max} (ng/mL)	1907.92	1689.17	112.95 (93.93, 135.82)
C_{tau} (ng/mL)	230.29	83.44	275.98 (171.56, 443.95)

Serum creatinine-based GFR estimations were statistically significantly decreased ($p < 0.05$) on Day 7 of COBI administration in both cohorts but not at Day 14. There were no statistically significant changes in eGFR on Day 7 of RTV or placebo or on Day 14 in the placebo group but there was a statistically significant increase in eGFR on Day 14 in subjects who had received RTV. Similar results were obtained both for eGFRMDRD and mGFR.

Table 38.

Treatment	Estimated GFR (Cockcroft-Gault) (mL/min) Mean (SD)		
	Day 0	Day 7	Day 14
Placebo			
eGFR ≥ 80 mL/min (n = 12) **Change from Day 0** (mL/min)	113.8 (26.72) ——	116.0 (23.87) 2.2 (9.10) (p = 0.42)	136.6 (59.04) 22.8 (59.86) (p = 0.21)
COBI			
eGFR ≥ 80 mL/min (n = 12) **Change from Day 0** (mL/min)	121.3 (22.88) ——	111.4 (26.62) –9.9 (13.14) (p = 0.024)	122.6 (28.03) 1.4 (11.5) (p = 0.69)
eGFR 50–79 mL/min (n = 18) **Change from Day 0** (mL/min)	68.7 (9.67) ——	56.8 (10.98) –11.9 (6.97) (p < 0.001)	66.5 (10.59) –2.2 (5.61) (p = 0.12)
RTV			
eGFR ≥ 80 mL/min (n = 12) **Change from Day 0** (mL/min)	116.9 (17.53) ——	117.9 (18.46) 1.0 (8.62) (p = 0.70)	122.6 (21.24) 5.7 (8.21) (p = 0.035)

In contrast, the aGFR was unchanged from baseline at Day 7 and 14 in the COBI, RTV or placebo groups. Consistent with these results, there were also no statistically significant changes from baseline at Day 7 or Day 14 in cysGFR, calculated using clearance of the endogenous serum protein cystatin C.

Whereas a statistically significant reversible decrease from baseline in eGFR was observed at Day 7 in Cohort 1 subjects who had received COBI compared with placebo the aGFR was unchanged.

The applicant concluded that the higher plasma exposures in subjects with mild/moderate renal impairment suggested reduced COBI clearance, with or without a change in bioavailability. Changes in eGFR values determined using serum creatinine but without changes in aGFR determined using iohexol or cystatin C indicated that COBI inhibits proximal tubular secretion of creatinine and does not affect the true GFR.

GS-US-236-0130 was requested, completed and reported during the procedure. This was a randomized, double-blind, placebo-controlled, multiple-dose, parallel design study in healthy adult subjects. The study

examines the effect of 5 treatments (COBI, TDF, COBI+TDF, Stribild and placebo when given once daily for 30 days in the fed state at the proposed or approved doses on renal function. Subjects were then followed for a further 30 days to document the reversibility of any effects observed. Demographics and baseline renal parameters were generally similar between groups.

Table 39. GS-US-236-0130: Renal Baseline Characteristics (Safety Analysis Set).

Characteristic[a, b, c]	COBI (N=14)	TDF (N=14)	COBI+TDF (N=15)	QUAD (N=14)	Placebo (N=14)	Total (N=71)
Actual GFR (mL/min)						
N	14	14	14	13	13	68
Mean (SD)	138.7 (23.79)	135.2 (27.87)	141.0 (27.84)	143.4 (20.00)	146.6 (19.83)	140.8 (23.84)
Median	133.2	135.2	141.6	143.0	143.9	140.2
Q1, Q3	119.9, 155.6	114.9, 156.6	134.4, 159.5	133.7, 158.0	132.0, 150.9	127.7, 157.3
Min, Max	103.7, 181.1	80.3, 183.5	63.5, 179.4	113.3, 174.1	122.1, 185.4	63.5, 185.4
PAH Renal Clearance (mL/min)						
N	14	14	15	14	14	71
Mean (SD)	754.4 (180.05)	674.1 (140.96)	727.6 (144.12)	722.4 (115.43)	735.0 (168.58)	722.8 (149.42)
Median	767.3	674.3	706.1	718.8	721.0	714.1
Q1, Q3	681.2, 853.7	606.2, 714.1	658.7, 866.7	621.5, 795.4	597.5, 841.3	611.0, 834.9
Min, Max	416.9, 1028.5	387.8, 1001.6	497.9, 949.1	572.2, 912.0	467.6, 1050.6	387.8, 1050.6
Estimated GFR by Cockcroft-Gault (mL/min)[d]						
N	14	14	15	14	14	71
Mean (SD)	124.0 (19.37)	108.6 (22.24)	115.9 (20.00)	112.3 (14.73)	106.0 (17.54)	113.4 (19.46)
Median	123.5	106.0	118.8	110.8	105.8	109.6
Q1, Q3	104.3, 136.6	95.6, 119.6	97.2, 129.4	107.4, 122.4	96.7, 109.6	98.1, 126.4
Min, Max	95.2, 156.0	76.6, 159.0	78.6, 151.1	84.0, 140.9	78.6, 140.0	76.6, 159.0
Estimated GFR by Modification of Diet in Renal Disease (mL/min/1.73 m^2)[d]						
N	14	14	15	14	14	71
Mean (SD)	100.1 (14.64)	88.6 (12.77)	98.1 (21.79)	94.2 (16.67)	95.4 (15.24)	95.3 (16.59)
Median	99.0	92.6	89.8	94.9	88.1	92.6
Q1, Q3	89.1, 111.0	78.7, 99.4	83.2, 122.0	82.7, 98.4	84.9, 110.2	83.2, 104.1
Min, Max	74.5, 125.5	63.5, 105.2	70.9, 135.5	72.0, 139.5	75.0, 125.8	63.5, 139.5

Mean plasma concentrations of COBI when given alone were similar to those for subjects receiving COBI+TDF and slightly lower vs. dosing with Stribild. These observations were consistent with data from studies in which COBI was given alone or as a component of Stribild.

Table 40. GS-US-236-0130: Summary of COBI Pharmacokinetic Parameters at Day 15 (COBI PK Analysis Set).

PK Parameter[a]	COBI N = 14	COBI+TDF N = 14	QUAD N = 13
AUC_{tau} (ng•h/mL)	14841.2 (30.0)	13607.3 (28.3)	10024.2 (25.6)
C_{max} (ng/mL)	1655.8 (18.5)	1718.4 (19.8)	1470.7 (16.4)
C_{tau} (ng/mL)	119.5 (77.1)	88.9 (73.3)	30.9 (77.2)
T_{max} (h)	3.50 (2.50, 4.50)	4.00 (3.00, 4.50)	4.50 (3.50, 4.50)
$T_{½}$ (h)	4.91 (4.00, 5.90)	4.31 (3.91,5.31)	3.07 (2.98, 3.61)

a Data are presented as mean (%CV), except T_{max} and $T_{½}$, which are presented as median (Q1, Q3).

Source: Section 9.1, Table 9.3

Table 41. GS-US-236-0130: Summary of COBI Pharmacokinetic Parameters at Day 30 (COBI PK Analysis Set).

PK Parameter[a]	COBI N = 14	COBI+TDF N = 14	QUAD N = 13
AUC_{tau} (ng•h/mL)	14337.6 (33.6)	13312.0 (24.5)	10090.6 (26.2)
C_{max} (ng/mL)	1722.2 (19.8)	1672.7(17.5)	1475.5 (20.3)
C_{tau} (ng/mL)	107.0 (96.2)	84.3 (78.3)	28.3 (67.1)
T_{max} (h)	3.50 (3.00, 3.50)	3.00 (3.00, 4.50)	4.50 (3.50, 4.50)
$T_{½}$ (h)	4.61 (3.74, 5.77)	4.19 (3.90, 5.05)	3.09 (3.00, 3.77)

a Data are presented as mean (%CV), except T_{max} and $T_{½}$, which are presented as median (Q1, Q3).

Mean plasma concentrations of TFV in the COBI+TDF and Stribild groups on Days 15 and 30 were modestly higher vs. TDF alone, consistent with GS-US-216-0134 and GS-US-236-0110. No relevant differences in the median Tmax or T½ of TFV were observed between these treatments.

Table 42. GS-US-236-0130: Summary of TFV Pharmacokinetic Parameters at Day 15 (TFV PK Analysis Set).

Table 5-3. GS-US-236-0130: Summary of TFV Pharmacokinetic Parameters at Day 15 (TFV PK Analysis Set)

PK Parameter[a]	TDF N = 14	COBI+TDF N = 14	QUAD N = 13
AUC_{tau} (ng•h/mL)	3215.8 (23.2)	3366.4 (33.3)	3753.2 (32.9)
C_{max} (ng/mL)	364.4 (31.0)	460.2 (36.3)	526.6 (42.0)
C_{tau} (ng/mL)	56.7 (29.7)	62.0 (33.4)	67.3 (37.0)
T_{max} (h)	2.25 (1.50, 2.50)	2.50 (2.00, 2.50)	3.00 (2.50, 3.50)
$T_{½}$ (h)	10.43 (9.99, 11.52)	11.51 (10.61, 13.08)	10.67 (10.22, 11.34)

a Data are presented as mean (%CV), except T_{max} and $T_{½}$, which are presented as median (Q1, Q3).
Source: Section 9.1, Table 9.4

Table 43. GS-US-236-0130: Summary of TFV Pharmacokinetic Parameters at Day 30 (TFV PK Analysis Set).

PK Parameter[a]	TDF N = 14	COBI+TDF N = 14	QUAD N = 13
AUC_{tau} (ng•h/mL)	3126.5 (20.2)	3398.7 (37.7)	3639.3 (31.2)
C_{max} (ng/mL)	354.5 (24.7)	456.4 (37.6)	519.1 (44.6)
C_{tau} (ng/mL)	56.9 (26.8)	60.7 (41.2)	66.2 (31.6)
T_{max} (h)	2.50 (1.25, 3.00)	2.50 (1.50, 2.50)	2.50 (2.50, 3.50)
$T_{½}$ (h)	11.26 (10.75, 11.76))	10.66 (9.85, 11.82)	11.45 (10.00, 12.14)

a Data are presented as mean (%CV), except T_{max} and $T_{½}$, which are presented as median (Q1, Q3).

EVG PK parameters were similar on Day 15 and Day 30 in the Stribild group and consistent with historical data (GS-US-236-0110). The FTC concentration-time profile following administration of Stribild was consistent with historical data (GS-US-236-0110).

The GLSM ratios and associated 90% CIs for each comparison of aGFR for test treatments vs. placebo were within 80% to 125% on Days 15, 30, 40 and 60 but the 90% CI did not span 100% for any of the comparisons between STB and placebo.

Table 44. GS-US-236-0130: Statistical Comparison of aGFR (Iohexol Plasma Clearance) for Active Treatments vs Placebo (PD Analysis Set).

	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Day 15				
COBI (Test) vs. Placebo (Reference)	133.12 (n=14)	141.58 (n=13)	94.03	(89.31, 98.99)
TDF (Test) vs. Placebo (Reference)	136.25 (n=14)	141.58 (n=13)	96.23	(90.86, 101.93)
COBI+TDF (Test) vs. Placebo (Reference)	137.22 (n=14)	141.58 (n=13)	96.92	(91.46, 102.71)
QUAD (Test) vs. Placebo (Reference)	127.74 (n=13)	141.58 (n=13)	90.22	(85.01, 95.75)
Day 30				
COBI (Test) vs. Placebo (Reference)	135.88 (n=14)	142.39 (n=13)	95.43	(91.41, 99.62)
TDF (Test) vs. Placebo (Reference)	136.56 (n=14)	142.39 (n=13)	95.91	(90.04, 102.16)
COBI+TDF (Test) vs. Placebo (Reference)	132.31 (n=14)	142.39 (n=13)	92.92	(88.66, 97.39)
QUAD (Test) vs. Placebo (Reference)	127.67 (n=13)	142.39 (n=13)	89.66	(85.50, 94.02)
Day 40 (10 days off treatment)				
COBI (Test) vs. Placebo (Reference)	133.62 (n=14)	138.71 (n=12)	96.33	(91.63, 101.27)
TDF (Test) vs. Placebo (Reference)	133.35 (n=14)	138.71 (n=12)	96.14	(90.88, 101.70)
COBI+TDF (Test) vs. Placebo (Reference)	135.51 (n=14)	138.71 (n=12)	97.70	(92.50, 103.19)
QUAD (Test) vs. Placebo (Reference)	131.04 (n=13)	138.71 (n=12)	94.47	(89.81, 99.38)
Day 60 (30 days off treatment)				
COBI (Test) vs. Placebo (Reference)	139.01 (n=13)	143.50 (n=12)	96.88	(92.26, 101.72)
TDF (Test) vs. Placebo (Reference)	139.48 (n=14)	143.50 (n=12)	97.20	(91.87, 102.83)
COBI+TDF (Test) vs. Placebo (Reference)	140.37 (n=14)	143.50 (n=12)	97.82	(93.40, 102.46)
QUAD (Test) vs. Placebo (Reference)	132.17 (n=13)	143.50 (n=12)	92.11	(86.55, 98.02)

In addition, the comparisons within each treatment group for change vs. the group baseline indicated that only in the STB group was there a clear effect of treatment on aGFR (next table). The data demonstrated the differences between groups for the D0 GLSM values, which underlines the importance of this additional analysis for interpreting the data shown above.

The table shows that the baseline aGFR GLSM was actually nearest to the placebo group for the STB subjects. In the STB group the comparisons of on-treatment and post-treatment values vs. baseline gave 90% CI that all fell below 100% and this was observed at all time points. The only other group in which this occurred was COBI (at D15 and at D40). In contrast, for TDF alone there was no perceptible change from D0 during the study and for COBI + TDF the only notable change was at D15.

Table 45. GS-US-236-0130: Statistical Comparison of aGFR (Iohexol Plasma Clearance) between Test (Day 15, Day 30, Day 40 and Day 60 visits) and Reference (Day 0 visit) within each Treatment (PD Analysis Set).

	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
COBI				
Day 15 (Test) vs. Day 0 (Reference)	131.87 (n=14)	136.79 (n=14)	96.40	(93.76, 99.12)
Day 30 (Test) vs. Day 0 (Reference)	134.50 (n=14)	136.79 (n=14)	98.32	(95.63, 101.09)
Day 40 (Test) vs. Day 0 (Reference)	132.51 (n=14)	136.79 (n=14)	96.87	(94.22, 99.59)
Day 60 (Test) vs. Day 0 (Reference)	136.50 (n=13)	136.79 (n=14)	99.78	(96.99, 102.66)
TDF				
Day 15 (Test) vs. Day 0 (Reference)	131.74 (n=14)	132.25 (n=14)	99.61	(95.32, 104.10)
Day 30 (Test) vs. Day 0 (Reference)	131.69 (n=14)	132.25 (n=14)	99.57	(95.29, 104.06)
Day 40 (Test) vs. Day 0 (Reference)	129.16 (n=14)	132.25 (n=14)	97.66	(93.46, 102.06)
Day 60 (Test) vs. Day 0 (Reference)	134.98 (n=14)	132.25 (n=14)	102.06	(97.66, 106.65)
COBI+TDF				
Day 15 (Test) vs. Day 0 (Reference)	136.47 (n=14)	137.55 (n=14)	99.21	(94.78, 103.86)
Day 30 (Test) vs. Day 0 (Reference)	131.53 (n=14)	137.55 (n=14)	95.62	(91.34, 100.10)
Day 40 (Test) vs. Day 0 (Reference)	134.91 (n=14)	137.55 (n=14)	98.08	(93.69, 102.67)
Day 60 (Test) vs. Day 0 (Reference)	139.32 (n=14)	137.55 (n=14)	101.29	(96.76, 106.03)
QUAD				
Day 15 (Test) vs. Day 0 (Reference)	130.07 (n=13)	142.16 (n=13)	91.50	(87.48, 95.70)
Day 30 (Test) vs. Day 0 (Reference)	130.19 (n=13)	142.16 (n=13)	91.58	(87.56, 95.79)
Day 40 (Test) vs. Day 0 (Reference)	133.49 (n=13)	142.16 (n=13)	93.91	(89.78, 98.22)
Day 60 (Test) vs. Day 0 (Reference)	133.99 (n=13)	142.16 (n=13)	94.26	(90.12, 98.59)
Placebo				
Day 15 (Test) vs. Day 0 (Reference)	146.51 (n=13)	145.39 (n=13)	100.77	(97.27, 104.40)
Day 30 (Test) vs. Day 0 (Reference)	147.75 (n=13)	145.39 (n=13)	101.63	(98.09, 105.28)
Day 40 (Test) vs. Day 0 (Reference)	144.87 (n=12)	145.39 (n=13)	99.64	(96.09, 103.32)
Day 60 (Test) vs. Day 0 (Reference)	146.38 (n=12)	145.39 (n=13)	100.68	(97.09, 104.40)

The comparisons between active groups showed that only for STB vs. either COBI or TDF alone did the 90% CI not span 100% and this occurred only at D30.

Note that this table did not compare STB with COBI + TDF; however, this comparison is further addressed below.

Table 46. GS-US-236-0130: Statistical Comparison of aGFR (Iohexol Plasma Clearance) for Test (QUAD or COBI+TDF) versus Reference (COBI or TDF) (PD Analysis Set).

	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Day 15				
COBI+TDF (Test) vs. COBI (Reference)	137.22 (n=14)	133.12 (n=14)	103.08	(97.28, 109.22)
COBI+TDF (Test) vs. TDF (Reference)	137.22 (n=14)	136.25 (n=14)	100.72	(94.56, 107.27)
QUAD (Test) vs. COBI (Reference)	127.74 (n=13)	133.12 (n=14)	95.95	(90.40, 101.85)
QUAD (Test) vs. TDF (Reference)	127.74 (n=13)	136.25 (n=14)	93.75	(87.87, 100.04)
Day 30				
COBI+TDF (Test) vs. COBI (Reference)	132.31 (n=14)	135.88 (n=14)	97.37	(93.43, 101.48)
COBI+TDF (Test) vs. TDF (Reference)	132.31 (n=14)	136.56 (n=14)	96.89	(91.08, 103.06)
QUAD (Test) vs. COBI (Reference)	127.67 (n=13)	135.88 (n=14)	93.96	(90.07, 98.01)
QUAD (Test) vs. TDF (Reference)	127.67 (n=13)	136.56 (n=14)	93.49	(87.82, 99.52)
Day 40 (10 days off treatment)				
COBI+TDF (Test) vs. COBI (Reference)	135.51 (n=14)	133.62 (n=14)	101.42	(97.04, 106.00)
COBI+TDF (Test) vs. TDF (Reference)	135.51 (n=14)	133.35 (n=14)	101.62	(96.58, 106.93)
QUAD (Test) vs. COBI (Reference)	131.04 (n=13)	133.62 (n=14)	98.07	(94.29, 102.01)
QUAD (Test) vs. TDF (Reference)	131.04 (n=13)	133.35 (n=14)	98.27	(93.76, 102.99)
Day 60 (30 days off treatment)				
COBI+TDF (Test) vs. COBI (Reference)	140.37 (n=14)	139.01 (n=13)	100.98	(96.20, 105.99)
COBI+TDF (Test) vs. TDF (Reference)	140.37 (n=14)	139.48 (n=14)	100.64	(95.20, 106.40)
QUAD (Test) vs. COBI (Reference)	132.17 (n=13)	139.01 (n=13)	95.08	(89.18, 101.37)
QUAD (Test) vs. TDF (Reference)	132.17 (n=13)	139.48 (n=14)	94.76	(88.37, 101.62)

To further evaluate the findings the applicant also compared aGFR between STB relative to TDF+COBI . The GLSM ratios and 90% CIs were within 80% to 125% and on this basis the applicant concluded that EVG does not alter renal function.

Table 47. GS-US-236-0130: Statistical Comparison of aGFR (Iohexol Plasma Clearance) for STB versus COBI+TDF (PD Analysis Set).

	GLSM		GLSM Ratio (%)	90% CI
aGFR (mL/min)	Test (STB, N = 13)	Reference (COBI+TDF, N = 14)		
Day 15 (On Treatment)	127.74	137.22	93.09	87.19, 99.39
Day 30 (On Treatment)	127.67	132.31	96.49	92.13, 101.06
Day 40 (Follow-Up)	131.04	135.51	96.70	92.43, 101.17
Day 60 (Follow-Up)	132.17	140.34	94.16	88.49, 100.19

The GLSM ratios and associated 90% CIs for each comparison of renal plasma flow were within 80% to 125% at these time points for each of the four active treatments vs. placebo (see the first table below for change in renal plasma flow vs. placebo).

In the second table below the change in renal plasma flow from D0 is shown within each group. These comparisons demonstrate that even in the placebo group there was some variability in the GLSM over time, which complicates interpretation of the data. Nevertheless, it was only in the COBI group at Day 40 and in the COBI + TDF and STB groups at D30 and D40 that the 90% CI fell below 100%.

Table 48. GS-US-236-0130: Statistical Comparison of Renal Plasma Flow (PAH CL_{renal}) between Active Treatments vs Placebo (PD Analysis Set).

	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Day 15				
COBI (Test) vs. Placebo (Reference)	695.56 (n=14)	729.06 (n=13)	95.41	(85.84, 106.04)
TDF (Test) vs. Placebo (Reference)	706.10 (n=14)	729.06 (n=13)	96.85	(88.32, 106.21)
COBI+TDF (Test) vs. Placebo (Reference)	749.52 (n=14)	729.06 (n=13)	102.81	(92.67, 114.05)
QUAD (Test) vs. Placebo (Reference)	722.68 (n=13)	729.06 (n=13)	99.13	(89.82, 109.40)
Day 30				
COBI (Test) vs. Placebo (Reference)	652.72 (n=14)	695.07 (n=13)	93.91	(85.03, 103.71)
TDF (Test) vs. Placebo (Reference)	660.28 (n=14)	695.07 (n=13)	94.99	(87.06, 103.66)
COBI+TDF (Test) vs. Placebo (Reference)	639.03 (n=14)	695.07 (n=13)	91.94	(83.98, 100.65)
QUAD (Test) vs. Placebo (Reference)	645.06 (n=13)	695.07 (n=13)	92.81	(84.89, 101.46)
Day 40 (10 days off treatment)				
COBI (Test) vs. Placebo (Reference)	602.75 (n=14)	664.42 (n=12)	90.72	(79.77, 103.17)
TDF (Test) vs. Placebo (Reference)	618.28 (n=14)	664.42 (n=12)	93.06	(82.94, 104.40)
COBI+TDF (Test) vs. Placebo (Reference)	623.98 (n=14)	664.42 (n=12)	93.91	(83.97, 105.04)
QUAD (Test) vs. Placebo (Reference)	645.29 (n=12)	664.42 (n=12)	97.12	(87.32, 108.02)
Day 60 (30 days off treatment)				
COBI (Test) vs. Placebo (Reference)	692.09 (n=14)	732.55 (n=12)	94.48	(87.93, 101.51)
TDF (Test) vs. Placebo (Reference)	755.10 (n=14)	732.55 (n=12)	103.08	(87.37, 121.61)
COBI+TDF (Test) vs. Placebo (Reference)	713.34 (n=14)	732.55 (n=12)	97.38	(90.78, 104.46)
QUAD (Test) vs. Placebo (Reference)	713.86 (n=13)	732.55 (n=12)	97.45	(89.36, 106.27)

Table 49. GS-US-236-0130: Statistical Comparison of Renal Plasma Flow (PAH CL_{renal}) between Test (Day 15, Day 30, Day 40, and Day 60 Visits) and Reference (Day 0 Visit) within Each Treatment (PD Analysis Set).

	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
COBI				
Day 15 (Test) vs. Day 0 (Reference)	723.73 (n=14)	732.17 (n=14)	98.85	(91.20, 107.14)
Day 30 (Test) vs. Day 0 (Reference)	680.13 (n=14)	732.17 (n=14)	92.89	(85.70, 100.69)
Day 40 (Test) vs. Day 0 (Reference)	624.62 (n=14)	732.17 (n=14)	85.31	(78.71, 92.47)
Day 60 (Test) vs. Day 0 (Reference)	711.62 (n=14)	732.17 (n=14)	97.19	(89.67, 105.35)
TDF				
Day 15 (Test) vs. Day 0 (Reference)	667.48 (n=14)	660.08 (n=14)	101.12	(90.39, 113.12)
Day 30 (Test) vs. Day 0 (Reference)	622.90 (n=14)	660.08 (n=14)	94.37	(84.35, 105.57)
Day 40 (Test) vs. Day 0 (Reference)	591.88 (n=14)	660.08 (n=14)	89.67	(80.15, 100.31)
Day 60 (Test) vs. Day 0 (Reference)	717.93 (n=14)	660.08 (n=14)	108.76	(97.22, 121.67)
COBI+TDF				
Day 15 (Test) vs. Day 0 (Reference)	751.12 (n=14)	703.05 (n=14)	106.84	(99.29, 114.96)
Day 30 (Test) vs. Day 0 (Reference)	640.44 (n=14)	703.05 (n=14)	91.09	(84.66, 98.02)
Day 40 (Test) vs. Day 0 (Reference)	626.86 (n=14)	703.05 (n=14)	89.16	(82.87, 95.94)
Day 60 (Test) vs. Day 0 (Reference)	711.32 (n=14)	703.05 (n=14)	101.18	(94.03, 108.86)

	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
QUAD				
Day 15 (Test) vs. Day 0 (Reference)	722.29 (n=13)	701.02 (n=13)	103.03	(96.21, 110.34)
Day 30 (Test) vs. Day 0 (Reference)	644.70 (n=13)	701.02 (n=13)	91.97	(85.88, 98.48)
Day 40 (Test) vs. Day 0 (Reference)	641.00 (n=12)	701.02 (n=13)	91.44	(85.24, 98.09)
Day 60 (Test) vs. Day 0 (Reference)	710.29 (n=13)	701.02 (n=13)	101.32	(94.62, 108.50)
Placebo				
Day 15 (Test) vs. Day 0 (Reference)	740.88 (n=13)	713.72 (n=13)	103.80	(96.07, 112.17)
Day 30 (Test) vs. Day 0 (Reference)	706.75 (n=13)	713.72 (n=13)	99.02	(91.64, 107.00)
Day 40 (Test) vs. Day 0 (Reference)	681.38 (n=12)	713.72 (n=13)	95.47	(88.18, 103.36)
Day 60 (Test) vs. Day 0 (Reference)	738.26 (n=12)	713.72 (n=13)	103.44	(95.54, 111.99)

Renal blood flow was calculated using PAH CLrenal and haematocrit. While renal blood flow estimates on Day 30 compared with Day 0 were lower for all active treatments, the value for the placebo group was also lower on Day 30 (see tables below). Again, the GLSM ratio and associated 90% CIs for change from baseline for each active treatment were within 80% to 125%.

Table 50.

Table 10-13. GS-US-236-0130: Statistical Comparison of Renal Blood Flow between Active Treatments and Placebo (PD Analysis Set)

	GLSM		GLSM Ratio (%)	90% CI
	Test Treatment	Reference Treatment		
Day 15				
COBI (Test) vs. Placebo (Reference)	1638.52 (n=14)	1697.76 (n=13)	96.51	(85.46, 108.99)
TDF (Test) vs. Placebo (Reference)	1639.66 (n=14)	1697.76 (n=13)	96.58	(85.88, 108.62)
COBI+TDF (Test) vs. Placebo (Reference)	1774.29 (n=14)	1697.76 (n=13)	104.51	(92.45, 118.14)
QUAD (Test) vs. Placebo (Reference)	1743.70 (n=13)	1697.76 (n=13)	102.71	(91.88, 114.81)
Day 30				
COBI (Test) vs. Placebo (Reference)	1540.20 (n=14)	1632.52 (n=13)	94.35	(85.64, 103.93)
TDF (Test) vs. Placebo (Reference)	1516.19 (n=14)	1632.52 (n=13)	92.87	(84.86, 101.64)
COBI+TDF (Test) vs. Placebo (Reference)	1496.43 (n=14)	1632.52 (n=13)	91.66	(83.14, 101.07)
QUAD (Test) vs. Placebo (Reference)	1523.59 (n=13)	1632.52 (n=13)	93.33	(85.36, 102.04)
Day 40 (10 days off treatment)				
COBI (Test) vs. Placebo (Reference)	1473.46 (n=14)	1587.84 (n=12)	92.80	(82.45, 104.44)
TDF (Test) vs. Placebo (Reference)	1491.60 (n=14)	1587.84 (n=12)	93.94	(84.36, 104.60)
COBI+TDF (Test) vs. Placebo (Reference)	1525.64 (n=14)	1587.84 (n=12)	96.08	(86.09, 107.24)
QUAD (Test) vs. Placebo (Reference)	1574.99 (n=12)	1587.84 (n=12)	99.19	(90.05, 109.26)
Day 60 (30 days off treatment)				
COBI (Test) vs. Placebo (Reference)	1660.33 (n=12)	1694.55 (n=10)	97.98	(88.75, 108.17)
TDF (Test) vs. Placebo (Reference)	1751.72 (n=13)	1694.55 (n=10)	103.37	(85.15, 125.51)
COBI+TDF (Test) vs. Placebo (Reference)	1650.61 (n=13)	1694.55 (n=10)	97.41	(87.18, 108.84)
QUAD (Test) vs. Placebo (Reference)	1674.68 (n=11)	1694.55 (n=10)	98.83	(88.75, 110.04)
Placebo				
Day 15 (Test) vs. Day 0 (Reference)	1731.72 (n=13)	1604.57 (n=13)	107.92	(99.17, 117.46)
Day 30 (Test) vs. Day 0 (Reference)	1665.31 (n=13)	1604.57 (n=13)	103.79	(95.36, 112.95)
Day 40 (Test) vs. Day 0 (Reference)	1642.08 (n=12)	1604.57 (n=13)	102.34	(93.83, 111.62)
Day 60 (Test) vs. Day 0 (Reference)	1672.21 (n=10)	1604.57 (n=13)	104.22	(95.04, 114.27)

There were the expected increases in serum creatinine and the associated decreases in eGFRCG and increases in urine fractional excretion of phosphate in the three groups that received COBI. No clinically relevant changes were seen in other renal laboratory parameters associated with tubular dysfunction (serum phosphorus, urine protein, or urine glucose).

Serum phosphorus at baseline and changes from baseline at Days 15, 30 and 40 were generally similar between the active treatment (COBI, TDF, COBI+TDF, and Stribild) and placebo groups; no clinically relevant changes were observed. Based on local laboratory data, Grade 1 hypophosphataemia occurred in 3 subjects (1 subject in each of the TDF, Stribild and placebo groups) and Grade 2 hypophosphataemia occurred in 1 subject in the TDF group. No graded proteinuria or glycosuria abnormalities occurred in any treatment group.

Relationship between plasma concentration and effect

EVG

In **GS-US-183-0101** EVG monotherapy at 200, 400 or 800 mg twice daily, at 800 mg once daily or 50 mg + RTV 100 mg QD for 10 days significantly reduced HIV-1 RNA vs. placebo. Maximal and comparable changes were observed with 400 or 800 mg twice daily and 50 mg + RTV 100 mg once daily. EVG C_{tau} values fitted well to a simple E_{max} (maximum PD effect) model with an EC50 value at 14.4 ng/mL and an

E_{max} of 2.32 log10 copies/mL reduction from baseline. The estimated inhibitory quotient (IQ), calculated as the observed mean C_{tau} divided by the protein binding-adjusted in vitro IC50 of 7.17 ng/mL, was 5.9, 6.7 and 18.8 at 400 mg twice daily, 800 mg twice daily and 50 mg + RTV once daily, respectively. Elvitegravir trough concentrations at these doses also exceeded the protein binding-adjusted in vitro IC95 (45 ng/mL; 100 nM) for the entire dosing interval.

Figure 5. Mean Change in HIV-1 RNA Through Day 21

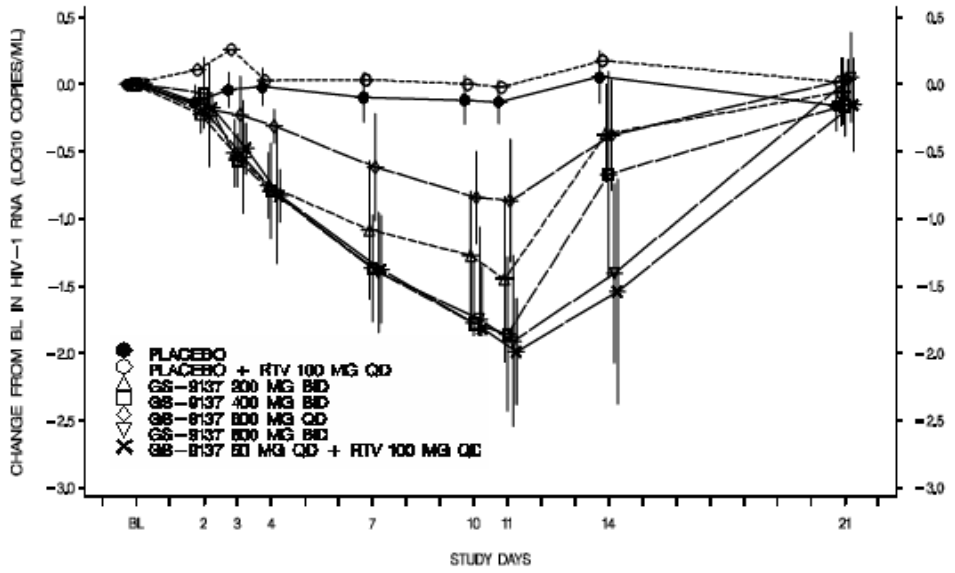
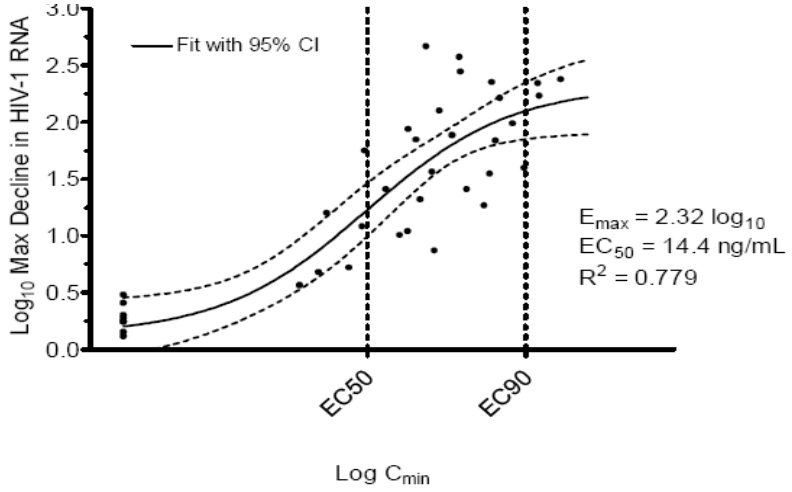


Figure 6. Pharmacokinetic/Pharmacodynamic Dose-Response Relationship For GS-9137



Stribild

In the Stribild Phase 3 studies the PK-PD analyses of the EVG exposure-efficacy relationship were performed using EVG population PK modelling and rates for HIV-1 RNA < 50 copies/mL level using Pure Virological Response (PVR) by Week 48. The PVR was chosen as the primary PD endpoint because it was considered to represent an assessment of virological response unaffected by non-virological factors (e.g. discontinuation for various reasons) that would define subjects as virological failures in some composite primary endpoints such as TLOVR or the snapshot analysis.

Table 51. Percentage of Pure Virologic Responders across Quantiles of EVG Exposure (N=373) (EVG PK/PD Analysis Set).

EVG C_{tau} Quartile (ng/mL)	PVR (%)	EVG C_{tau} Quintile (ng/mL)	PVR (%)	EVG C_{tau} Octile (ng/mL)	PVR (%)
N = 93 to 94		N = 74 to 75		N = 46 to 47	
58 to < 296	89	58 to < 264	89	58 to < 208	87
296 to < 423	88	264 to < 383	89	208 to < 296	92
423 to < 560	93	383 to < 456	87	296 to < 359	94
560 to 2341	87	456 to < 610	95	359 to < 423	83
		610 to 2341	87	423 to < 475	89
				475 to < 561	96
				561 to < 703	85
				703 to 2341	89

Pure virologic responder was not defined in Study GS-US-236-0104, so subjects (n = 46) in GS-US-236-0104 were excluded from this analysis.

Virological response was uniformly high across the categories EVG C_{trough} by all approaches with no trends in exposure-response relationship observed. The applicant considered that the results were consistent with the data-driven dose selection of EVG 150 mg for the Stribild, which provided exposures corresponding to E_{max} and mean and overall C_{trough} values that exceeded by ~ 10-fold the protein binding-adjusted IC95 (45 ng/mL).

2.4.4. Discussion on clinical pharmacology

The in-vitro activity of EVG has been adequately investigated.

The EVG dose-escalation studies of selection of resistance-associated mutations were of different methodologies. However, they indicated that T66I could be selected by passage 7 whereas E92Q emerged at passage 30. Using the viral breakthrough method Viruses with IN resistance mutations were observed at EVG concentrations corresponding to 10-fold the EC50 (T66I/T) and 40- and 80-fold the EC50 (Q148R). Viruses with emergent IN resistance mutations were also observed for RAL at concentrations corresponding to 5-fold the EC50 (N155H) and 40-fold the EC50 (Q148K).

There is incomplete cross-resistance between EVG and RAL. For example, viruses carrying only T66I remained susceptible to RAL whereas viruses carrying N155H and Q148K each showed resistance to RAL and EVG. However, 11 isolates from subjects who received the Stribild in clinical studies and developed genotypic resistance to EVG (n = 11) showed a mean of 67-fold reduced susceptibility vs. wild-type and all of these viruses showed reduced susceptibility to RAL (mean 7.9-fold).

The results of the in-vitro studies and the data regarding isolates obtained during the clinical studies with Stribild suggested that the genetic barrier to resistance of EVG is relatively low, as is that of RAL.

The potential for EVG to contribute to the overall antiviral effect of Stribild was supported by the EVG monotherapy study in which EVG/rtv 50/100 achieved comparable viral suppression over 10 days to that of 400 mg and 800 mg EVG BID (~2 log drop). Elvitegravir trough concentrations at these doses also exceeded the protein binding-adjusted in vitro IC95 (45 ng/mL; 100 nM) for the entire dosing interval. The Stribild data showed that 150 mg EVG (plus 150 mg COBI) provided uniform rates of PVF across the trough concentration quantiles, supporting the sufficiency of the EVG/COBI doses.

The TQT studies with each of EVG/rtv (up to 250/100 mg) and COBI 250 mg delivered supra-therapeutic exposures compared to anticipated plasma levels achieved with Stribild and did not suggest clinically important effects on QTc. In addition, COBI did not appear to have an important effect on left ventricular function.

In the first study of the effect of COBI on renal function (GS-US-216-0121) plasma COBI levels were higher in those with mild to moderate renal impairment vs. controls and comparable to those observed in subjects with severe renal impairment in GS-US-216-0124. Taking into account the effects on eGFR but lack of effect on aGFR (and cysGFR) it appears that COBI inhibits the proximal tubular secretion of creatinine via inhibition of MATE1.

GS-US-236-0130 showed that aGFR decreased with each active treatment vs. placebo and the difference persisted post-treatment. The data indicated consistently that the largest decreases occurred with Stribild and on Day 30 the comparisons for Stribild vs. each of TDF and COBI alone gave 90% CI that did not span 100. At Day 30 the PAH CLrenal was lower with each active treatment vs. placebo and the 90% CI barely spanned 100%. The comparisons within treatments for change in renal plasma flow from baseline point to the most marked effect in the COBI + TDF and the STB groups.

The reason for the apparent greater effect of STB than any of the other groups is not clear. Given the variability observed in aGFR and renal plasma flow it is not impossible that the observations could have arisen by chance in this parallel group study but the consistent effect within the STB group makes this unlikely. Also, there is no known reason why STB might have a greater effect on aGFR than TDF + COBI. The CHMP concluded that an effect cannot be ruled out. On the other hand, it is not possible to conclude whether the actual effects observed are potentially clinically relevant. Please see further discussion on clinical safety on this issue.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted are considered satisfactory.

For detailed discussion regarding renal toxicity of Stribild compared to tenofovir + COBI and additional pharmacovigilance activities see section on clinical safety.

In order to further characterise the PK profile of STB, the following measure will be performed by the applicant, as detailed in the Risk Management Plan.

- PK study of EVG in subjects with UGT1A1*28/*28 genotype administered STB (information on EVG exposure in patients with UGT1A1 polymorphism associated with decreased activity of UGT1A1) (by Q2 2015)

2.5. Clinical efficacy

The critical efficacy data for the FDC are derived from two Phase 3 studies (GS-US-236-102 and 103) conducted in ARV naïve subjects. These followed initial results from a Phase 2 study (GS-US-236-0104).

Table 52. Pivotal studies

Pivotal	
Stribild	Study GS-US-236-0102 is an ongoing Phase 3 study of Stribild compared with ATR in HIV-1 infected, ARV treatment-naive adult subjects.
	Study GS-US-236-0103 is an ongoing Phase 3 study of Stribild compared with ATV/r plus TVD in HIV-1 infected ARV treatment-naive adult subjects.
	Study GS-US-236-0104 is an ongoing Phase 2 study of the Stribild compared with ATR in HIV-1 infected, ARV treatment-naive adult subjects.

Studies considered being supportive for dose selection and efficacy are listed below.

Table 53. Supportive studies

Supportive	
EVG	GS-US-183-0145 is an ongoing Phase 3 study of the safety and efficacy of EVG/r compared with RAL each administered with a background regimen in HIV-1 infected, ARV treatment-experienced adults.
	GS-US-183-0105 was a dose-finding study that assessed the non-inferiority of EVG/r relative to an RTV-boosted comparative PI (CPI/r).
	GS-US-183-0130 was a Phase 2 study of the safety of EVG/r administered in combination with other ARV agents for the treatment of HIV-1 infected subjects.
COBI	GS-US-216-0105 is an ongoing Phase 2 study of COBI-boosted ATV (ATV/co) compared to ATV/r in combination with TVD in HIV-1 infected ARV treatment-naive adults.
Stribild	GS-US-236-0101 evaluated the relative bioavailability of EVG boosted with different doses of COBI, FTC, and TFV when administered as the Stribild.

In addition, the following studies with Stribild were ongoing at the time of submission:

Table 54. On-going studies

GS-US-236-0115	Phase 3b randomized, open-label study to evaluate switching from regimens consisting of a ritonavir-boosted protease inhibitor plus emtricitabine/tenofovir disoproxil fumarate to the QUAD in virologically-suppressed, HIV-1 infected patients.	Due to commence Q1 12. Duration 96 weeks. Primary endpoint 48 weeks. 48 week report available Q4 2013.	96 week report available Q4 2014.
GS-US-236-0121	Phase 3b randomized, open-label study to evaluate switching from regimens consisting of a non-nucleoside reverse transcriptase inhibitor plus emtricitabine/tenofovir disoproxil fumarate to the QUAD in virologically-suppressed, HIV-1 infected patients.	Due to commence Q1 12. Duration 96 weeks. Primary endpoint 48 weeks. 48 week report available Q4 2013.	96 week report available Q4 2014.

2.5.1. Dose response studies

There were no clinical dose-finding studies with Stribild itself. However, a preliminary study of the safety and efficacy of the selected doses for the Stribild was conducted (GS-US-236-0104), as described below. This study employed the F1 tablet formulation.

The applicant states that the dose of EVG (150 mg) was selected based on the PK/PD study GS-US-183-0101, the Phase 2 study in heavily treatment-experienced HIV-1 infected subjects GS-US-183-0105 and study GS-US-183-0140, which established bioequivalence between the 125 mg tablet used GS-US-183-0105 and the 150 mg F2 tablet intended for commercial use.

The applicant states that the dose of COBI (150 mg) was selected based on GS-US-216-0101, which described the pharmacokinetics of COBI 50, 100 and 200 mg doses, and GS-US-236-0101, which evaluated the relative bioavailability of tablets containing EVG 150 mg, FTC 200 mg, TDF 300 mg plus COBI at either 100 mg or 150 mg vs. EVG/r 150/100 mg and vs. FTC 200 mg + TDF 300 mg

Administration of Stribild with food in treatment naïve subjects would be expected to provide at least comparable antiviral activity of FTC and TFV as would be obtained using Truvada or Emtriva + Viread.

GS-US-236-0104 provided preliminary data on the antiviral effect of the selected doses of the components of the F1 Stribild tablet in treatment-naïve subjects when compared to Atripla in a 2:1 randomisation ratio. Stribild tablets were taken once daily with food. Atripla was taken once daily on an empty stomach and at bedtime. The primary endpoint was proportion with < 50 copies/ml at week 24 and the results were considered to support the selection of Stribild component doses with rates at < 50 copies/ml in excess of 80% regardless of the method of data analysis.

Table 55. GS-US-236-0104: Percentage of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 24 (ITT Analysis Set)

Week 24[a, b]	QUAD n/N (%)	ATR n/N (%)	QUAD vs ATR[c]	
			p-value	Difference in Percentages (95% CI)
Missing = Failure[d]				
< 50 copies/mL	43/48 (89.6%)	20/23 (87.0%)	0.72	2.8% (–14.5% to 20.1%)
95% CI	77.3% to 96.5%	66.4% to 97.2%	—	—
Missing/ART Switch = Failure[e]				
< 50 copies/mL	43/48 (89.6%)	19/23 (82.6%)	0.39	7.2% (–11.7% to 26.0%)
95% CI	77.3% to 96.5%	61.2% to 95.0%	—	—
Missing = Excluded[f]				
< 50 copies/mL	43/45 (95.6%)	20/21 (95.2%)	0.90	0.7% (–13.4% to 14.8%)
95% CI	84.9% to 99.5%	76.2% to 99.9%	—	—

a HIV-1 RNA results were from HIV Cobas Amplicor PCR version 1.5 assay only.

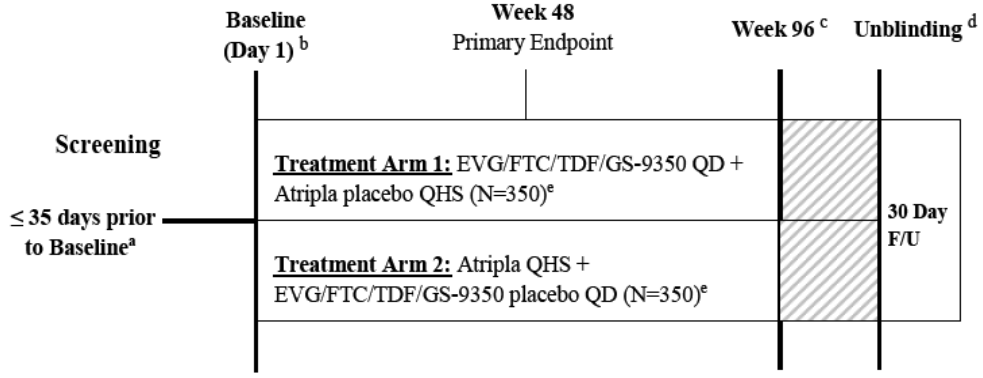
2.5.2. Main studies

GS-US-236-0102 and GS-US-236-0103

Methods

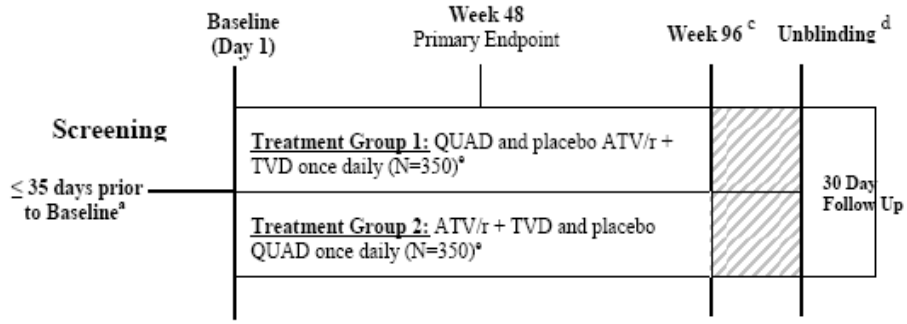
The two Phase III studies with Stribild (GS-US-236-0102 and GS-US-236-0103) generally followed comparable designs except as stated. The study outlines are shown below:

Figure 7. GS-US-236-0102: Study Schema



GS-9350, cobicistat; QD, once daily; QHS, once daily prior to bedtime; F/U, follow-up

Figure 8. GS-US-236-0103: Study Schema



Study Participants

The critical inclusion criteria required:

- Plasma HIV-1 RNA ≥ 5000 copies/mL
- No prior use of any approved or investigational antiretroviral drug for any length of time
- Screening HIV-1 genotype report must have shown sensitivity to FTC, TDF, and EFV HIV-1 (genotype [reverse transcriptase and protease] was assessed at screening).
- Normal ECG
- Adequate renal function: CG formula GFR ≥ 70 mL/min
- AST and ALT ≤ 5 × ULN
- Total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin
- Absolute neutrophil count ≥ 1000/mm3; platelets ≥ 50,000/mm3; haemoglobin ≥ 8.5 g/dL
- Serum amylase ≤ 5 × ULN (or if amylase > 5 × ULN, serum lipase was to be ≤ 5 × ULN)
- Use of highly effective contraception

HIV-1 RNA plasma concentrations were assessed using the COBAS Amplicor HIV-1 Monitor Test (Version 1.5). At screening, the protease/reverse transcriptase (PR/RT) genotype was assessed using the GeneSeq™ assay (Monogram Biosciences, South San Francisco, CA). This assay also determined the HIV-1 subtype.

Post-baseline resistance analyses included PR/RT and integrase (IN) genotyping and phenotyping. The PhenoSense GT™ (PhenoSense IN) and GeneSeq IN assays (Monogram Biosciences, South San Francisco, CA) were used for this purpose. Samples with successful PhenoSense GT results for PR/RT but with IN assay failure were retested for the IN genotype using the GenoSure assay (LabCorp Center for Molecular Biology and Pathology, Research Triangle Park, NC). Integrase testing was also conducted at baseline for those subjects in the resistance analysis population (RAP).

Randomisation

Randomisation was by IVRS in a 1:1 ratio and stratified according to screening HIV-1 RNA ≤ 100.000 or > 100,000 copies/ml.

Treatments

In both studies the Stribild or its matching placebo tablet was administered orally as one tablet once daily with food and at approximately the same time each day.

- In GS-US-236-0102 Atripla or its matching placebo tablet was administered orally as one tablet once daily taken on an empty stomach prior to bedtime and at approximately the same time each day.

- In GS-US-236-0103 all treatment (active or placebo for each of Stribild, atazanavir [ATV], ritonavir [rtv] and Truvada [TVD]) was taken once daily with food at approximately the same time each day.

Blinding (masking)

The studies were planned to be of double-blind and double-dummy design up to Week 96. After week 96 until unblinding of the database the subjects continue on assigned therapy. There are then roll-over studies in which subjects are offered open label Stribild.

Outcomes/endpoints

The primary objective of each study was as follows:

To evaluate the efficacy of the Stribild [EVG/COBI/FTC/TDF] vs. a comparative regimen in HIV-1 infected, antiretroviral treatment-naïve adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48.

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as defined by the FDA snapshot analysis algorithm.

Secondary efficacy endpoints were as follows:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 96, as defined by the snapshot analysis algorithm
- The achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 and 96, as defined by TLOVR

Sample size/ Statistical methods

A total sample size of 700 subjects randomised in a 1:1 ratio to 2 groups (350 subjects per group) had at least 95% power to establish non-inferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 48 between the two treatment groups, as defined by the FDA snapshot analysis. For sample size and power computation, it was assumed that both treatment groups had a response rate of 0.795 (based on study GS-01-934), a non-inferiority margin of 0.12 and a 1-sided, 0.025 significance level. Calculations were made using the software package nQuery Advisor, Version 6.0.

Analysis populations for efficacy analyses were defined as follows:

Randomised Analysis Set

Included all randomised subjects (added for analysis in the SAP).

Intent-to-Treat Analysis Set

The ITT analysis set included all randomised who received at least 1 dose of study drug. This was the primary analysis set for efficacy analyses.

Per Protocol Analysis Set

The PP analysis set included all randomised who received at least 1 dose of study drug and had no major protocol violation (including violation of major entry criteria).

There were two interim IDMC analyses performed at Weeks 12 and 24. The sponsor did not have a prior intent to ask the IDMC to consider early termination of the study even if there was early evidence of favourable efficacy. Since there was no intent to stop the study early, the Haybittle procedure was used as a stopping rule. An alpha penalty of 0.001 was applied for each interim analysis performed by the IDMC. Therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

The baseline HIV-1 RNA stratum (≤ 100,000 copies/mL or > 100,000 copies/mL])-weighted difference in the response rate (P1 – P2) and its 95% CI were calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion.

The Stribild was to be considered non-inferior to the comparative regimen if the lower bound of the 2-sided 95% CI of the difference in the response rate (Stribild – ATR) was > −12%. If non-inferiority was established, the same 95% CI used to evaluate non-inferiority was used to evaluate superiority using the ITT analysis set. Thus, superiority of Stribild over comparator was established if the lower bound of the 95% CI was greater than 0. The baseline HIV-1 RNA stratum (≤ 100,000 copies/mL or > 100,000 copies/mL)-weighted, 2-sided CMH test was used to assess superiority as a supportive analysis.

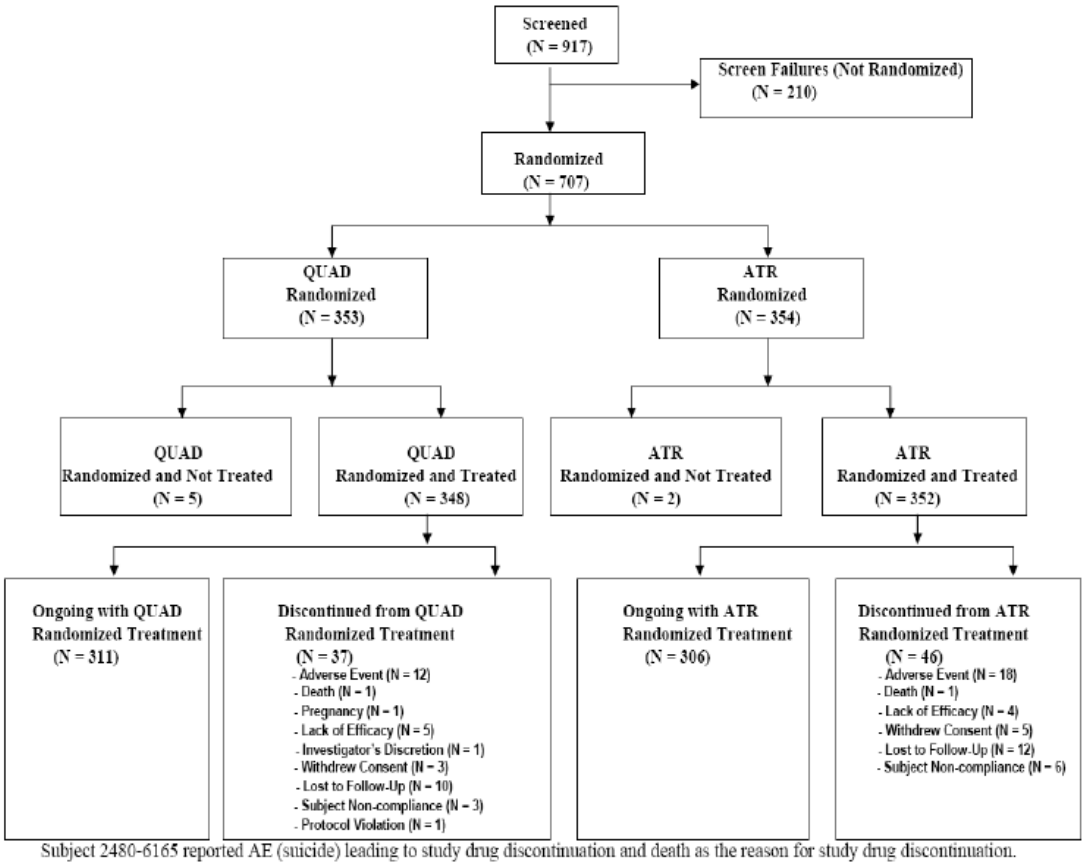
A secondary analysis based on the PP analysis set was to evaluate the robustness of the primary analysis. Subjects excluded from the PP analysis set were determined before database lock. In addition, a series of sensitivity analyses were performed using the ITT analysis set.

Results
GS-US-236-0102

Participant flow

This study enrolled subjects at 97 US sites and 5 sites in Puerto Rico. Up to the data cut-off date 10.6% in the Stribild group and 13.1% in the Atripla group had discontinued study drug while 8.3% and 10.2% had discontinued from the study, the most common reasons being AEs and LTFU in both groups.

Figure 9. GS-US-236-0102: Disposition of Study Subjects



Subject 2480-6165 reported AE (suicide) leading to study drug discontinuation and death as the reason for study drug discontinuation.

Baseline data
In general the baseline subject and disease characteristics were comparable between treatment groups. The majority of subjects were white males aged between 30-40 years. About one third had > 100,000 copies/ml at baseline with mean and median values ~ 4.7 log10 copies/ml. Most subjects had HIV-1 subtype B (98%) while only 3 had subtype C, 2 had AE, 2 had AG and single subjects had A, A1 and "complex" mixtures of subtypes. Just under half had < 350 CD4 cells/µl and > 80% were asymptomatic. Few (< 5%) were co-infected with HBV or HCV.

Adherence to active study drug, as measured by pill count, was comparable (median 98.0% per group) between groups and 75% had an adherence rate of ≥ 95%.

Outcomes and estimation

In the primary analysis at Week 48 non-inferiority was demonstrated for Stribild vs. Atripla.

Table 56. GS-US-236-0102: Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set).

HIV-1 RNA Category	QUAD (N=348)	ATR (N=352)	QUAD vs. ATR p-value[a]	Difference in Percentages (95.2% CI)[b, c]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	305 (87.6%)	296 (84.1%)	0.17	3.6% (-1.6% to 8.8%)
Virologic Failure at Week 48	25 (7.2%)	25 (7.1%)		
HIV-1 RNA >= 50 copies/mL	13 (3.7%)	11 (3.1%)		
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	2 (0.6%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[d]	8 (2.3%)	12 (3.4%)		
No Virologic Data in Week 48 Window[e]	18 (5.2%)	31 (8.8%)		
Discontinued Study Drug Due to AE/Death	10 (2.9%)	19 (5.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	8 (2.3%)	11 (3.1%)		
Missing Data During Window but on Study Drug	0	1 (0.3%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.

Non-inferiority was also demonstrated in the PP analysis set although actual success rates were higher (94.9% and 96.0% had < 50 copies/ml; 95% CI -4.4%, 2.4%). Non-inferiority was also demonstrated in the analysis based on TLOVR at week 48 with responder rates of 85.9% vs. 83.2% (95% CI -2.6%, 8.1%).

Pure virological failure (PVF; HIV-1 cut-off at 50 copies/mL and premature study drug discontinuation by Week 48) occurred in 10.9% (38/348) in the Stribild group and 13.4% (47/352) in the Atripla group.

Sensitivity analysis of the primary endpoint showed:

- After excluding study drug discontinuations not related to virological response and including all HIV-1 RNA data for late discontinuation (ITT analysis set) the success rates were 89.7% in the Stribild group and 86.8% in the Atripla group (95% CI: −1.9% to 7.8%).
- Including study drug discontinuations not related to virological response as successes and all HIV-1 RNA data for late discontinuation (ITT set) the rates were 89.9% vs. 87.2% (95% CI: −2.0% to 7.5%).
- Odds ratios were 1.35 (95% CI: 0.88 to 2.07) for baseline HIV-1 RNA level and 1.36 (95% CI: 0.89 to 2.09) for region, indicating that the treatment effect was not confounded by these factors.

A higher percentage in the Atripla group (8%) was never suppressed vs. the Stribild group (4%). Convergence of the KM curves began to occur after Week 12 and similar percentages had loss of virological response in each treatment group by Week 48 (14% Stribild vs. 17% Atripla; p = 0.65).

In each of the M = F analysis and M = E analysis, the percentages with HIV-1 RNA levels < 50 copies/mL were comparable between treatments and the lower bound of the 95% CI fell within -4%.

Table 57. GS-US-236-0102: Number and Percentage of Subjects with Plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT Analysis Set).

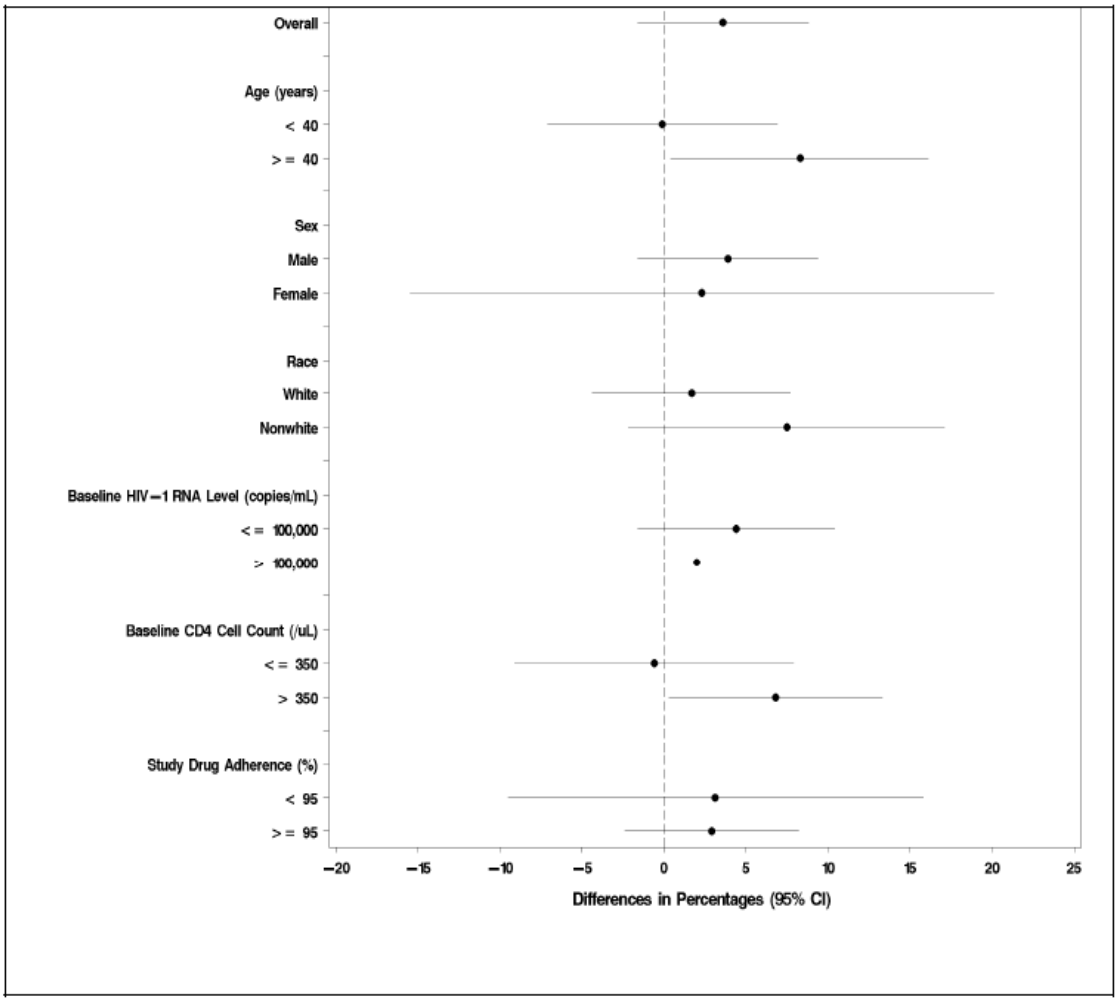
Subjects with Plasma HIV-1 RNA < 50 copies/mL (n, %)[a]	QUAD (N = 348)	ATR (N = 352)	QUAD vs. ATR[b]	
			P-value[c]	Difference in Percentages (95% CI)[d]
Missing = Failure				
At Week 48	309/348 (88.8%)	301/352 (85.5%)	0.19	3.3% (-1.6% to 8.3%)
95% CI[e]	85.0% to 91.9%	81.4% to 89.0%	—	—
Missing = Excluded				
At Week 48	309/325 (95.1%)	301/316 (95.3%)	0.94	-0.1% (-3.5% to 3.3%)
95% CI[e]	92.1% to 97.2%	92.3% to 97.3%	—	—

In the corresponding analyses in the PP analysis set the percentages with < 50 copies/mL were higher than in the ITT analysis set but similar trends were observed.

Mean decreases from baseline in HIV-1 RNA levels were greater in the Stribild group through Week 8 and then comparable between treatments at all subsequent time points. Mean increases from baseline in CD4 cell counts were numerically higher in the Stribild group at all time points.

Subgroup analyses (see diagram below) revealed high and generally comparable rates of virological success between treatments with point estimates that mostly favoured the Stribild group. In subjects with HIV RNA > 100,000 copies/ml at baseline the success rates were 83.9% for Stribild and 81.9% for Atripla (95% CI -7.6%, 11.6%).

Figure 10. GS-US-236-0102: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 48 (HIV-1 RNA <50 copies/mL, Snapshot Analysis, ITT Analysis Set).



There were 31 virological failures (14 Stribild) that were included in the Resistance Analysis Population.

In the Stribild group 8/14 subjects had virus that showed emergent resistance to a study drug. Seven of these 8 viruses had the EVG resistance mutations IN E92Q alone or with H51Y, T66I, L68V, Q148R and/or N155H. All eight viruses developed RT M184V/I and phenotypic resistance to FTC and 3 developed K65R. The other 6/14 lacked emergent resistance mutations in IN or RT and remained phenotypically susceptible to all drugs in the regimen. In addition, there was no development of primary PI-R mutations. The viruses that developed genotypic resistance to EVG showed a mean of 61-fold reduced susceptibility compared to wild-type. The biological cut-off for EVG is 2.5-fold in the PhenoSense assay, and all subjects with ≥ 2.5-fold change in susceptibility to EVG had primary EVG resistance mutations. Viruses resistant to EVG also showed reduced susceptibility to RAL.

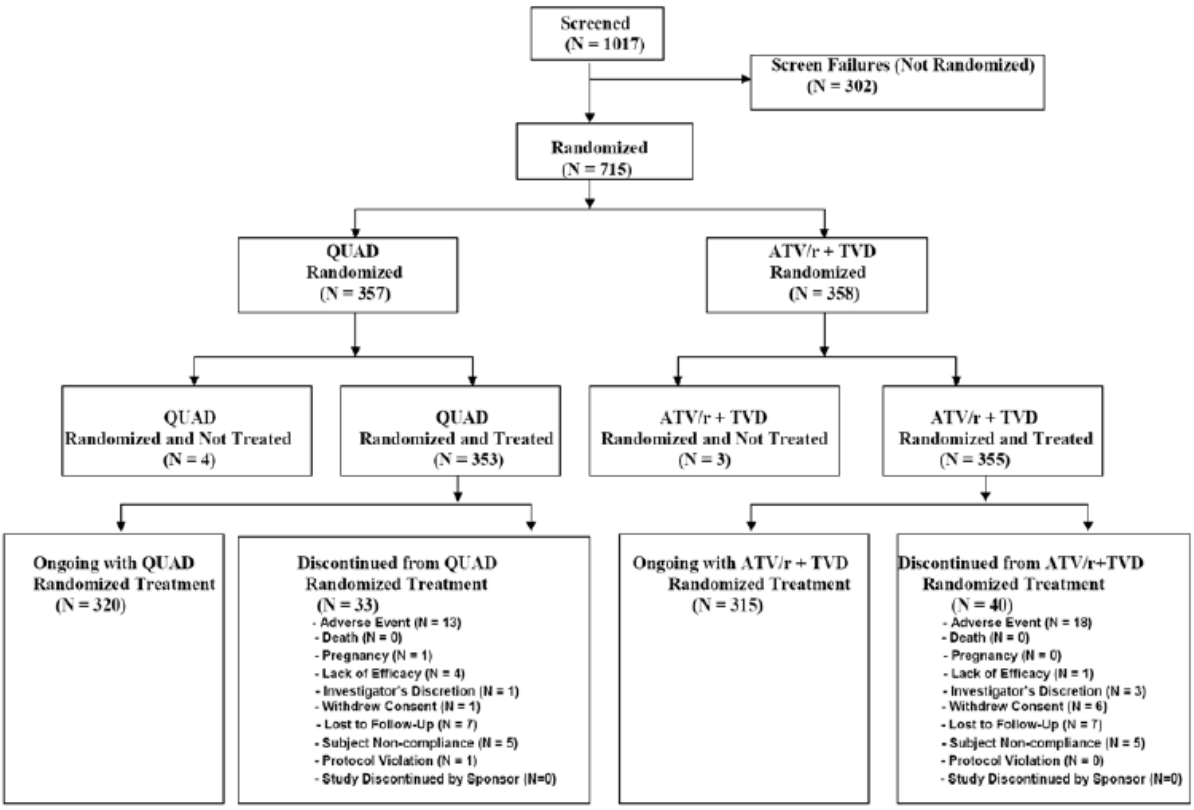
In the Atripla group 8/17 subjects had viruses that showed emergent resistance to a study drug. Seven of these 8 viruses developed the EFV resistance mutation RT K103N alone or with other known NNRTI resistance mutations (V90I, K101E, V108I, Y188F/H/L, G190A and/or M230L). One developed K101E/K alone but did not show reduced susceptibility to EFV, possibly due to the mixture with wild type. Two with K103N also developed K65R and M184V and phenotypic resistance to FTC. The other 9/17 viruses lacked emergent resistance mutations and remained phenotypically susceptible to all drugs in the regimen. There was also no development of primary PI-R mutations.

GS-US-236-0103

Participant flow

There were 715 subjects randomised across 146 sites in 16 countries. A large proportion came from N. America, including sites that participated in study 0102; other sites were located in Europe, Australia and Thailand. At the data cut-off 9.3% in the Stribild group and 11.3% in the comparative group had discontinued study drug while 6.2% and 8.7% had discontinued study, mostly due to AEs and LTFU.

Figure 11. GS-US-236-0103: Disposition of Study Subjects



Conduct of the study
A routine GCP inspection was conducted, involving three study sites in GS-US-236-0103. Overall, compliance with ICH GCP and European and National legislation was considered satisfactory at all three sites.

Baseline data
In general the baseline subject and disease characteristics were comparable between treatment groups. The majority of subjects were white males aged between 30-40 years. About 40% had > 100,000 copies/ml at baseline with mean and median values ~ 4.8 log10 copies/ml. Most subjects had HIV-1 subtype B (91%) while 11 had subtype C, 16 had AE, 13 had AG, 5 had A1, 5 had G, < 5 had others and 9 had "complex" mixtures of subtypes. About one half had < 350 CD4 cells/µl and > 80% were asymptomatic. Few (< 5%) were co-infected with HBV or HCV. Adherence to study drug was comparable between treatments at ~ 98.5%. Most subjects had an adherence rate of ≥ 95% (73.3% in the Stribild group and 78.0% in the comparative group).

Outcomes and estimation
In the primary analysis at Week 48 non-inferiority was demonstrated for the Stribild vs. comparator (see below). In addition, 5.4% per group had virological failure while 5.1% (18/353) in the Stribild group and 7.9% (28/355) in the comparator group had no virological data in the Week 48 analysis window. Non-inferiority was also demonstrated in the PP analysis set although actual success rates were higher. Non-inferiority was also demonstrated in the analysis based on TLVOR with rates of 86.1% vs. 84.8% (95% CI -3.6, 6.8). Pure virological failure (PVF; HIV-1 cut-off at 50 copies/mL and premature study drug discontinuation by Week 48) occurred in 10.2% (36/353) in the Stribild group and 11.0% (39/355) in the comparator.

Sensitivity analysis of the primary endpoint showed:

- After excluding study drug discontinuations not related to virological response and including all HIV-1 RNA data for late discontinuation (ITT analysis set) the success rates were 91.0% in the Stribild group and 89.0% in the comparator group (95% CI: −2.3% to 6.7%).
- Including study drug discontinuations not related to virological response as successes and all HIV-1 RNA data for late discontinuation (ITT analysis set) the rates were 91.2% vs. 89.3% (95% CI: −2.3% to 6.5%).
- In the third sensitivity analysis Odds ratios were 1.33 (95% CI: 0.84 to 2.12) for baseline HIV-1 RNA level and 1.35 (95% CI: 0.84 to 2.15) for region, indicating that the treatment effect for the primary endpoint was not confounded by these factors.

Table 58. GS-US-236-0103: Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis) (ITT Analysis Set).

HIV-1 RNA Category	QUAD (N=353)	ATV/r+TVD (N=355)	QUAD vs. ATV/r+TVD p-value[a]	Difference in Percentages (95.2% CI)[b,c]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	316 (89.5%)	308 (86.8%)	0.22	3.0% (-1.9% to 7.8%)
Virologic Failure at Week 48	19 (5.4%)	19 (5.4%)		
HIV-1 RNA >= 50 copies/mL	7 (2.0%)	8 (2.3%)		
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[d]	8 (2.3%)	11 (3.1%)		
No Virologic Data in Week 48 Window[e]	18 (5.1%)	28 (7.9%)		
Discontinued Study Drug Due to AE/Death	11 (3.1%)	18 (5.1%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	7 (2.0%)	9 (2.5%)		
Missing Data During Window but on Study Drug	0	1 (0.3%)		

At Week 48, 5.4% (19/353) in the Stribild group and 4.2% (15/355) in the comparator group had confirmed viral rebound (12 vs. 8 subjects) or never achieved viral suppression (7 per group) through Week 48 and were considered non-responders. Similar percentages had loss of virological response in each treatment group by Week 48 (16% Stribild vs. 17% comparator; p = 0.48).

In each of the M = F analysis and M = E analysis, the percentages with HIV-1 RNA levels < 50 copies/mL were comparable between treatments and the lower bound of the 95% CI fell within -3%. In the corresponding analyses in the PP analysis set the percentages with < 50 copies/mL were higher than in the ITT analysis set but similar trends were observed.

Table 59. GS-US-236-0103: Number and Percentage of Subjects with Plasma HIV-1 RNA <50 copies/ML at Week 48 (ITT Analysis Set).

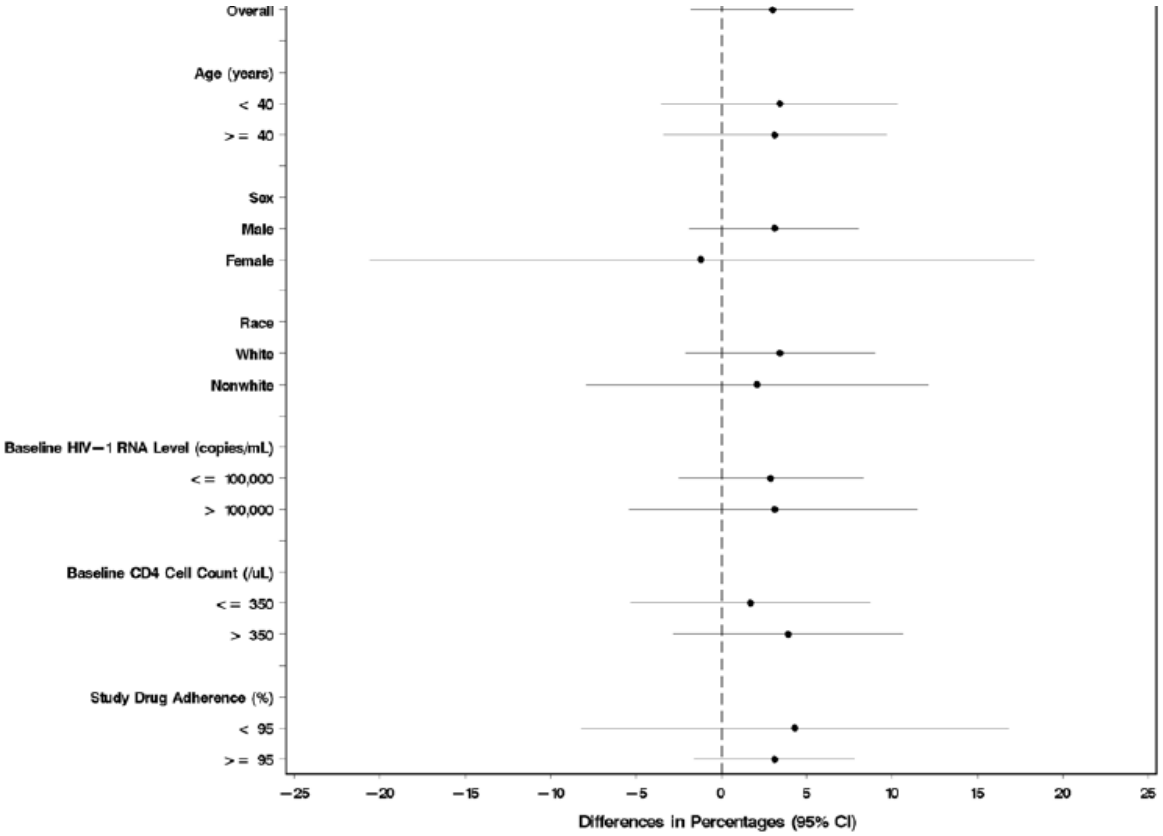
Subjects with Plasma HIV-1 RNA < 50 copies/mL (n, %)[a]	QUAD (N=353)	ATV/r+TVD (N=355)	QUAD vs. ATV/r+TVD[b]	
			P-value[c]	Difference in Percentages (95% CI)[d]
Missing = Failure				
At Week 48	323/353 (91.5%)	313/355 (88.2%)	0.12	3.5% (-1.0% to 8.0%)
95% CI[e]	88.1% to 94.2%	84.3% to 91.3%	—	—
Missing = Excluded				
At Week 48	323/334 (96.7%)	313/323 (96.9%)	0.98	-0.0% (-2.8% to 2.8%)
95% CI[e]	94.2% to 98.3%	94.4% to 98.5%	—	—

Mean decreases from baseline in HIV-1 RNA levels were greater in the Stribild group through Weeks 2-12 and then comparable between treatments at all subsequent time points. Mean increases from baseline in CD4 cell counts were comparable between treatments at all time points.

Subgroup analyses (see diagram below) revealed high and generally comparable rates of virological success between the treatment groups. Point estimates mostly favoured the Stribild except that within the subgroup of female subjects (n = 68) the difference in response rate (−1.2%) favoured the

comparator and the relatively small number of subjects contributed to the wide CI (95% CI: −20.6% to 18.3%).

Figure 12. GS-US-236-0103: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 48 (HIV-1 RNA <50 copies/mL, Snapshot Analysis) (ITT Analysis Set).



Homogeneity tests performed for the primary endpoint did not show a significant difference in treatment effects between subgroups

There were 20 virological failures (12 Stribild) that were included in the Resistance Analysis Population.

In the Stribild group 5/12 subjects had virus that showed emergent resistance to a study drug. Four of these 5 viruses had emergent IN resistance mutations including Q148R, N155H or a complex mixture of T661, E92Q and N155H and phenotypic resistance to EVG. Four viruses developed RT M184V/I and phenotypic resistance to FTC and one developed K65R. Six lacked emergent resistance mutations in IN or RT and remained phenotypically susceptible to all drugs in the regimen and three of these cases showed re-suppression to < 50 copies/ml without a change in regimen. The viruses that developed genotypic resistance to EVG showed a mean of 78-fold reduced susceptibility compared to wild-type. All subjects with ≥ 2.5-fold change in susceptibility to EVG had primary EVG resistance mutations. Viruses resistant to EVG also showed reduced susceptibility to RAL.

In the ATV/rtv group no subjects had viruses that showed emergent resistance to a study drug. There was also no development of primary NNRTI mutations.

Longer-term data from Phase 3 studies

During the procedure the applicant reported on analyses performed when all subjects had completed 96 weeks of treatment (or had discontinued) in the two Phase 3 studies (GS-US-236-0102 and 0103). While the critical efficacy data are summarised below the CSRs will be submitted in a later procedure.

- At Week 96 in GS-US-236-0102, 84.2% in the Stribild group and 81.5% in the ATR group had < 50 copies/mL (ITT, snapshot analysis). The difference in the percentage with virological success was 2.7% (95% CI: −2.9% to 8.3%).
- Corresponding data from GS-US-236-0103 showed rates of 83.3% for Stribild vs. 82.3% for ATV/r+TVD (difference 1.1%; 95% CI: −4.5% to 6.7%).
- At Week 96 in GS-US-236-0102, the mean (SD) increases from baseline in CD4 cell count were 295 (213.3) cells/μL in the Stribild group and 273 (189.7) cells/μL in the ATR group. The difference in LSM was 22 (95% CI: −10 to 54).
- At Week 96 in GS-US-236-0103, the mean (SD) increases from baseline in CD4 cell count were 256 (167.1) cells/μL in the Stribild group and 261 (188.0) cells/μL in the ATV/r+TVD group. The difference in LSM was −8 (95% CI: −35 to 19). In both studies, CD4 cell counts continued to increase from Week 48 to Week 96.

Table 60. GS-US-236-0102 and -0103: Virologic Outcome at Week 96 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis; ITT Analysis Set)

	236-0102		236-0103	
	QUAD (N=348)	ATR (N=352)	QUAD (N=353)	ATV/r + TVD (N=355)
Virologic Success at Week 96[a]				
HIV-1 RNA < 50 copies/mL	293 (84.2%)	287 (81.5%)	294 (83.3%)	292 (82.3%)
Difference in Percentages (95% CI)[b]	2.7% (-2.9% to 8.3%)		1.1% (-4.5% to 6.7%)	
p-value[c]	0.35		0.70	
Virologic Failure at Week 96	22 (6.3%)	27 (7.7%)	24 (6.8%)	26 (7.3%)
HIV-1 RNA >= 50 copies/mL	4 (1.1%)	7 (2.0%)	7 (2.0%)	11 (3.1%)
Discontinued Study Drug Due to Lack of Efficacy	6 (1.7%)	5 (1.4%)	4 (1.1%)	1 (0.3%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[d]	12 (3.4%)	15 (4.3%)	13 (3.7%)	14 (3.9%)
No Virologic Data in Week 96 Window	33 (9.5%)	38 (10.8%)	35 (9.9%)	37 (10.4%)
Discontinued Study Drug Due to AE/Death	17 (4.9%)	22 (6.3%)	15 (4.2%)	21 (5.9%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	16 (4.6%)	14 (4.0%)	17 (4.8%)	16 (4.5%)
Missing Data During Window but on Study Drug	0	2 (0.6%)	3 (0.8%)	0

a Week 96 window is between Day 631 and 714 (inclusive).

b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c P-values for treatment comparisons were from the CMH test stratified by baseline HIV-1 RNA stratum.

d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 61. Summary of Efficacy for trial *GS-US-236-0103*

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults			
Study identifier	Study No.: GS-US-236-0103 EudraCT No.: 2009-026758-42		
Design	Study GS-US-236-0103 is a Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled study to assess the safety and efficacy of the QUAD STR versus a ATV/r+TVD regimen in HIV-1 infected, antiretroviral treatment-naive adult subjects. Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: Treatment Group 1: STR of EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (QUAD) once daily + placebos to match RTV 100 mg, ATV 300 mg, and TVD (FTC 200 mg/TDF 300 mg) once daily Treatment Group 2: RTV 100 mg, ATV 300 mg, and TVD (FTC 200 mg/TDF 300 mg) once daily + placebo to match STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (QUAD) once daily A total of 700 subjects were planned to be enrolled into this study (350 subjects in eachtreatment group). Randomization was stratified based on HIV-1 RNA level (≤ 100,000 copies/mL or> 100,000 copies/mL) at screening. HIV-1 genotype (reverse transcriptase and protease) was assessed at screening. Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA levels, CD4 cell count, and complete or symptom-directed physical examinations were performed at screening, baseline (Day 1), and all subsequent study visits. Adverse events (AEs) and concomitant medications were assessed at each visit. During the double-blind treatment period, study visits occurred at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and then will occur every 12 weeks through Week 96. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded. At the unblinding visit, subjects will be given the option to participate in an open-label rollover study to receive the QUAD STR until it becomes commercially available or until Gilead Sciences elects to terminate its development. Subjects who complete the study through the unblinding visit and do not wish to participate in the open-label rollover study will be required to return to the clinic 30 days after the completion of study drugs for a 30-day follow-up visit.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		192 weeks Maximum of 6 weeks Until commercially available
Hypothesis	Non-inferiority		
Treatments groups	Treatment Group 1: EVG/COBI/FTC/TDF		STR of EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (QUAD) once daily + placebos to match RTV 100 mg, ATV 300 mg, and TVD (FTC 200 mg/TDF 300 mg) once daily, 192 weeks, 357 patients
	Treatment Group 2: ATV/r + FTC/TDF		RTV 100 mg, ATV 300 mg, and TVD (FTC 200 mg/TDF 300 mg) once daily + placebo to match STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (QUAD) once daily, 192 weeks, 358 patients
Endpoints and definitions	Primary endpoint	Snapshot at Week 48 (ITT)	Percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the United States (US) Food and Drug Administration (FDA)-defined snapshot analysis for intent to treat population.
	Primary endpoint	Snapshot at Week 48 (PP)	Percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using FDA-defined snapshot analysis for per-protocol population.

	Secondary endpoint	TLOVR at Week 48 (ITT)	Achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 and 96, as defined by the time to loss of virologic response (TLOVR) Algorithm for intent to treat population
Database lock	16 SEP 2011		

Results and Analysis

Analysis description	Primary Analysis of Primary Endpoint : Snapshot at Week 48 (ITT)		
Analysis population and time point description	Intent to treat – 48 weeks		
Descriptive statistics and estimate variability	Treatment group	EVG/COBI/FTC/TDF	ATV/r + FTC/TDF
	Number of subject	N=353	N=355
	HIV-1 RNA < 50 copies/mL	316 (89.5%)	308 (86.8%)
Effect estimate per comparison	Primary endpoint	Comparison groups	EVG/COBI/FTC/TDF vs ATV/r + FTC/TDF
		Difference in percentages	3.0 %
		95% CI	-1.9% to 7.8%
		P-value[a]	0.22
Notes	[a] P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum (<=100,000 or >100,000 copies/mL).		

Analysis description	Secondary analysis of Primary Endpoint: Snapshot at Week 48 (PP)		
Analysis population and time point description	Per protocol – 48 weeks		
Descriptive statistics and estimate variability	Treatment group	EVG/COBI/FTC/TDF	ATV/r + FTC/TDF
	Number of subject	N=318	N=310
	HIV-1 RNA < 50 copies/mL	310 (97.5%)	303 (97.7%)
Effect estimate per comparison	Primary endpoint	Comparison groups	EVG/COBI/FTC/TDF vs ATV/r + FTC/TDF
		Difference in percentages	-0.1 %
		95% CI	-2.6% to 2.4%
		P-value[a]	0.95
Notes	[a] P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum (<=100,000 or >100,000 copies/mL).		

Analysis description	**Primary analysis of Secondary Endpoint: TLOVR at Week 48 (ITT)**		
Analysis population and time point description	Intent to treat – 48 weeks		
Descriptive statistics and estimate variability	Treatment group	EVG/COBI/FTC/TDF	ATV/r + FTC/TDF
	Number of subject	N=353	N=355
	HIV-1 RNA < 50 copies/mL through Week 48	304 (86.1%)	301 (84.8%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	EVG/COBI/FTC/TDF vs ATV/r + FTC/TDF
		Difference in percentages	1.6%
		95% CI	-3.6% to 6.8%
		P-value[a]	0.55
Notes	[a] P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum (<=100,000 or >100,000 copies/mL).		

Table 62. Summary of Efficacy for trial *GS-US-236-0102*

Title: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults		
Study identifier	Study No.: GS-US-236-0102 EudraCT No.: N/A	
Design	Study GS-US-236-0102 is a Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled study to assess the safety and efficacy of the QUAD STR versus the ATR STR in HIV-1 infected, antiretroviral treatment-naive adult subjects. Subjects were randomized in a 1:1 ratio to 1 of the following 2 treatment groups: **Treatment Group 1:** STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (QUAD) once daily + placebo for ATR once daily prior to bedtime **Treatment Group 2:** STR containing EFV 600 mg/FTC 200 mg/TDF 300 mg (ATR) once daily prior to bedtime + placebo for QUAD once daily. Randomization was stratified based on HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening. During the double-blind treatment period, study visits occurred at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; and then every 12 weeks through Week 96. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded. At the unblinding visit, subjects will be given the option to participate in an open-label rollover study to receive the QUAD STR until it becomes commercially available or until Gilead Sciences elects to terminate its development.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	192 weeks Maximum of 6 weeks Until commercially available
Hypothesis	Non-inferiority	
Treatments groups	Treatment Group 1: EVG/COBI/FTC/TDF	STR containing EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg (QUAD) once daily + placebo for ATR once daily prior to bedtime. 192 weeks, 348 patients.

	Treatment Group 2: EFV/FTC/TDF		STR containing EFV 600 mg/FTC 200 mg/TDF 300 mg (ATR) once daily prior to bedtime + placebo for QUAD once daily. 192 weeks, 352 patients.
Endpoints and definitions	Primary endpoint	Snapshot at Week 48 (ITT)	Percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the United States (US) Food and Drug Administration (FDA)-defined snapshot analysis for intent to treat population.
	Primary endpoint	Snapshot at Week 48 (PP)	Percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the United States (US) Food and Drug Administration (FDA)-defined snapshot analysis for per-protocol population
	Secondary endpoint	TLOVR at Week 48 (ITT)	Achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48, as defined by the time to loss of virologic response (TLOVR) algorithm for intent to treat population. .
Database lock	12 AUG 2011		

Results and Analysis

Analysis description	**Primary Analysis of Primary Endpoint: Snapshot at Week 48 (ITT)**		
Analysis population and time point description	Intent to treat – 48 weeks		
Descriptive statistics and estimate variability	Treatment group	EVG/COBI/FTC/TDF	EFV/FTC/TDF
	Number of subject	N=348	N=352
	HIV-1 RNA < 50 copies/mL	305 (87.6%)	296 (84.1%)
Effect estimate per comparison	Primary endpoint	Comparison groups	EVG/COBI/FTC/TDF vs EFV/FTC/TDF
		Difference in percentages	3.6 %
		95% CI	-1.6% to 8.8%
		P-value[a]	0.17
Notes	[a] P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum (<=100,000 or >100,000 copies/mL).		

Analysis description	**Secondary analysis of Primary Endpoint: Snapshot at Week 48 (PP)**		
Analysis population and time point description	Per protocol – 48 weeks		
Descriptive statistics and estimate variability	Treatment group	EVG/COBI/FTC/TDF	EFV/FTC/TDF
	Number of subject	N=312	N=300
	HIV-1 RNA < 50 copies/mL	296 (94.9%)	288 (96.0%)
Effect estimate per comparison	Primary endpoint	Comparison groups	EVG/COBI/FTC/TDF vs EFV/FTC/TDF
		Difference in percentages	-1.0 %
		95% CI	-4.4% to 2.4%
		P-value[a]	0.54
Notes	a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum (<=100,000 or >100,000 copies/mL). .		

Analysis description	**Primary analysis of Secondary Endpoint: TLOVR at Week 48 (ITT)**		
Analysis population and time point description	Intent to treat – 48 weeks		
Descriptive statistics and estimate variability	Treatment group	EVG/COBI/FTC/TDF	EFV/FTC/TDF
	Number of subject	N=348	N=352
	HIV-1 RNA < 50 copies/mL through Week 48	299 (85.9%)	293 (83.2%)
Effect estimate per comparison	Secondary endpoint	Comparison groups	EVG/COBI/FTC/TDF vs EFV/FTC/TDF
		Difference in percentages	2.7%
		95% CI	-2.6% to 8.1%
		P-value[a]	0.31
Notes	[a] P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum (<=100,000 or >100,000 copies/mL).		

Supportive studies

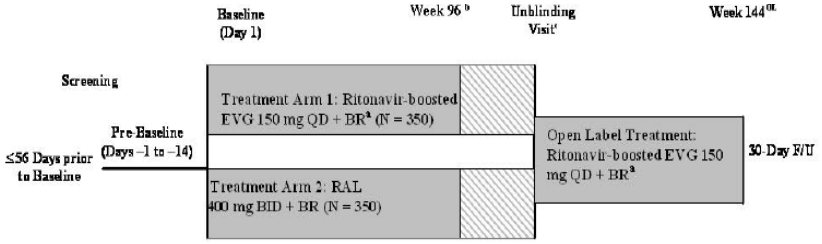
Three studies were initially submitted as being supportive.

EVG	GS-US-183-0145 is an ongoing Phase 3 study of EVG/r vs. RAL (each + OBR) in HIV-1 infected, ARV treatment-experienced adults.
	GS-US-183-0130 was a Phase 2 study of EVG/r administered in combination with other ARV agents for the treatment of HIV-1 infected subjects.
COBI	GS-US-216-0105 is an ongoing Phase 2 study of COBI-boosted ATV (ATV/co) vs. to ATV/r + TVD in HIV-1 infected ARV treatment-naive adults.

During the procedure the applicant also provided data to week 48 from the COBI pivotal Phase 3 study GS-US-216-0114.

GS-US-183-0145 - This study enrolled ARV-experienced but INI-naïve subjects with ≥ 1000 copies/mL and with viruses showing resistance to (IAS-USA) 2 or more classes of ARVs and/or at least 6 months experience with 2 or more different classes of ARVs. Randomisation was to EVG/rtv or raltegravir (RAL) and was stratified by ≤ 100,000 copies/mL or > 100,000 copies/mL and according to the class of the second agent (NRTI vs. other classes). The primary analysis was at Week 48.

Figure 13. GS-US-183-0145: Study Schema



The pre-defined non-inferiority margin was based on an assumed TLOVR response rate of 74%, derived by review of recent RAL and etravirine studies in treatment-experienced subjects. The study met the pre-defined criteria for concluding non-inferiority at Week 48, as summarised below. In the PP analysis using the TLOVR approach the proportions reaching < 50 copies/ml were 74.5% for EVG vs. 73.2% for RAL (95% CI -5.9, 8.6). Very similar results were obtained with the snapshot analysis in the PP population.

Table 63. GS-US-183-0145: Key Treatment Outcomes (ITT Analysis Set).

Table 10. GS-US-183-0145: Key Treatment Outcomes (ITT Analysis Set)

Treatment Outcomes	EVG N = 351	RAL N = 351	EVG vs. RAL	
			P-value	Prop Diff (95% CI)
Virologic Responder (HIV-1 RNA < 50 copies/mL) at Week 48 using TLOVR Analysis (n, %)	207 (59.0%)	203 (57.8%)	0.76[a]	1.1% (−6.0% to 8.2%)[b]
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48 using Snapshot Analysis (n, %)	210 (59.8%)	202 (57.5%)	0.55[a]	2.2% (−5.0% to 9.3%)[b]
Virologic Responder at Week 48 (HIV-1 < 50 copies/mL; M = F) (n, %)	214 (61.0%)	213 (60.7%)	—	0.2% (−6.9% to 7.3%)[b]
Mean (SD) Change from Baseline in HIV-1 RNA at Week 48 (log_{10} copies/mL)[c]	−2.17 (1.162)	−2.18 (1.178)	—	0.01 (−0.16, 0.19)[d]
Mean (SD) Change from Baseline in CD4 cell count at Week 48 (cells/μL)	138 (141.4)	147 (148.9)	—	−9 (−33, 16)[d]

GS-US-216-0105 - Phase 2 study.. This study showed that ATV/co+TVD was non-inferior to ATV/r+TVD based on the FDA-defined snapshot analysis (85.2% vs. of 87.4% with virological success in the ITT analysis set). The baseline HIV-1 RNA stratum-weighted difference in the percentages of subjects with virological success was −2.2% (95% CI: −7.4% to 3.0%) and ATV/co+TVD was determined to be non-inferior to ATV/r+TVD. CD4 counts showed comparable mean increases between treatments at all time points. At Week 48, the mean (SD) increases from baseline were 213 (151.0) cells/μL in the ATV/co+TVD group and 219 (150.4) cells/μL in the ATV/r+TVD group. The difference in LSM was −5 (95% CI: −28 to 18).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Building on virological response rates at < 50 copies/ml to the F1 Stribild tablet in the Phase 2 study, the applicant conducted two Phase 3 studies with the F2 Stribild tablet that used different comparative regimens (see study specific sections below regarding the comparators). The design of these studies, with a primary analysis at week 48, is in line with CHMP guidance on clinical development programmes in ART-naive populations.

While Stribild was to be dosed with food, Atripla was taken in the evening without food and TVD+ATV/rtv were to be taken with food. These dosing conditions reflect the SmPCs.

The two studies involved a range of countries but the majority of subjects were enrolled in N. America and the baseline characteristics of the two study populations were mostly closely comparable. It should be noted that subjects were to have eGFR at least 70 ml/min and that many concomitant medications were precluded in accordance with known and predicted DDIs. There was no limit set on baseline CD4 count. Poor (<70% at any visit) adherence to treatment (based on pill counts) was the commonest protocol deviation.,

Efficacy data and additional analyses

- The virological response rates at < 50 copies/ml at week 48 (FDA snapshot analysis) were 87.6% vs. 84.1% for Stribild vs. Atripla and 89.5% vs. 86.8% for Stribild vs. ATV/r+TVD. The lower bound of the 95% CI was well within the pre-defined margin (-12%). Actual 95% CIs were (-1.6%, 8.8%) and (-1.9%, 7.8%). A range of sensitivity analyses, including a TLOVR analysis, showed consistently comparable response rates for Stribild vs. comparators. The actual response rates were in the range ~84% to ~98% depending on the analysis and the study population.
- The analyses according to baseline characteristics did not show any disadvantages for Stribild, including groups with >100,000 copies/ml and CD4 counts < 350/mm3.
- Decreases in viral load were closely comparable between treatments in both studies.
- Increments in CD4 counts up to week 48 were higher in the Stribild group in 0102 and comparable between treatments in 0103.

These analyses support a conclusion that Stribild is at least as effective as the selected comparative regimens. Some further observations on the evidence of efficacy in the two Phase III studies include:

Selection of comparative regimens

Since the applicant provides two non-inferiority studies the selection of the comparative agents is a critical factor for the validity of the findings and analyses.

GS-US-236-0102

Stribild was compared to Atripla in previously ARV-naïve subjects. This use of Atripla contrasts with the EU SmPC, which restricts use to subjects who have already achieved virological suppression on another regimen. The reasons for the EU-worded approval (vs. that elsewhere in the world) can be found in the Atripla EPAR) . However, in light of the very specific EU approval, the validity of the comparison between Stribild and Atripla in one of the two pivotal efficacy studies merits some further re-examination.

Since doubts were raised from the EU approval of Atripla regarding the possible adequacy of Atripla when used to treat previously ARV-naïve subjects it seems relevant to examine the response rates documented in study 0102 with other studies in ARV naïve populations.

Perhaps one of the most relevant comparisons is with the raltegravir study vs. efavirenz (P021) in which both agents were administered with Truvada taken with food (i.e. TFV plasma levels would be expected to be higher vs. those achieved with the same regimen administered as Atripla). The study population was

not identical to that in GS-US-236-0102 in that it comprised ~80% males but a mix mainly of white and Hispanic races and ~20% had non-clade B virus. Just over 50% had > 100,000 copies/ml and also just over 50% had CD4 counts > 200 cells/mm3 while ~ 10% had < 50 cells/mm3 at baseline. Using the NC=F approach 86% RAL and 82% EFV subjects had < 50 copies/ml at week 48. The OF analysis gave rates of 92% vs. 89%. In the various subgroups rates for achieving < 50 copies/ml fell somewhere between 85-95% in both groups. Increments in CD4 counts were 189 and 163 in RAL and EFV groups, respectively.

Response rates in the ARV-naïve are also available from the darunavir study C211, which compared once daily dosing vs. Kaletra, both administered in conjunction with Truvada. The study population was again slightly different (e.g. 70% male, 60% clade B, 35% with > 100,000 copies/ml and near to 60% with CD4 counts > 200 cells/mm3). At week 48 rates for < 50 copies/mL were ~ 85% for darunavir and 79% for Kaletra (TLOVR). In the snapshot analysis rates were ~84% and 78%. For observed data rates were around 90% per group.

A third example to note is the rilpivirine study C209 in which rilpivirine was compared with EFV, both administered with FTC/TDF. The study population was about 75% male, 60% white and ~70% had clade B virus. Just under half had >100,000copies/ml and > 60% had CD4 counts > 200 cells/mm3. The primary analysis in ITT subjects used the TLOVR algorithm and showed rates for <50 copies/ml at week 48 of 83% in each treatment group with rates of 82% for both in the snapshot analysis.

Making comparisons across studies must be viewed with considerable caution. Nevertheless, taking into account the results mentioned above the CHMP finds no reason to dismiss the conclusion of Stribild vs. Atripla solely on the basis that use of Atripla from the outset is not approved in the EU.

GS-US-236-0103

The combination of ATV/rtv plus Truvada is not one of the favourite starting regimens in the EU. Opinions vary regarding the use of a boosted PI plus 2 NRTIs as initial therapy and some guidelines suggest reserving this combination for those in whom 2 NRTIs plus one NNRTI is not appropriate for some reason. Nevertheless, ATV/rtv is approved in the EU for use in ARV-naïve subjects and CHMP has accepted comparisons of test regimens vs. boosted PI-containing regimens to support use in the ARV-naïve. In study 0138 ATV/rtv was compared with Kaletra, each administered with Truvada, to ARV-naïve subjects. Rates for <50 copies/ml at week 48 were 78% and 76%, respectively.

Selection of virus with RAMs

In a pooled analysis of antiretroviral-naïve patients receiving Stribild in Phase 3 studies GS US 236 0102 and GS US 236 0103, as of week 48, the development of 1 or more primary elvitegravir, emtricitabine, or tenofovir resistance-associated substitutions was observed in the HIV 1 from 13 of the 25 patients with evaluable genotypic data from paired baseline and Stribild treatment failure isolates (1.9%, 13/701 patients. The available data showed that not all failures were associated with acquisition of RAMs. In the Stribild group the resistance analysis strongly pointed to co-selection of virus containing IN mutations along with resistance to FTC, with or without TFV. These results may reflect a relatively low genetic barrier to resistance to EVG.

2.5.4. Conclusions on the clinical efficacy

The efficacy data for Stribild support its use in ARV-naïve subjects or in subjects infected with virus that has no known RAMs for any of EVG, FTC or TFV.

The outstanding issues are minor and do not preclude recommendation for granting a Marketing Authorisation.

The CHMP considers the following clinical measures necessary post-authorisation, which are included in the Risk Management Plan:

- Clinical study of STB in HIV-1 infected women (GS-US-236-0128) including information on BMD in HIV-1 infected women from a subset of subjects from Study GS US 236 0128 in which DEXA scans will be performed with up to 96 weeks of STB therapy (Week 48 report by Q4 2016 and final results by Q4 2017).

2.6. Clinical safety

Patient exposure

The following evaluation focuses on the safety data, updated during the procedure, for each of EVG and COBI and for Stribild in Phase 2 and 3 studies in HIV-infected subjects. Details of AEs are provided only for the Stribild studies.

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EVG - The principal safety data came from the week 96 analysis of GS-US-183-0145 in ARV treatment-experienced subjects. Supportive data come from GS-US-183-0105 and GS-US-183-0130.

Table 64. GS-US-183-0145, 0105, and 0130: Summary of Treatment Groups and Exposures.

Study	Duration	Treatment Group	Number of Subjects
GS-US-183-0145	96 weeks	Group 1: EVG 150 mg once daily plus background regimen (BR) containing a PI/r (EVG 85 mg for subjects taking ATV/r or LPV/r as part of their BR)	354
		Group 2: RAL 400 mg twice daily plus BR containing a PI/r	358
GS-US-183-0130	192 weeks[a]	EVG 85-mg, 150-mg, or 300-mg strength tablets once daily, with RTV and BR	192
GS-US-183-0105	48 weeks	EVG 20 mg once daily with 100 mg RTV and BR	71
		EVG 50 mg once daily with 100 mg RTV and BR	71
		EVG 125 mg once daily with 100 mg RTV and BR	73
		Comparator PI/r and BR	63

COBI - The principal safety data came from the Phase 2 and 3 studies as follows:

Table 65.

Study	Duration	Treatment Group	Number of Subjects
GS-US-216-0105	60 weeks[a]	COBI 150 mg + ATV 300 mg + TVD (single-tablet FTC/TDF 200/300 mg) once daily	50
		RTV 100 mg + ATV 300 mg + TVD (single-tablet FTC/TDF 200/300 mg) once daily	29
GS-US-216-0114	48 weeks	COBI 150 mg + ATV 300 mg + TVD (single-tablet FTC/TDF 200/300 mg) once daily	344
		RTV 100 mg + ATV 300 mg + TVD (single-tablet FTC/TDF 200/300 mg) once daily	348

Stribild - The principal data came from Phase 2 and 3 studies GS-US-236-0102, 0103 and 0104.

This safety update was provided during the procedure following CHMP request. The principal sources of this update are from at least 96 weeks of the 2 phase III studies for Stribild with numbers as follows:

Table 66. GS-US-236-0102 and GS-US-236-0103: Duration of Exposure to Study Drug (Safety Analysis Set).

	QUAD 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
Total Exposure to Study Drug (Weeks)[a, b]			
N	701	352	355
Mean (SD)	92.6 (25.33)	92.3 (31.38)	88.5 (27.35)
Median	96.6	107.7	96.1
Q1, Q3	95.3, 108.0	96.0, 108.3	94.6, 97.7
Min, Max	0.1, 115.3	0.1, 119.3	0.6, 111.1
Total Exposure to Study Drug			
>= 4 Weeks (28 days)	691 (98.6%)	339 (96.3%)	342 (96.3%)
>= 8 Weeks (56 days)	685 (97.7%)	336 (95.5%)	339 (95.5%)
>= 12 Weeks (84 days)	681 (97.1%)	330 (93.8%)	334 (94.1%)
>= 16 Weeks (112 days)	671 (95.7%)	322 (91.5%)	332 (93.5%)
>= 24 Weeks (168 days)	663 (94.6%)	316 (89.8%)	328 (92.4%)
>= 32 Weeks (224 days)	653 (93.2%)	314 (89.2%)	323 (91.0%)
>= 40 Weeks (280 days)	643 (91.7%)	311 (88.4%)	317 (89.3%)
>= 48 Weeks (336 days)	642 (91.6%)	308 (87.5%)	317 (89.3%)
>= 60 Weeks (420 days)	628 (89.6%)	304 (86.4%)	313 (88.2%)
>= 72 Weeks (504 days)	617 (88.0%)	301 (85.5%)	309 (87.0%)
>= 84 Weeks (588 days)	609 (86.9%)	297 (84.4%)	304 (85.6%)
>= 96 Weeks (672 days)	479 (68.3%)	272 (77.3%)	207 (58.3%)
>= 108 Weeks (756 days)	199 (28.4%)	150 (42.6%)	48 (13.5%)

a Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.

b Imputed last dose date for subjects with the last dose date completely missing, or only year known, or for subjects still on study drug: either study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date), whichever gave the latest date, was used to impute the last dose date; in case of the last study drug end date was nonmissing, then it was used to impute the last dose date.

Adverse events

For most TEAEs the important data were included in the initial study reports up to at least Week 48, which can be summarised as follows:

Table 67. GS-US-236-0102, 0103, 0104: Overall Summary of Adverse Events (Safety Analysis Set).

	QUAD 236-0102, 0103, 0104 (N=749)	ATR 236-0102, 0104 (N=375)	ATV/r + TVD 236-0103 (N=355)
Subjects Experiencing Any Treatment-Emergent Adverse Event	694 (92.7%)	355 (94.7%)	333 (93.8%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event	414 (55.3%)	206 (54.9%)	220 (62.0%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	92 (12.3%)	41 (10.9%)	48 (13.5%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event	343 (45.8%)	250 (66.7%)	203 (57.2%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event	97 (13.0%)	98 (26.1%)	60 (16.9%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event	20 (2.7%)	15 (4.0%)	13 (3.7%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	69 (9.2%)	25 (6.7%)	31 (8.7%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event	5 (0.7%)	7 (1.9%)	2 (0.6%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	26 (3.5%)	19 (5.1%)	18 (5.1%)
Subjects Who Had Treatment-Emergent Death[a]	1 (0.1%)	2 (0.5%)	3 (0.8%)

Specific and important updates on these initial data are covered in the sections that follow.

In the week 48 analyses the most frequently reported TEAEs are shown in the table below. Rates were lower in the Stribild group for dizziness, somnolence, abnormal dreams, insomnia and rash but higher in the Stribild group for nausea. The minority of TEAEs were of Grade 3 or 4.

Table 68. GS-US-236-0102, 0103, 0104: Treatment-Emergent Adverse Events Reported for at Least 5% of Subjects in Any Treatment Group (Safety Analysis Set).

Adverse Events by System Organ Class and Preferred Term[a, b, c]	QUAD 236-0102, 0103, 0104 (N=749)	ATR 236-0102, 0104 (N=375)	ATV/r + TVD 236-0103 (N=355)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	694 (92.7%)	355 (94.7%)	333 (93.8%)
Eye Disorders	41 (5.5%)	25 (6.7%)	78 (22.0%)
Ocular Icterus	2 (0.3%)	0	51 (14.4%)
Gastrointestinal Disorders	403 (53.8%)	168 (44.8%)	201 (56.6%)
Diarrhoea	170 (22.7%)	70 (18.7%)	97 (27.3%)
Nausea	146 (19.5%)	50 (13.3%)	69 (19.4%)
Vomiting	41 (5.5%)	16 (4.3%)	24 (6.8%)
Flatulence	28 (3.7%)	5 (1.3%)	29 (8.2%)
General Disorders and Administration Site Conditions	176 (23.5%)	106 (28.3%)	94 (26.5%)
Fatigue	98 (13.1%)	49 (13.1%)	45 (12.7%)
Pyrexia	26 (3.5%)	19 (5.1%)	14 (3.9%)
Hepatobiliary Disorders	8 (1.1%)	7 (1.9%)	38 (10.7%)
Jaundice	0	1 (0.3%)	31 (8.7%)
Infections and Infestations	470 (62.8%)	224 (59.7%)	232 (65.4%)
Upper Respiratory Tract Infection	106 (14.2%)	44 (11.7%)	58 (16.3%)
Nasopharyngitis	53 (7.1%)	21 (5.6%)	28 (7.9%)
Sinusitis	41 (5.5%)	33 (8.8%)	18 (5.1%)
Bronchitis	49 (6.5%)	22 (5.9%)	18 (5.1%)
Musculoskeletal and Connective Tissue Disorders	160 (21.4%)	61 (16.3%)	55 (15.5%)
Back Pain	42 (5.6%)	14 (3.7%)	13 (3.7%)
Nervous System Disorders	201 (26.8%)	154 (41.1%)	93 (26.2%)
Headache	109 (14.6%)	38 (10.1%)	44 (12.4%)
Dizziness	42 (5.6%)	89 (23.7%)	25 (7.0%)
Somnolence	11 (1.5%)	29 (7.7%)	4 (1.1%)
Psychiatric Disorders	209 (27.9%)	174 (46.4%)	81 (22.8%)
Abnormal Dreams	70 (9.3%)	103 (27.5%)	14 (3.9%)
Insomnia	65 (8.7%)	51 (13.6%)	18 (5.1%)
Depression	57 (7.6%)	41 (10.9%)	23 (6.5%)
Respiratory, Thoracic and Mediastinal Disorders	151 (20.2%)	89 (23.7%)	76 (21.4%)
Cough	42 (5.6%)	17 (4.5%)	28 (7.9%)
Oropharyngeal Pain	29 (3.9%)	27 (7.2%)	18 (5.1%)
Skin and Subcutaneous Tissue Disorders	200 (26.7%)	137 (36.5%)	102 (28.7%)
Rash	52 (6.9%)	47 (12.5%)	22 (6.2%)

A lower percentage of subjects in the Stribild group compared with the Atripla or ATV/r + TVD groups reported any TEAE considered related to study drug by the investigator (Stribild 45.8%, 343 subjects; ATR 66.7%, 250 subjects; ATV/r+TVD 57.2%, 203 subjects).

In the two Phase 3 studies the specific comparisons between the Stribild and comparator groups are also of note rather than the pooled Stribild comparisons shown above. In GS-US-236-0102 the safety profiles of the Stribild and Atripla regimens were very closely comparable with the exception of the differences imposed by the efavirenz-associated TEAEs. The Stribild was associated with higher rates of gastrointestinal TEAEs and these were more likely to be of severe intensity.

Table 69. GS-US-236-0102: Treatment-Emergent Adverse Events Reported for at Least 10% of Subjects in Either Treatment Group (Safety Analysis Set).

Table 11-3. GS-US-236-0102: Treatment-Emergent Adverse Events Reported for at Least 10% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a]	QUAD (N=348)	ATR (N=352)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event[b,c]	327 (94.0%)	334 (94.9%)
Gastrointestinal Disorders	188 (54.0%)	161 (45.7%)
Diarrhoea	80 (23.0%)	66 (18.8%)
Nausea	72 (20.7%)	48 (13.6%)
General Disorders and Administration Site Conditions	68 (19.5%)	99 (28.1%)
Fatigue	40 (11.5%)	45 (12.8%)
Infections and Infestations	206 (59.2%)	211 (59.9%)
Upper Respiratory Tract Infection	48 (13.8%)	38 (10.8%)
Nervous System Disorders	95 (27.3%)	146 (41.5%)
Dizziness	23 (6.6%)	86 (24.4%)
Headache	49 (14.1%)	34 (9.7%)
Psychiatric Disorders	118 (33.9%)	163 (46.3%)
Abnormal Dreams	53 (15.2%)	95 (27.0%)
Insomnia	30 (8.6%)	49 (13.9%)
Depression	33 (9.5%)	39 (11.1%)
Skin and Subcutaneous Tissue Disorders	87 (25.0%)	129 (36.6%)
Rash	22 (6.3%)	43 (12.2%)

In GS-US-236-0103 TEAE reporting rates were mostly comparable or lower in the Stribild group. The same observations broadly applied to rates for Grade 3 or 4 and drug-related TEAEs.

Table 70. GS-US-236-0103: Treatment-Emergent Adverse Events Reported for at Least 10% of Subjects in Either Treatment Group (Safety Analysis Set).

Adverse Events by System Organ Class and Preferred Term[a]	QUAD (N=353)	ATV/r+TVD (N=355)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event[b,c]	323 (91.5%)	333 (93.8%)
Eye Disorders	18 (5.1%)	78 (22.0%)
Ocular Icterus	2 (0.6%)	51 (14.4%)
Gastrointestinal Disorders	189 (53.5%)	201 (56.6%)
Diarrhoea	77 (21.8%)	97 (27.3%)
Nausea	70 (19.8%)	69 (19.4%)
General Disorders and Administration Site Conditions	96 (27.2%)	94 (26.5%)
Fatigue	50 (14.2%)	45 (12.7%)
Infections and Infestations	234 (66.3%)	232 (65.4%)
Upper Respiratory Tract Infection	54 (15.3%)	58 (16.3%)
Nervous System Disorders	91 (25.8%)	93 (26.2%)
Headache	53 (15.0%)	44 (12.4%)

Rates of TEAEs of interest are shown in the next table below.

Renal events

As shown in the table, the number of renal AEs of interest increased from 6 to 12 (and from 5 to 11 in the Stribild group) between the cut-off for the initial application dossier and that for the Stribild safety update. While no additional subjects had renal findings consistent with the applicant's initial or later revised (more inclusive) pre-specified criteria for PRT vs. the initial dossier the actual nature of these renal AEs of interest merits further scrutiny.

Table 71.

	QUAD 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
FRACTURE EVENTS	14 (2.0%)	8 (2.3%)	14 (3.9%)
ANKLE FRACTURE	0	0	1 (0.3%)
CERVICAL VERTEBRAL FRACTURE	0	1 (0.3%)	0
CLAVICLE FRACTURE	1 (0.1%)	1 (0.3%)	0
FACIAL BONES FRACTURE	2 (0.3%)	1 (0.3%)	0
FEMUR FRACTURE	1 (0.1%)	0	0
FIBULA FRACTURE	1 (0.1%)	0	0
FOOT FRACTURE	5 (0.7%)	1 (0.3%)	3 (0.8%)
HAND FRACTURE	1 (0.1%)	1 (0.3%)	3 (0.8%)
LOWER LIMB FRACTURE	0	0	1 (0.3%)
LUMBAR VERTEBRAL FRACTURE	2 (0.3%)	0	0
RIB FRACTURE	1 (0.1%)	1 (0.3%)	1 (0.3%)
THORACIC VERTEBRAL FRACTURE	0	0	1 (0.3%)
TIBIA FRACTURE	1 (0.1%)	0	0
TRAUMATIC FRACTURE	1 (0.1%)	1 (0.3%)	1 (0.3%)
UPPER LIMB FRACTURE	0	2 (0.6%)	3 (0.8%)
WRIST FRACTURE	0	1 (0.3%)	1 (0.3%)
RENAL EVENTS	11 (1.6%)	1 (0.3%)	0
FANCONI SYNDROME ACQUIRED	1 (0.1%)	0	0
RENAL FAILURE	8 (1.1%)	1 (0.3%)	0
RENAL FAILURE ACUTE	2 (0.3%)	0	0

The safety update clarified that in the two Phase 3 studies there were **16 subjects** (2.3%) in the Stribild group who had a renal SAE, discontinued study drug due a renal AE and/or had a pre-specified renal AE of interest. One subject (0.3%) in the ATR group (shown in the table above) had a pre-specified renal AE of interest. There were also two subjects (0.6%) in the ATV/r+TVD group who discontinued study drug due to renal AEs but did not have a renal AE of interest. The summary of these events by event category is as follows:

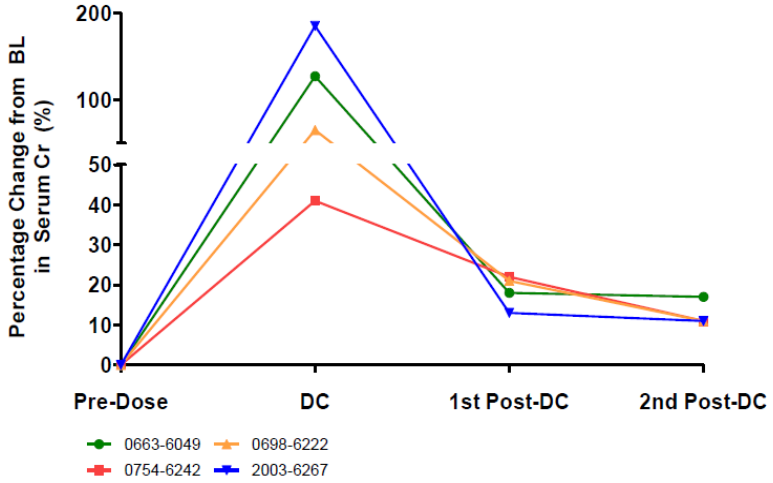
- One subject (0.1%) in the Stribild group had an SAE of renal failure
- Ten subjects (1.4%) in the Stribild group discontinued study drug due to renal events (blood creatinine increased for 4 subjects, renal failure for 3 subjects, acute renal failure for 1 subject, Fanconi syndrome acquired for 1 subject and GFR abnormal for 1 subject)
- Two subjects (0.6%) in the ATV/r+TVD group discontinued study drug due to renal events (creatinine renal clearance decreased for 1 subject and toxic nephropathy for 1 subject).
- Renal AEs of interest were reported for 11 subjects (1.6%) in the Stribild group and for 1 subject (0.3%) in the ATR group ($p = 0.071$ for Stribild vs. ATR; $p = 0.020$).
- In the Stribild group, the renal AEs of interest reported were renal failure (8 subjects), acute renal failure (2 subjects), and Fanconi syndrome acquired (1 subject).
- The renal AE of interest reported for a subject in the ATR group was renal failure.
- For 4 subjects (0.6%) in the Stribild group, the renal AEs and laboratory findings were consistent with PRT. Two of the 4 subjects had eGFR < 70 mL/min at screening or baseline. Each of these subjects discontinued study drug due to renal AEs. While laboratory findings in all of these subjects with evidence of PRT improved after discontinuation they did not necessarily return to baseline and/or fall within normal ranges at the last documented measurement.

Table 72. GS-US-236-0102 and GS-US-236-0103: Subjects with Renal Events Associated with Proximal Renal Tubulopathy.

Subject ID	Group	Renal Event Category	Baseline Characteristics[a]	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
0663-6049	QUAD	DC, AEoI	56yo White male; history of hypertension and hypercholesterolemia; concomitant amlodipine and ramipril; screening Cr 1.30 mg/dL and $eGFR_{CG}$ 66.77 mL/min	Renal failure, Grade 3 (D59–cont.)	DC (D66)	At Wk8 (D59), Cr 2.86 mg/dL ($eGFR_{CG}$ 31.82 mL/min) with +2 proteinuria (confirmed), but no glycosuria or hypophosphatemia. The magnitude of Cr increase to more than double the screening value, and confirmed +2 proteinuria, suggests PRT. After DC, Cr improved and proteinuria normalized within a few weeks. Last available (D755) Cr 1.48 mg/dL ($eGFR_{CG}$ 64.56 mL/min) and +1 proteinuria. Post-DC regimen ATV/r, ABC/3TC was started on D164 then MVC+DRV/r on D304.
0754-6242	QUAD	DC, AEoI	29yo White male; HIV wasting syndrome; unintentional weight loss; concomitant acyclovir use; screening Cr 1.26 mg/dL, $eGFR_{CG}$ 114.81 mL/min, +1 proteinuria	Fanconi syndrome acquired, Grade 3 (D284–cont.)	DC (D323)	At Wk40 (D284), Cr 1.81 mg/dL ($eGFR_{CG}$ 79.55 mL/min) with normoglycemic +4 glycosuria (confirmed), +2 proteinuria (confirmed), and phosphate 1.8 mg/dL (FE_{PO4} 51.4%) (confirmed). The presence of multiple concurrent renal lab abnormalities suggests PRT. After DC, all laboratory abnormalities improved except proteinuria, with last available (D381) Cr 1.54 mg/dL ($eGFR_{CG}$ 90.87 mL/min). There are no further data except last reported Cr from a local lab of 1.4 mg/dL at Week 60.
0698-6222	QUAD	DC	20yo White male; baseline Cr 1.00 mg/dL, $eGFR_{CG}$ 82.33 mL/min, trace proteinuria at baseline; AE of weight decreased (D399)	Blood creatinine increased, Grade 3 (D399–cont.)	DC (D411)	At Wk48 (D337-414), Cr 1.65 mg/dL ($eGFR_{CG}$ 49.38 mL/min) with ≥ +1 proteinuria (confirmed) and normoglycemic ≥ +1 glycosuria (confirmed). The presence of multiple concurrent renal lab abnormalities suggests PRT. D55 TFV C_{max} 1.6-fold above median and AUC 2.1-fold above median. After DC, all laboratory abnormalities improved; both glycosuria and proteinuria completely resolved. Last available (D755) Cr 1.21 mg/dL ($eGFR_{CG}$ 79.24 mL/min). Post-DC regimen RPV+ABC/3TC was started on D415.
2003-6267	QUAD	DC	60yo White male; history of renal disease, hypertension and hypercholesterolemia; concomitant quinapril and simvastatin use; baseline Cr 1.52 mg/dL, $eGFR_{CG}$ 68.27 mL/min	Blood creatinine increased, Grade 3 (D16–cont.)	DC (D37)	At Wk4 (D37), Cr 4.33 mg/dL ($eGFR_{CG}$ 24.10 mL/min) with normoglycemic +2 glycosuria (confirmed) and +2 proteinuria (previously confirmed). The presence of multiple concurrent renal lab abnormalities suggests PRT. After DC, all laboratory abnormalities improved with proteinuria and glycosuria normalizing. At Wk84 (D618), Cr 1.98 mg/dL ($eGFR_{CG}$ 59.36 mL/min). Last available (D776) Cr 5.41 mg/dL ($eGFR_{CG}$ 22.61 mL/min) with normoglycemic +1 glycosuria, negative urine protein, and hyperphosphatemia (5.1 mg/dL); per investigator, hypertension suspected as the underlying cause for deteriorating eGFR as the subject not on TDF. D16 TFV C_{max} and AUC were 3.1- and 4.5-fold higher than the median value of QUAD subjects in the PK substudy. Post-DC regimen DRV/r+RAL was started on D168.

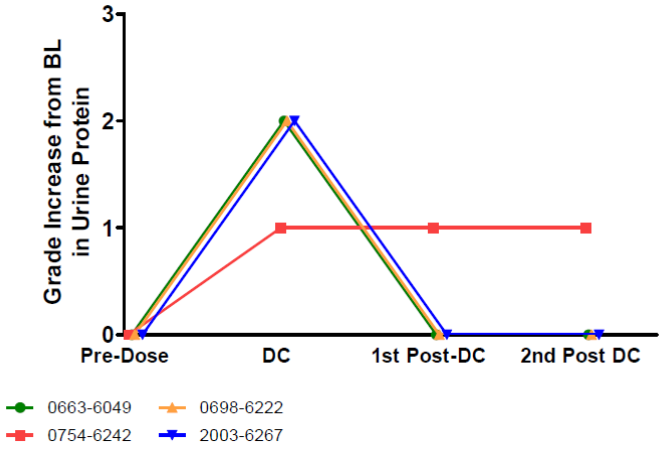
These four subjects attended scheduled visits for determination of reversibility. Serum creatinine returned to within approximately 25% of the baseline level in all 4 subjects at 2 consecutive visits post-discontinuation, during which time 3 initiated RPV or a PI/r. The fourth subject withdrew consent and no further follow-up data are available.

Figure 14. GS-US-236-0102: Percentage Change from Baseline in Serum Creatinine for Subjects with Renal Events Consistent with PRT who Received STB.



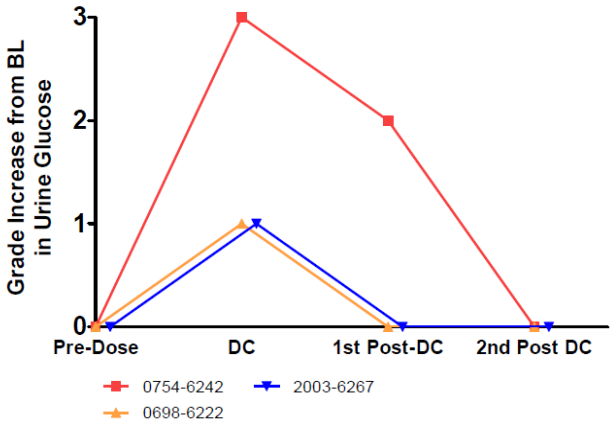
Proteinuria returned to baseline post-discontinuation in the 3 subjects affected. One had +1 urine protein at screening and +2 (Grade 1) at discontinuation and up to the last result at ~ 60 days.

Figure 15. GS-US-236-0102: Grade Change from Baseline in Urine Protein for Subjects with Renal Events Consistent with PRT who Received STB.



Normoglycaemic glycosuria resolved with a confirmed return to baseline values for 2 subjects and the other improved from +4 (Grade 3) (serum glucose 50 mg/dL) to +3 (Grade 2) and trace (Grade 0) at consecutive visits after discontinuation up to the last result at ~ 60 days.

Figure 16. GS-US-236-0102: Grade Change from Baseline in Normoglycemic Glycosuria for Subjects with Renal Events Consistent with PRT who Received STB.



Hypophosphataemia returned to baseline post-discontinuation in the single subject that had this abnormality.

More detailed individual summary figures for these 4 STB subjects who had evidence of PRT and discontinued showed that two subjects continued to have variable proteinuria after discontinuing STB. Only one subject showed early and marked abnormalities in creatinine, proteinuria and glycosuria.

There were also six subjects in the COBI Phase 3 study who developed PRT while taking ATV/co + TVD. For the most part, and where data are available, these subjects did trend towards improvement or resolution of the findings over time.

For the other 12/16 subjects in the Stribild group who had a renal SAE, discontinued study drug due a renal AE and/or had a pre-specified renal AE of interest. 6/12 subjects had AEs reported as renal failure, increased serum creatinine or decreased GFR that were associated with proteinuria.

The relationship between TFV and COBI PK and effects on renal parameters was explored. Subjects in the Phase 2 and 3 STB studies (n = 419) were classified according to < 0.4 mg/dL or ≥ 0.4 mg/dL change in serum creatinine, with or without at least 1 grade-level increases in renal tubular markers. The analysis showed a similar range of TFV and COBI AUC, C_{max} and C_{min} across these categories, indicating the absence of exposure-driven trends in parameters.

In a further exploration, the applicant tabulated subjects with *confirmed* laboratory abnormalities (see the footnotes), which included the four subjects considered to meet the applicant's PRT criteria.

As shown in the next table six STB (0.9%) and 5 ATV/r+TVD (1.4%) subjects (but no ATR subjects) had confirmed increases from baseline in serum creatinine and a ≥ 1 grade-level increase from baseline in one renal tubular marker, which was proteinuria in all subjects. Four of the 6 STB subjects did not have PRT and 3 of them continued study drug. Not all had concurrent abnormalities.

Of the 5 subjects in the ATV/r+TVD group, 4 subjects continued study drug but 0663-7308 discontinued due to a renal AE as reported previously. None had findings consistent with PRT and all 5 subjects had at least one renal risk factor.

Table 73. GS-US-236-0102 and GS-US-236-0103: Percentage of Subjects by the Number of Confirmed Renal Laboratory Abnormalities (Safety Analysis Set).

Number of Confirmed Renal Laboratory Abnormalities[a]	STB 236-0102, 0103 (N=701)	ATV/r+TVD 236-0103 (N=355)	ATR 236-0102 (N=352)
≤ 1 Renal Laboratory Abnormality	**98.6% (n = 691)**	**98.3% (n = 349)**	**99.7% (n = 351)**
2 or More Renal Laboratory Abnormalities	**1.4% (n = 10)**	**1.7% (n = 6)**	**0.3% (n = 1)**
Serum Creatinine Increase and One Renal Tubular Abnormality	0.9% (n = 6)[b]	1.4% (n = 5)[c]	0
Serum Creatinine Increase and Two Renal Tubular Abnormalities	0.3% (n = 2)[d]	0	0.3% (n = 1)[e]
Serum Creatinine Increase and Three Renal Tubular Abnormalities	0.1% (n = 1)[f]	0	0
Two Renal Tubular Abnormalities (Without Serum Creatinine Increase)	0.1% (n = 1)[g]	0.3% (n = 1)[h]	0

a Renal laboratory abnormalities are confirmed increase from baseline in serum creatinine (≥ 0.4 mg/dL for STB and ATV/r+TVD; ≥ 0.24 mg/dL for ATR), and ≥ 1 grade-level increase from baseline in proteinuria, normoglycemic glycosuria, or hypophosphatemia

b Subjects 0663-6049 (PRT), 0698-6222 (PRT), 0659-6369, 0663-6014, 0991-6633, 2058-6709; all subjects had proteinuria

c Subjects 0315-7392, 0315-7695, 0663-7308, 1236-7513, 2058-7546; all subjects had proteinuria

d Subject 2003-6267 (PRT) with proteinuria and normoglycemic glycosuria; Subject 2675-7428 with proteinuria and hypophosphatemia

e Subject 2675-6010 with proteinuria and hypophosphatemia

f Subject 0754-6242 (PRT) with proteinuria, normoglycemic glycosuria, and hypophosphatemia

g Subject 3027-7605 with proteinuria and hypophosphatemia

h Subject 2728-7070 with proteinuria and hypophosphatemia

Three STB subjects and one ATR subject had confirmed increase from baseline in serum creatinine and ≥ 1 grade-level increase from baseline in two or more renal tubular markers (none on ATV/r+TVD). Two of the 3 in the STB group had findings consistent with PRT as previously described. The other subject did not have PRT and was continuing study drug with confirmed hypophosphataemia, proteinuria (≥ 1 grade-level increases from baseline) and serum creatinine increase (≥ 0.4 mg/dL) at different times during the study. Maximum serum creatinine was 1.64 mg/dL at Week 60 but dropped to 1.13 mg/dL at Week 96. The proteinuria was pre-existing (+1 to +2 at baseline) and hypophosphataemia was based on 2.8 mg/dL at baseline, 2.6-3.8 mg/dL at Week 20 through Week 96 and was improved at the next visit.

One STB subject and one ATV/r+TVD subject had ≥ 1 grade-level increase from baseline in proteinuria and hypophosphataemia without a confirmed increase from baseline in serum creatinine. The STB subject had confirmed hypophosphataemia and proteinuria (≥ 1 grade-level increase from baseline) non-concurrently. There was an unconfirmed increase in serum creatinine (1.40 mg/dL; eGFRCG 89.41 mL/min) at Week 16 only. Hypophosphataemia and proteinuria improved at sequential visits while continuing study drug.

Rates for confirmed increases in serum creatinine (using the applicant's criteria to differentiate COBI and RTV-associated effects from other treatment effects) were STB 4.1%, ATV/r+TVD 3.1% and ATR 2.6%.

Table 74.

			Confirmed >= 0.4 mg/dL Increase from BL in Serum Creatinine			Confirmed >= 0.24 mg/dL Increase from BL in Serum Creatinine		
			QUAD (N=701)			ATR (N=352)		
			Yes (N=29)	No (N=672)	Total (N=701)	Yes (N=9)	No (N=343)	Total (N=352)
	Normoglycemic							
Proteinuria	Glycosuria	Hypophosphatemia						
Yes	Yes	Yes	1 (0.1%)	0	1 (0.1%)	0	0	0
Yes	Yes	No	1 (0.1%)	0	1 (0.1%)	0	0	0
Yes	No	Yes	1 (0.1%)	1 (0.1%)	2 (0.3%)	1 (0.3%)	0	1 (0.3%)
Yes	No	No	6 (0.9%)	73 (10.4%)	79 (11.3%)	0	26 (7.4%)	26 (7.4%)
No	Yes	Yes	0	0	0	0	0	0
No	Yes	No	0	2 (0.3%)	2 (0.3%)	0	0	0
No	No	Yes	0	5 (0.7%)	5 (0.7%)	0	1 (0.3%)	1 (0.3%)
No	No	No	20 (2.9%)	591 (84.3%)	611 (87.2%)	8 (2.3%)	316 (89.8%)	324 (92.0%)
Total	Total	Total	29 (4.1%)	672 (95.9%)	701 (100.0%)	9 (2.6%)	343 (97.4%)	352 (100.0%)

			Confirmed >= 0.4 mg/dL Increase from BL in Serum Creatinine		
			ATV/r+TVD (N=355)		
(Continued)			Yes (N=11)	No (N=344)	Total (N=355)
	Normoglycemic				
Proteinuria	Glycosuria	Hypophosphatemia			
Yes	Yes	Yes	0	0	0
Yes	Yes	No	0	0	0
Yes	No	Yes	0	1 (0.3%)	1 (0.3%)
Yes	No	No	5 (1.4%)	31 (8.7%)	36 (10.1%)
No	Yes	Yes	0	0	0
No	Yes	No	0	2 (0.6%)	2 (0.6%)
No	No	Yes	0	2 (0.6%)	2 (0.6%)
No	No	No	6 (1.7%)	308 (86.8%)	314 (88.5%)
Total	Total	Total	11 (3.1%)	344 (96.9%)	355 (100.0%)

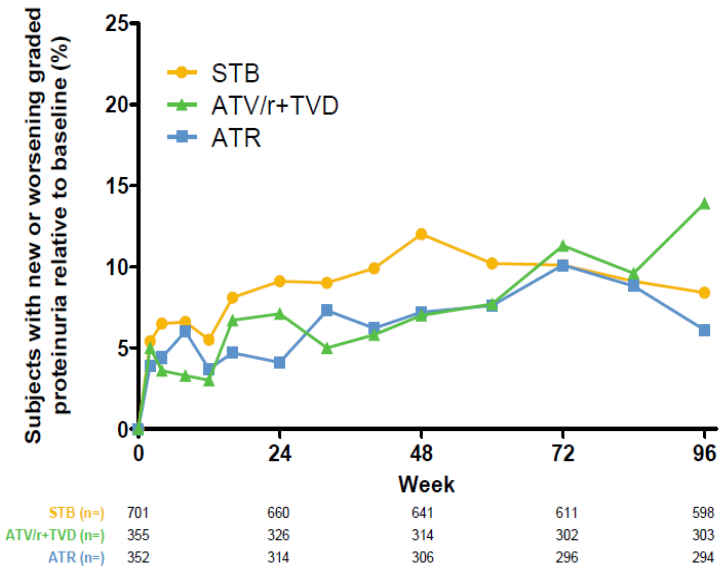
The changes in serum creatinine from Week 4 onwards were minimal (≤ 0.04 mg/dL) and similar between treatment groups.

At Week 48 treatment-emergent proteinuria was reported for 38.6% STB, 24.1% ATV/r+TVD and 28.8% ATR subjects. Differences between groups were still apparent at Week 96 (STB 46.2%; ATV/r+TVD 36.6%; ATR 37.6%). However, the incremental incidence of treatment-emergent proteinuria (new onset or worsening grading relative to baseline) from Week 48 to Week 96 in the STB group was 7.6% vs. ATV/r+TVD 12.5% and ATR 8.8%). In addition, the cumulative rates of confirmed increases in proteinuria through Week 96 were similar between groups (STB 11.8%; ATV/r+TVD 10.4%; ATR 7.7%).

Treatment-emergent proteinuria that persisted for more than 2 consecutive visits occurred in STB 5.1%, ATV/r+TVD 3.7% and ATR 1.7%. There were similar findings for the analysis by the presence (≥ +1) or absence (negative or trace) of proteinuria at baseline.

Percentages of subjects with new or worsening proteinuria in each visit window were higher in the STB group than in the comparator groups in visit windows from Week 24 to Week 60. Rates were generally similar between treatments in other visit windows. Percentages in each visit window after Week 48 did not increase progressively. The applicant considered that STB does not increase the risk of persistent proteinuria over time compared to ATV/r+TVD or ATR.

Figure 17. GS-US-236-0102 and GS-US-236-0103: Rates of New or Worsening Graded Proteinuria Relative to Baseline in Each Visit Window Through Week 96 (Safety Analysis Set).



Bone fracture events

The majority of the reported fractures occurred due to traumatic injury. Non-traumatic fractures were reported for one subject in each group in GS-US-236-0103.

Rash events

In the Stribild studies percentages that reported any rash AE based on a pre-specified analysis were 17.5% in the Stribild group [131 subjects], 27.7% Atripla [104 subjects] and 18% [64 subjects] ATV/r+TVD. No rash SAEs were reported in the Stribild group and only one led to drug discontinuation.

ECG effects

- In GS-US-236-0102 there were no clinically relevant changes from baseline for ECG parameters and no notable differences between treatment groups in percentages with ECG abnormalities.
- In GS-US-236-0103 there were no notable differences between treatment groups in percentages with ECG abnormalities. Two subjects in the Stribild group developed clinically significant abnormal ECGs by Week 48 that concerned atrial fibrillation and sinus bradycardia.

Serious adverse event and deaths

In the pooled Phase 2/3 studies there were 6 treatment-emergent deaths, all were considered not related to the medication– one in the Stribild group (0.1%; a case of suicide), two in the Atripla group (0.5%; hanging and metastatic carcinoma) and 3 ATV/r + TVD subjects (0.8%; septic shock, *P. carinii* pneumonia and cardiopulmonary arrest).

In the original MAA, the frequencies of SAEs were Stribild 9.6% (67 subjects), ATR 6.8% (24 subjects) and ATV/r+TVD 8.7% (31 subjects). By the time of the safety update the rates had increased to 12.8%, 9.4% and 14.1%, respectively. Cellulitis was the only individual SAE reported in at least 1% of subjects in any treatment group (Stribild 1.0%, 7 subjects; ATR 0 subjects; ATV/r+TVD 0.6%, 2 subjects).

The rates of SAEs considered related to study drug by the investigator were low and comparable between groups (Stribild 0.7%, 5 subjects; ATR 2.0%, 7 subjects; ATV/r+TVD 0.6%, 2 subjects). No individual SAE considered related was reported for more than one subject in any treatment group (table below).

Table 75.

	QUAD 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
Number of Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event	5 (0.7%)	7 (2.0%)	2 (0.6%)
Number of Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event By System Organ Class And Preferred Term			
GASTROINTESTINAL DISORDERS	0	1 (0.3%)	0
ABDOMINAL PAIN	0	1 (0.3%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (0.3%)	0
PYREXIA	0	1 (0.3%)	0
HEPATOBILIARY DISORDERS	1 (0.1%)	0	0
LIVER INJURY	1 (0.1%)	0	0
IMMUNE SYSTEM DISORDERS	1 (0.1%)	0	0
DRUG HYPERSENSITIVITY	1 (0.1%)	0	0
INFECTIONS AND INFESTATIONS	0	0	1 (0.3%)
IMPETIGO	0	0	1 (0.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.1%)	0	0
BURKITT'S LYMPHOMA	1 (0.1%)	0	0
NERVOUS SYSTEM DISORDERS	1 (0.1%)	3 (0.9%)	0
GRAND MAL CONVULSION	0	1 (0.3%)	0
HEADACHE	0	1 (0.3%)	0
MIGRAINE	1 (0.1%)	0	0
SYNCOPE	0	1 (0.3%)	0
PSYCHIATRIC DISORDERS	1 (0.1%)	2 (0.6%)	0
COMPLETED SUICIDE	0	1 (0.3%)	0
DEPRESSION	1 (0.1%)	0	0
SUICIDE ATTEMPT	0	1 (0.3%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.3%)	0
DYSPNOEA	0	1 (0.3%)	0
DYSPNOEA EXERTIONAL	0	1 (0.3%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.3%)	1 (0.3%)
DRUG ERUPTION	0	0	1 (0.3%)
RASH MACULO-PAPULAR	0	1 (0.3%)	0

A possible excess of observed NHL/Hodgkin cases was observed across the EVG and Stribild studies. Cases observed in Stribild recipients include one case of Burkitt's lymphoma in study 103 (Day 342, patient 1021-7348) and a case of lymphoma in study 102 (Day 80, patient 0315-6335; reported to be a large cell lymphoma). In addition, B-cell lymphoma was reported in 2 subjects (2.8%) in the EVG/r 20/100-mg group in the EVG dose-finding study GS-US-183-0105. The applicant provided a detailed report of all NHL/Hodgkin cases observed during the EVG and Stribild development programmes and compared rates with those documented in other settings. It was concluded that there is no clear signal for an association between EVG and risk of lymphoma

Laboratory findings

The frequencies of Grade 3 or 4 laboratory abnormalities in the original MAA were Stribild 16.6% (116/699), ATR 23.4% (82/351) and ATV/r+TVD 67.9% (239/352). The rates at the time of the safety update were Stribild 20.9% (146/699), ATR 30.2% (106/351) and ATV/r+TVD 75.6% (266/352). In particular, changes from baseline in serum creatinine and eGFRCG and changes from baseline in BMD remained stable from Week 48 to 96. The table below summarises the data.

Table 76. GS-US-236-0102 and GS-US-236-0103: Treatment-Emergent Grade 3 and 4 Laboratory Abnormalities Reported for at Lease 1% of Subjects in Any Treatment Group (Safety Analysis Set).

	QUAD 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
Hematology			
Neutrophils	699	351	352
Grade 3 or 4	13 (1.9%)	11 (3.1%)	6 (1.7%)
Chemistry			
ALT	699	351	352
Grade 3 or 4	13 (1.9%)	13 (3.7%)	12 (3.4%)
Amylase	699	351	352
Grade 3 or 4	20 (2.9%)	8 (2.3%)	15 (4.3%)
AST	699	351	352
Grade 3 or 4	17 (2.4%)	20 (5.7%)	20 (5.7%)
Creatine Kinase (CK)	699	351	352
Grade 3 or 4	46 (6.6%)	50 (14.2%)	36 (10.2%)
GGT	699	351	352
Grade 3 or 4	9 (1.3%)	23 (6.6%)	8 (2.3%)
Lipase[c]	61	36	36
Grade 3 or 4	9 (14.8%)	6 (16.7%)	9 (25.0%)
Serum Glucose (Hyperglycemia)[d]	699	351	352
Grade 3 or 4	7 (1.0%)	2 (0.6%)	7 (2.0%)
Total Bilirubin (Hyperbilirubinemia)	699	351	352
Grade 3 or 4	5 (0.7%)	1 (0.3%)	228 (64.8%)
Total Cholesterol (Fasting, Hypercholesterolemia)	666	320	329
Grade 3 or 4	8 (1.2%)	9 (2.8%)	2 (0.6%)
Triglycerides (Fasting)	666	320	329
Grade 3 or 4	1 (0.2%)	5 (1.6%)	5 (1.5%)
Urinalysis			
Urine Glucose (Glycosuria)	699	351	352
Grade 3 or 4	8 (1.1%)	5 (1.4%)	7 (2.0%)
Urine RBC (Hematuria, Quantitative)[e]	699	351	352
Grade 3 or 4	23 (3.3%)	7 (2.0%)	13 (3.7%)

a Denominator for percentage is the number of subjects in the safety analysis set with at least 1 postbaseline laboratory value for each test.

b Subjects were counted once for the postbaseline maximum severity for each laboratory test.

c Lipase test was only performed for subjects with serum amylase > 1.5 x upper limit of normal.

d Serum glucose was graded based on the Division of AIDS (DAIDS) toxicity grading scale (2009 version) for fasting and nonfasting serum glucose values.

e Urine RBC (hematuria, quantitative) was graded based on DAIDS grading scale (with the modification of urine RBC > 75 cells /HPF as Grade 3).

However, virtually all subjects had grade 1 laboratory abnormalities. The majority of the abnormalities reported were Grade 1 or Grade 2 in severity and the supplementary tables provide the following data:

Table 77.

	QUAD 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
Creatinine	**699**	**351**	**352**
Grade 1	**65 (9.3%)**	**3 (0.9%)**	**17 (4.8%)**
Grade 2	**2 (0.3%)**	**1 (0.3%)**	**1 (0.3%)**
Grade 3	**1 (0.1%)**	**0**	**0**
Grade 4	**0**	**0**	**0**
Any Grade	**68 (9.7%)**	**4 (1.1%)**	**18 (5.1%)**
Phosphate (Hypophosphatemia)	**699**	**351**	**352**
Grade 1	**39 (5.6%)**	**15 (4.3%)**	**17 (4.8%)**
Grade 2	**16 (2.3%)**	**5 (1.4%)**	**9 (2.6%)**
Grade 3	**1 (0.1%)**	**0**	**2 (0.6%)**
Grade 4	**0**	**0**	**0**
Any Grade	**56 (8.0%)**	**20 (5.7%)**	**28 (8.0%)**

Urine Glucose (Glycosuria)	699	351	352
Grade 1	4 (0.6%)	0	7 (2.0%)
Grade 2	5 (0.7%)	1 (0.3%)	10 (2.8%)
Grade 3	8 (1.1%)	5 (1.4%)	7 (2.0%)
Grade 4	0	0	0
Any Grade	17 (2.4%)	6 (1.7%)	24 (6.8%)
Urine Protein (Proteinuria)	699	351	352
Grade 1	269 (38.5%)	125 (35.6%)	102 (29.0%)
Grade 2	52 (7.4%)	7 (2.0%)	26 (7.4%)
Grade 3	2 (0.3%)	0	1 (0.3%)
Grade 4	0	0	0
Any Grade	323 (46.2%)	132 (37.6%)	129 (36.6%)

Therefore the data showed an excess of raised serum creatinine with Stribild and also showed a higher rate of proteinuria but there was no excess of hypophosphataemia or glycosuria.

The supplementary tables also showed the correlation between serum creatinine increases and the other three parameters for the three treatments. It is important to appreciate the footnotes, which explains why the numbers (e.g. total with proteinuria in this table refers only to those few with at least a 2-grade increase from baseline) are so different vs. those shown above for any grade proteinuria. Hence the table does not show the correlation between occurrence of *any* abnormalities in these parameters and rates of co-existence of these abnormalities.

Table 78.

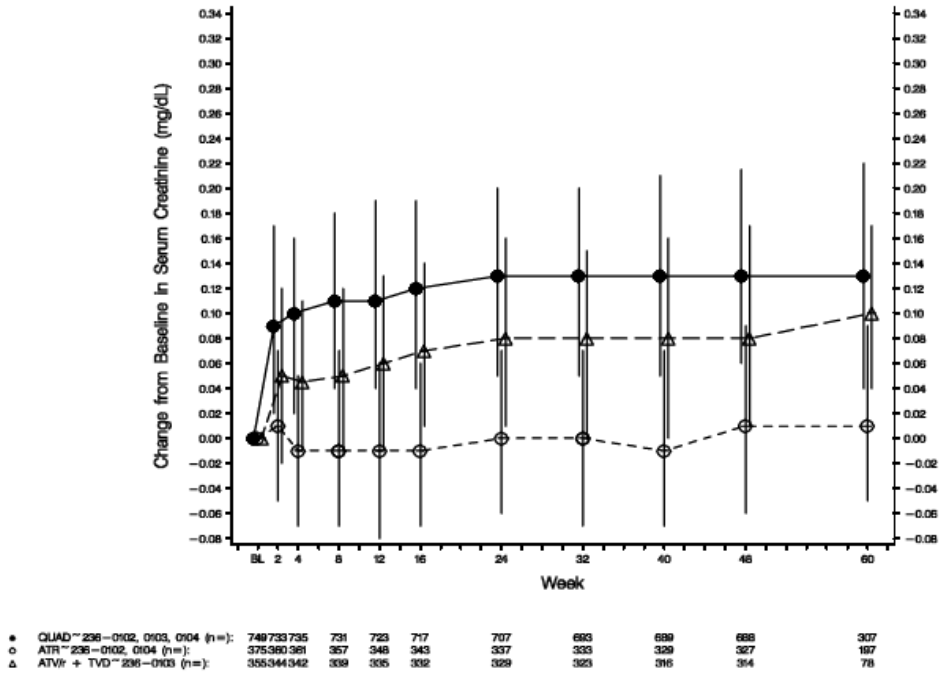
			Confirmed >= 0.4 mg/dL Increase from BL in Serum Creatinine			Confirmed >= 0.24 mg/dL Increase from BL in Serum Creatinine		
			QUAD (N=701)			ATR (N=352)		
			Yes (N=29)	No (N=672)	Total (N=701)	Yes (N=9)	No (N=343)	Total (N=352)
Proteinuria	Normoglycemic Glycosuria	Hypophosphatemia						
Yes	Yes	Yes	1 (0.1%)	0	1 (0.1%)	0	0	0
Yes	Yes	No	1 (0.1%)	0	1 (0.1%)	0	0	0
Yes	No	Yes	0	0	0	0	0	0
Yes	No	No	2 (0.3%)	2 (0.3%)	4 (0.6%)	0	0	0
No	Yes	Yes	0	0	0	0	0	0
No	Yes	No	0	2 (0.3%)	2 (0.3%)	0	0	0
No	No	Yes	1 (0.1%)	6 (0.9%)	7 (1.0%)	1 (0.3%)	1 (0.3%)	2 (0.6%)
No	No	No	24 (3.4%)	662 (94.4%)	686 (97.9%)	8 (2.3%)	342 (97.2%)	350 (99.4%)
Total	Total	Total	29 (4.1%)	672 (95.9%)	701 (100.0%)	9 (2.6%)	343 (97.4%)	352 (100.0%)

Proteinuria is defined as confirmed >= 2 grade-level increase from baseline (BL) in graded urine protein, normoglycemic glucosuria is defined as confirmed >= 1 grade-level increase from BL in graded urine glucose concurrent with confirmed serum glucose <= 100 mg/dL; hypophosphatemia is defined as confirmed >= 1 grade-level increase from BL in graded phosphate.
Confirmed laboratory abnormalities are defined as abnormalities observed at 2 consecutive measurements.
The serum creatinine (Scr) cutoff for each treatment is based on mean + 2 SD of the change in Scr at Wk 48 from the combined data (236-0102, 0103).

Increases in serum creatinine in the Stribild group were noted from Week 2, when the median change from baseline was 0.09 mg/dL, after which values generally stabilised so that the median change from baseline at Week 48 was 0.13 mg/dL. The pattern of change in the ATV/r+TVD group was comparable but the median changes from baseline were 0.05 mg/dL and 0.08 mg/dL at Weeks 2 and 48 while there were no notable changes from baseline in the Atripla group.

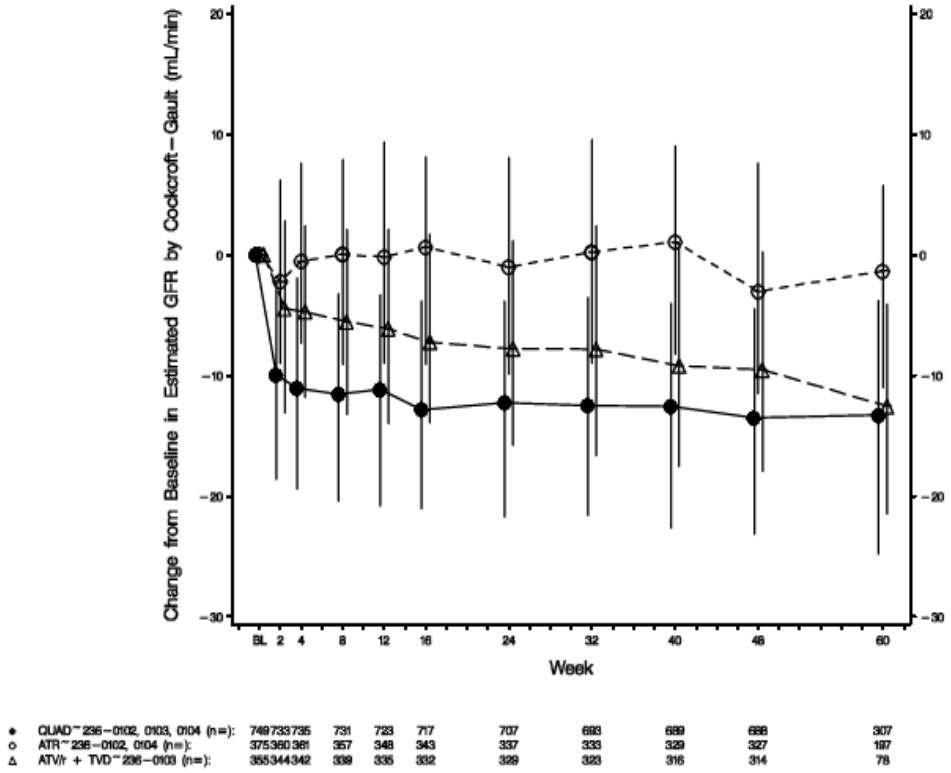
A higher percentage in the Stribild vs. other groups had Grade 1 serum creatinine abnormalities reported (Stribild 6.4%, 48 subjects; Atripla 0.8%, 3 subjects; ATV/r+TVD 4.0%, 14 subjects) but rates for Grade 2 abnormalities were 0.3% in each group. One in the Stribild group had a Grade 3 increase on Day 16 and was discontinued after which renal laboratory abnormalities improved to baseline levels. There were no Grade 4 values.

Figure 18. GS-US-236-0102, 0103, 0104: Median (Q1, Q3) of Change from Baseline in Serum Creatine (Safety Analysis Set).



A corresponding modest decrease in median eGFRCG was observed in the Stribild group. Baseline median was 114.2 mL/min and the median change from baseline at Week 48 was -13.5 mL/min. Decreases in eGFRCG were seen from Week 2 with only minimal additional change thereafter. In the ATV/r+TVD group the baseline median was 114.7 mL/min and the median change from baseline at Week 48 was −9.5 mL/min. Corresponding values in the Atripla group were 114.4 mL/min and −3.0 mL/min.

Figure 19. GS-US-236-0102, 0103, 0104: Median (Q1, Q3) of Change from Baseline in Estimated GFR_{CG} (Safety Analysis Set).



The results for eGFRMDRD were consistent with those observed for eGFRCG. Consistent with the findings in GS-US-216-0121 that COBI appeared to inhibit proximal tubular secretion of creatinine but did not alter aGFR the cysGFR showed modest increases in all treatment groups.

A summary of liver enzyme abnormalities and a summary of liver-related laboratory test results relative to the ULN did not suggest an excess risk in the Stribild group vs. the comparators. Elevations of AST or ALT to > 3 times the ULN along with elevations in total bilirubin to > 2 times the ULN were reported for a lower percentage of subjects in the Stribild group (0.3%, 2 subjects; ATV/r+TVD 4.0%, 14 subjects [ATR 0 subjects]). One of the 2 in the Stribild group had a history of alcohol abuse and the other had hepatitis C infection reported during the study.

Mean increases from baseline through Week 48 in fasting total cholesterol, LDL cholesterol and HDL cholesterol were significantly lower for the Stribild group vs. Atripla. Mean increases up to Week 48 in fasting triglycerides were lower in the Stribild vs. ATV/r+TVD group.

In GS-US-236-0104 there were no clinically relevant changes from baseline in median values for TSH, T3 or T4 in either group during the randomised phase. There were small decreases in median values for IgG and IgM in both groups but these remained in the normal range.

Bone mineral density was assessed using DEXA scans in a subset of subjects at selected sites in GS-US-236-0103. There were numerically smaller mean percentage decreases from baseline in BMD at the lumbar spine and hip in the Stribild group compared with the ATV/r+TVD group (changes at Week 48: spine -2.63% vs. -3.33%; hip -3.06% vs. -3.88%).

Safety in special populations

<u>The pooled Stribild Phase II/III safety analysis showed the following:</u>

Sex - comparable percentages of male and female subjects in each group reported at least one TEAE. Since relatively few females were enrolled no firm conclusions can be drawn.

Age - comparable percentages of subjects aged < 40 or ≥ 40 years of age in each group reported at least one TEAE.

Race - comparable percentages of white and non-white subjects in each group reported at least one TEAE. No differences between white and non-white subjects were apparent in the pattern of TEAEs reported.

Co-infection with HBV or HCV – very few HIV-1 infected subjects were co-infected with HBV (1.8%, 26 subjects) or HCV (4.1%, 60 subjects). The hepatic adverse reaction profile in subjects co-infected with HBV or HCV who received Stribild was consistent with underlying hepatitis infection. As expected in this subject population, elevations in AST and ALT occurred more frequently than in the general HIV-1 infected population.

Renal Impairment - GS-US-216-0124

TEAEs were reported for 6/13 with severe renal impairment and 6/11 matched controls but only increased blood creatinine (2/13 with pre-existing impairment) was reported in more than one subject. All AEs were Grade 1 (mild) and no subject discontinued due to a TEAE.

Hepatic Impairment - GS-US-183-0133

Five of 10 controls and 4/10 with moderate hepatic impairment experienced a treatment-emergent AE during the study but only headache (in 2) occurred in > 1 subject. All TEAEs were assessed as Grade 1 or 2 in severity. Three with impairment had Grade 2 laboratory abnormalities and three had Grade 3 treatment-emergent laboratory abnormalities but none was reported as a TEAE.

Discontinuation due to AES

In the original MAA, the frequencies of discontinuation due to AEs were Stribild 3.7% (26), ATR 5.1% (18) and ATV/r+TVD 5.1% (18). By the time of the safety update the rates were 4.6%, 6.8% and 5.9%, respectively. Study drug discontinuation due to renal AEs increased from 6 to 10 subjects in the Stribild group and from 1 to 2 subjects in the ATV/r+TVD group. No individual AE that resulted in study drug discontinuation was reported in more than 1% of subjects in the Stribild group. In the ATR group, depression resulted in study drug discontinuation for 1.1% (4 subjects) while in the ATV/r+TVD group 1.1% (4 subjects) discontinued due to ocular icterus and the same number due to nausea. Most of the AEs leading to study drug discontinuation were considered by the investigator to be related to study drug.

Table 79.

	QUAD 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event Leading To Premature Study Drug Discontinuation	32 (4.6%)	24 (6.8%)	21 (5.9%)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event Leading To Premature Study Drug Discontinuation By System Organ Class And Preferred Term			
CARDIAC DISORDERS	0	1 (0.3%)	0
INTRACARDIAC MASS	0	1 (0.3%)	0
EYE DISORDERS	0	0	4 (1.1%)
OCULAR ICTERUS	0	0	4 (1.1%)
GASTROINTESTINAL DISORDERS	5 (0.7%)	0	6 (1.7%)
NAUSEA	2 (0.3%)	0	4 (1.1%)
DIARRHOEA	2 (0.3%)	0	1 (0.3%)
VOMITING	1 (0.1%)	0	2 (0.6%)
ABDOMINAL DISCOMFORT	1 (0.1%)	0	0
COLITIS ULCERATIVE	0	0	1 (0.3%)
FLATULENCE	0	0	1 (0.3%)
HYPOAESTHESIA ORAL	1 (0.1%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (0.6%)	5 (1.4%)	2 (0.6%)
FATIGUE	2 (0.3%)	2 (0.6%)	2 (0.6%)
PYREXIA	2 (0.3%)	1 (0.3%)	0
FEELING ABNORMAL	0	1 (0.3%)	0
SLUGGISHNESS	0	1 (0.3%)	0

	QUAD 236-0102, 0103 (N=701)	ATR 236-0102 (N=352)	ATV/r + TVD 236-0103 (N=355)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event Leading To Premature Study Drug Discontinuation	32 (4.6%)	24 (6.8%)	21 (5.9%)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event Leading To Premature Study Drug Discontinuation By System Organ Class And Preferred Term			
HEPATOBILIARY DISORDERS	1 (0.1%)	0	2 (0.6%)
JAUNDICE	0	0	2 (0.6%)
LIVER INJURY	1 (0.1%)	0	0
IMMUNE SYSTEM DISORDERS	1 (0.1%)	1 (0.3%)	0
DRUG HYPERSENSITIVITY	1 (0.1%)	1 (0.3%)	0
INFECTIONS AND INFESTATIONS	2 (0.3%)	1 (0.3%)	3 (0.8%)
HEPATITIS C	2 (0.3%)	1 (0.3%)	1 (0.3%)
PNEUMOCYSTIS JIROVECI PNEUMONIA	0	0	1 (0.3%)
TUBERCULOUS PLEURISY	0	0	1 (0.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (0.1%)	1 (0.3%)	1 (0.3%)
CONTUSION	0	1 (0.3%)	0
INTENTIONAL OVERDOSE	1 (0.1%)	0	0
OVERDOSE	0	0	1 (0.3%)
INVESTIGATIONS	6 (0.9%)	0	1 (0.3%)
BLOOD CREATININE INCREASED	4 (0.6%)	0	0
ALANINE AMINOTRANSFERASE INCREASED	1 (0.1%)	0	0
ASPARTATE AMINOTRANSFERASE INCREASED	1 (0.1%)	0	0
CREATININE RENAL CLEARANCE DECREASED	0	0	1 (0.3%)
GLOMERULAR FILTRATION RATE ABNORMAL	1 (0.1%)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (0.4%)	0	0
LIMB DISCOMFORT	1 (0.1%)	0	0
MUSCLE SPASMS	1 (0.1%)	0	0
RHABDOMYOLYSIS	1 (0.1%)	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3 (0.4%)	1 (0.3%)	1 (0.3%)
BURKITT'S LYMPHOMA	2 (0.3%)	0	0
HODGKIN'S DISEASE	0	0	1 (0.3%)
LYMPHOMA	1 (0.1%)	0	0
METASTATIC NEOPLASM	0	1 (0.3%)	0
NERVOUS SYSTEM DISORDERS	3 (0.4%)	3 (0.9%)	2 (0.6%)
DIZZINESS	0	0	2 (0.6%)
AMNESIA	0	1 (0.3%)	0
CERVICOBRACHIAL SYNDROME	1 (0.1%)	0	0
DYSGEUSIA	1 (0.1%)	0	0
GRAND MAL CONVULSION	0	1 (0.3%)	0
MIGRAINE	1 (0.1%)	0	0
PRESYNCOPE	0	1 (0.3%)	0
PSYCHIATRIC DISORDERS	6 (0.9%)	9 (2.6%)	1 (0.3%)
DEPRESSION	1 (0.1%)	4 (1.1%)	0
ABNORMAL DREAMS	0	2 (0.6%)	0
ANXIETY	0	2 (0.6%)	0
INSOMNIA	0	2 (0.6%)	0
PARANOIA	1 (0.1%)	1 (0.3%)	0
CLAUSTROPHOBIA	0	1 (0.3%)	0
COMPLETED SUICIDE	1 (0.1%)	0	0
HALLUCINATION	0	1 (0.3%)	0
LOSS OF LIBIDO	0	0	1 (0.3%)
NIGHTMARE	0	1 (0.3%)	0
SCHIZOPHRENIA	1 (0.1%)	0	0
SELF ESTEEM DECREASED	1 (0.1%)	0	0
PSYCHIATRIC DISORDERS (cont)			
SUICIDAL BEHAVIOUR	1 (0.1%)	0	0
SUICIDE ATTEMPT	0	1 (0.3%)	0
RENAL AND URINARY DISORDERS	5 (0.7%)	0	1 (0.3%)
RENAL FAILURE	3 (0.4%)	0	0
FANCONI SYNDROME ACQUIRED	1 (0.1%)	0	0
NEPHROPATHY TOXIC	0	0	1 (0.3%)
RENAL FAILURE ACUTE	1 (0.1%)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.1%)	1 (0.3%)	0
DYSPNOEA	0	1 (0.3%)	0
DYSPNOEA EXERTIONAL	0	1 (0.3%)	0
PNEUMONIA ASPIRATION	1 (0.1%)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (0.4%)	5 (1.4%)	4 (1.1%)
DRUG ERUPTION	0	1 (0.3%)	2 (0.6%)
RASH	1 (0.1%)	2 (0.6%)	0
RASH MACULO-PAPULAR	0	1 (0.3%)	1 (0.3%)
DERMATITIS EXFOLIATIVE	1 (0.1%)	0	0
HYPERHIDROSIS	0	1 (0.3%)	0
RASH GENERALISED	0	0	1 (0.3%)
SKIN ODOUR ABNORMAL	1 (0.1%)	0	0
VASCULAR DISORDERS	0	1 (0.3%)	0
HOT FLUSH	0	1 (0.3%)	0

Post marketing experience

Adverse reactions to treatment with emtricitabine, and tenofovir disoproxil fumarate from post-marketing experience, when used with other antiretrovirals were reflected in the SmPC of the existing MAs.

2.6.1. Discussion on clinical safety

Overall the rates of TEAEs and drug-related TEAEs in the Phase III studies were mostly comparable or lower for Stribild vs. either comparative regimen, except in certain cases as described below.
EVG and Stribild data suggest a particular association with diarrhoea, including Grades 2-4, and also with nausea. For example, rates were higher for EVG vs. RAL in study GS-US-183-0145 and higher for Stribild vs. Atripla (although not vs. ATV/rtv+TVD). Rates of vomiting were generally comparable although addition of Stribild to oral contraceptive in the DDI study was associated with increases in rates of vomiting as well as nausea.
In the comparison with ATV/r+TVD the Stribild was associated with slightly higher rates of abnormal dreams, insomnia, depression and headache. Headache was more common with Stribild than with Atripla.

Renal effects

Renal effects driven by tenofovir were thoroughly discussed and further analyses/data were requested to the applicant as described below.

Initially, the data of most concern regarding renal injury came from GS-US-236-0102 in which there were 5 Stribild subjects with renal events of interest including four reported to have renal failure (one was Grade 3; two discontinued) and one subject with Grade 3 Fanconi syndrome (discontinued). Four of the five (including the case of Fanconi syndrome) had evidence of proximal renal tubular injury. There were three other subjects with increased creatinine in the Stribild group in this study (two discontinued) and all three had evidence of proximal renal tubular injury.

During the procedure:

- Updated data from the two STB Phase 3 studies showed that 12 subjects had a renal AE of interest including 11 who received STB (1.6%) and one who received ATR (0.3%) but none in the ATV/r+TVD group. The renal AEs of interest in SBD subjects were renal failure (8 subjects), acute renal failure (2 subjects) and Fanconi syndrome acquired (1 subject).
- In addition, the safety update clarified that in the two Phase 3 studies there were 16 STB subjects (2.3%) who had a renal SAE, discontinued study drug due a renal AE and/or had a pre-specified renal AE of interest. These 16 include the 11 mentioned above. One subject (0.3%; as above) in the ATR group had a pre-specified renal AE of interest and two subjects (0.6%) in the ATV/r+TVD group discontinued study drug due to renal AEs but did not have a renal AE of interest.
- For 4/16 subjects (0.6% of STB Phase 3 safety population) the renal AEs and laboratory findings were consistent with the applicant's definition of PRT. Two had eGFR < 70 mL/min at screening or baseline. Each of these subjects discontinued study drug due to renal AEs. For the other 12/16 subjects the findings did not meet the applicant's definition of PRT but 6 did have renal failure, decrease in GFR and/or increase in serum creatinine that was accompanied by proteinuria.
- The summary of laboratory findings reflected the effect of COBI on serum creatinine but almost all cases in the STB group were Grade 1 and there was no excess of higher grade increases.
- At Week 48 treatment-emergent proteinuria was reported for 38.6% STB, 24.1% ATV/r+TVD and 28.8% ATR subjects. Rates at Week 96 were STB 46.2%, ATV/r+TVD 36.6% and ATR 37.6%. However, the incremental incidence of treatment-emergent proteinuria (new onset or worsening grading relative to baseline) from Week 48 to Week 96 in the STB group was 7.6% vs. ATV/r+TVD 12.5% and ATR 8.8%. In addition, the cumulative rates of confirmed increases in proteinuria through Week 96 (i.e. observed at 2 consecutive visits) were similar between groups (STB 11.8%; ATV/r+TVD 10.4%; ATR 7.7%).
- There was no overall excess of hypophosphataemia or glycosuria for STB vs. the comparators.

Further updates showed the following:

- The applicant searched the database for any possible additional cases of PRT by applying slightly different (more inclusive) criteria and did not identify further cases vs. those reported above.

- On the basis of the tabulation of *confirmed abnormalities*, the rates were not higher for STB vs. ATV/r+TVD. These laboratory data for confirmed abnormalities contrasts with the AE data reported above, which clearly showed an excess of STB subjects who had a renal SAE, discontinued study drug due a renal AE and/or had a pre-specified renal AE of interest in these double-blind studies.

- Rates for confirmed increases in serum creatinine were STB 4.1%, ATV/r+TVD 3.1% and ATR 2.6%. Rates for confirmed proteinuria that persisted for more than 2 consecutive visits were STB 5.1%, ATV/r+TVD 3.7% and ATR 1.7%.

- The assessment of reversibility of changes in renal parameters refers mainly to 4 subjects with PRT who discontinued STB in GS-US-236-0102. The laboratory findings in these 4 subjects with evidence of proximal tubulopathy improved without clinical consequence upon discontinuation of Stribild, but did not completely resolve in all subjects.

- In the STB safety update it was reported that study drug discontinuation due to renal TEAEs had increased from 6 to 10 subjects in the STB group and from 1 to 2 subjects in the ATV/r+TVD group with no change in the ATV/co group.

The CHMP requested the study GS-US-236-0130 to examine the effect of 5 treatments (COBI, TDF, COBI+TDF, Stribild and placebo when given once daily for 30 days followed for a further 30 days to document the reversibility of any effects observed. Day 60 data from this study showed that STB had the greatest effect on aGFR and the follow-up data indicate that the 90% CI around the comparison vs. placebo did not span 100% after 30 days off treatment. The comparisons within treatments for change in renal plasma flow from baseline point to the most marked effect in the COBI + TDF and the STB groups. The reason for the apparent greater effect of STB is not clear. Given the variability observed in aGFR and renal plasma flow it is not impossible that the observations could have arisen by chance in this parallel group study. Also, there is no known reason why STB might have a greater effect on aGFR than TDF + COBI.

Currently there is no known mechanism by which COBI may have a causative role in PRT. Non-clinical data suggest that FTC, COBI and EVG do not affect the cytotoxicity of TFV in renal proximal tubule cells and that COBI has no effect on TFV accumulation in isolated renal cortical tissue. In-vitro experiments were completed in cultured primary human renal proximal tubule cells (RPTECs) to assess the cytotoxicity of TFV alone and in the presence of STB components. The results generated with cells from two independent donors indicated low cytotoxicity of TFV (CC_{50} > 4,000 µM) that was not affected by COBI, EVG, or FTC at pharmacologically relevant concentrations. Since it is known that RPTECs may down-regulate some of the active renal transport functions due to de-differentiation process triggered by their *in vitro* culturing, the applicant has also initiated studies in HEK-293 cells co-transfected with OAT1 and MRP4, the two key transporters responsible for the active tubular secretion of TFV. Preliminary experiments confirmed the functionality of both transporters following co-transfection and the applicant will proceed to optimize cytotoxicity measurement in the HEK-293 cell culture model. The studies will continue with the assessment of the effect of individual STB components on the cytotoxicity of TFV (see additional pharmacovigilance activities).

From the above it can be concluded that there are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat. The CHMP requested a SAG consultation to have the views of additional experts on this issue (see below).

Following consideration of the SAG recommendations, the CHMP concluded that the renal effects of STB can be addressed via adequate advice in the SmPC that will allow early identification of patients at risk of developing STB-related renal toxicity. Therefore, the SmPC was amended as follows:

- Inclusion of a recommendation not to institute TDF-containing regimens in subjects who have been discontinued from Stribild due to renal toxicity (section 4.4 of the SmPC).

- Inclusion of a recommendation that patients with any known risk factors for renal impairment and any who develop a confirmed increase in serum creatinine ≥ 26.5 µmmol/l should receive more intensive monitoring of renal safety (section 4.4 of the SmPC).

- Inclusion of a recommendation that not only eGFR but also the presence of glycosuria and/or proteinuria should be documented before commencing Stribild (section 4.4 of the SmPC).

Furthermore, a paragraph was introduced recommending that Stribild is not initiated in patients with creatinine clearance < 90 mL/min unless, after review of the available treatment options, it is considered that Stribild is the preferred treatment for the individual patient. Additionally, a recommendation was introduced concerning the discontinuation of Stribild in patients with creatinine clearance that falls to < 70 mL/min while on treatment unless it is considered that the potential benefit of this combination of antiretroviral agents for the individual patient outweighs the possible risks of continuing with therapy (sections 4.2 and 4.4 of the SmPc).

From the safety database all the adverse reactions reported in clinical trials and post-marketing when individual components used with other antiretrovirals have been included in the Summary of Product Characteristics.

The RMP was updated to include the request for further studies (see additional pharmacovigilance activities) as recommended by the additional expert consultation.

Additional expert consultation

During a meeting of the HIV / viral diseases SAG on 6 February 2013 experts were convened to address questions raised by the CHMP related to renal toxicity of Stribild.

Based on the data available at present, there was a consensus from the group that there was no firm evidence pointing to an increased risk of PRT with Stribild or with COBI + TDF versus other TDF-containing products. More extensive and longer term exposure to Striblid and or COBI associated to TDF should be requested in the 'real life situation' to better assess characteristics and risk factors for renal toxicity.

Given the uncertainties related to the results of study 0130 (in healthy subjects) the experts recommended by consensus that the applicant should be requested to conduct a comparative study in HIV-infected subjects to further evaluate the possible relevance of the data generated by study 130 and suggested a study design for CHMP's consideration.

In addition, some experts expressed interest in understanding the mechanism of the potential renal effect of Stribild and TDF + COBI on aGFR and encouraged the applicant to investigate it.

Given uncertainties on reversibility of renal effects, the experts recommended the applicant gather additional information on this point.

Overall the SAG considers the risks can be managed via appropriate advice in the SmPC and recommended the inclusion of further comments on the SmPC.

2.6.2. Conclusions on the clinical safety

The safety of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. The safety conclusions are further discussed in the context of the overall benefit-risk balance.

In order to further characterise the safety profile of STB, the following measures will be performed by the applicant, as detailed in the Risk Management Plan.

- Drug utilization study for STB (information on the effectiveness of the renal risk minimization measures for STB, factors potentially associated with the risk of proximal renal tubulopathy, and the reversibility of proximal renal tubulopathy) (Protocol synopsis by May 2013)

- Clinical study of STB, a TDF-containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected ARV treatment-naive patients to be conducted after an assessment of feasibility, and upon agreement on the study design with the CHMP (information on renal function and markers of renal tubular function) (feasibility and protocol by July 2013)

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Safety concerns

Table 80. Summary of the risk management plan

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Important Identified Risks			
Renal Toxicity	TDF	Routine pharmacovigilance activities including a renal tubulopathy targeted follow-up questionnaire for postmarketing reports Observational study (GS-US-104-0353) Clinical studies (GS-US-216-0134, GS-US-236-0118) Planned drug utilization study for STB Planned clinical study of STB, a TDF-containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected ARV treatment-naive patients to be conducted after an assessment of feasibility, and upon agreement on the study design with the CHMP Cumulative review of reversibility of renal tubulopathy in HIV-1 and HBV infected adult patients In vitro studies of the individual STB components on the cytotoxicity of TFV in HEK-293 cells co-transfected with OAT1 and MRP4 Planned post-authorization safety study of HIV-1 infected pediatric patients	Routine Risk Minimization Activities **Statements in Section 4.2 of STB SmPC:** *Renal impairment: Stribild should not be initiated in patients with creatinine clearance below 70 mL/min (see sections 4.4 and 5.2). See section 4.4 regarding initiation of Stribild in patients with creatinine clearance below 90 mL/min.* *Stribild should be discontinued if creatinine clearance declines below 50 mL/min during treatment with Stribild as dose interval adjustment is required for emtricitabine and tenofovir disoproxil fumarate and this cannot be achieved with the fixed-dose combination tablet (see sections 4.4 and 5.2). See section 4.4 regarding patients with creatinine clearance that falls below 70 mL/min while on treatment with Stribild.* **Contraindication in Section 4.3 of STB SmPC:** Patients who have previously discontinued treatment with tenofovir disoproxil fumarate due to renal toxicity, with or without reversal of the effects post-discontinuation. **Warnings in Section 4.4 of STB SmPC:** *Effects on renal function: Emtricitabine and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir disoproxil fumarate (see section 4.8).* *There are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat.*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		Planned drug utilization study in HIV-1 infected pediatric patients Monitoring of renal parameters in subjects in clinical studies who discontinue TDF due to renal tubulopathy	*Patients who have previously discontinued treatment with tenofovir disoproxil fumarate due to renal toxicity, with or without reversal of the effects post-discontinuation, should not be treated with Stribild (see section 4.3).* *<u>Before initiating treatment with Stribild</u>: Creatinine clearance should be calculated and urine glucose and urine protein should be determined in all patients. Stribild should not be initiated in patients with creatinine clearance < 70 mL/min. It is recommended that Stribild is not initiated in patients with creatinine clearance < 90 mL/min unless, after review of the available treatment options, it is considered that Stribild is the preferred treatment for the individual patient.* *<u>During treatment with Stribild</u>: Creatinine clearance, serum phosphate, urine glucose and urine protein should be monitored every four weeks during the first year and then every three months during Stribild therapy. In patients at risk for renal impairment consideration should be given to more frequent monitoring of renal function.* *Cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance (see section 4.8). Patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3 mg/dL) from baseline should be closely monitored for renal safety.* *If serum phosphate is < 0.48 mmol/L (1.5 mg/dL) or creatinine clearance is decreased to < 70 mL/min renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8). It is recommended that Stribild is discontinued in patients with creatinine clearance that falls to < 70 mL/min while on treatment unless it is considered that the potential benefit of this combination of antiretroviral agents for the individual patient outweighs the possible risks of continuing with therapy.* *Stribild should be discontinued in patients with confirmed creatinine clearance that falls to < 50 mL/min (since the required dose interval adjustments are not possible using this fixed dose combination tablet) or with decreases in serum phosphate to < 0.32 mmol/L (1.0 mg/dL) (see sections 4.2 and 5.2).* *Concomitant use with nephrotoxic medicinal products: Use of Stribild should be avoided with concurrent or recent use of a nephrotoxic medicinal product, e.g aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine,*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			vancomycin, cidofovir or interlekin-2 (also called aldesleukin) (see section 4.5). If concomitant use of Stribild and nephrotoxic agents is unavoidable, renal function must be monitored weekly. *<u>Bone effects:</u> Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.* **Statements in Section 4.5 of the STB SmPC:** *<u>Renally eliminated medicinal products:</u> Since emtricitabine and tenofovir are primarily eliminated by the kidneys, co-administration of Stribild with medicinal products that reduce renal function or compete for active tubular secretion (e.g. cidofovir) may increase serum concentrations of emtricitabine, tenofovir and/or the co-administered medicinal products.* *Use of Stribild should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2 (also called aldesleukin).* **Statements and Adverse Reactions in Section 4.8 of the STB SmPC:** *<u>Summary of the safety profile</u>* *In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Stribild (see section 4.4).* *<u>Tabulated summary of adverse reactions</u>* *<u>Renal and urinary disorders:</u>* *Uncommon: renal failure, proximal renal tubulopathy including Fanconi syndrome acquired, blood creatinine increased, proteinuria* *Rare: acute tubular necrosis[1], nephritis (including acute interstitial nephritis) [1], nephrogenic diabetes insipidus[1]* *<u>Metabolism and nutrition disorders:</u>* *Very common: hypophosphataemia[1,3]*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			Uncommon: hypokalaemia[1,3] *<u>Musculoskeletal and connective tissue disorders:</u>* *Uncommon: rhabdomyolysis[1,3], muscular weakness[1,3]* *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures) [1,3], myopathy[1,3]* *[1] This adverse reaction was not observed in the Phase 3 clinical studies for Stribild but identified from clinical studies or post marketing experience for emtricitabine or tenofovir disoproxil fumarate when used with other antiretrovirals.* *[3] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* *<u>Description of selected adverse reactions</u>* *<u>Renal impairment:</u> In the clinical studies of Stribild over 48 weeks (n = 701), 6 (0.9%) subjects in the Stribild group and 1 (0.3%) subject in the ritonavir-boosted atazanavir (ATV/r) plus fixed-dose combination of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) group discontinued study drug due to a renal adverse reaction. The types of renal adverse reactions seen with Stribild were consistent with previous experience with tenofovir disoproxil fumarate. Four (0.6%) of the subjects who received Stribild developed laboratory findings consistent with proximal renal tubular dysfunction leading to discontinuation of Stribild. Two of the four subjects had renal impairment (i.e. estimated creatinine clearance less than 70 mL/min) at baseline. The laboratory findings in these 4 subjects with evidence of proximal tubulopathy improved without clinical consequence upon discontinuation of Stribild, but did not completely resolve in all subjects (see section 4.4).* *The cobicistat component of Stribild has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In studies GS-US-236-0102 and GS-US-236-0103, decreases in estimated creatinine clearance occurred early in treatment with Stribild, after which they stabilised. The mean change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.9 ± 14.9 mL/min for Stribild, -1.6 ± 16.5 mL/min for EFV/FTC/TDF, and -9.3 ± 15.8 mL/min for ATV/r+FTC/TDF.*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			Other special population(s) *Patients with renal impairment: Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with Stribild (see sections 4.2, 4.4 and 5.2).* Update of labeling as appropriate. Additional Risk Minimization Activities Educational initiatives ('HIV and the Kidney' educational program, educational material distributed to prescribers) Update of educational program as appropriate.
Bone events due to proximal renal tubulopathy/loss of bone mineral density	TDF	Routine pharmacovigilance activities including monitoring and review in PSURs. Clinical studies (GS-99-903, GS-US-236-0103, GS-US-174-0102, GS-US-174-0103, GS-US-174-0115, GS-US-174-0121, GS-US-104-0321, GS-US-104-0352) Planned clinical study in HBV infected pediatric patients (GS-US-174-0144) Planned cross-sectional study to assess bone mineral density (BMD) in HIV-1 infected patients of interest who include those over 50 years of age, particularly women, and who have been exposed to TDF for at least 3 years (GS-US-104-0423). Clinical study of STB in HIV-1 infected women (GS-US-236-0128) Planned post-authorization safety study of HIV-1 infected pediatric patients Planned drug utilization study in	Routine Risk Minimization Activities **Warnings in Section 4.4 of STB SmPC:** *Bone effects: In the Phase 3 study GS-US-236-0103, mean percentage decreases in bone mineral density (BMD) from baseline to week 48 in the Stribild group (n = 54) were comparable to the ritonavir-boosted atazanavir (ATV/r) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) group (n = 66) at the lumbar spine (-2.6% versus -3.3%, respectively) and at the hip (-3.1% versus -3.9%, respectively). In the Phase 3 studies GS-US-236-0102 and GS-US-236-0103, bone fractures occurred in 9 subjects (1.3%) in the Stribild group, 6 subjects (1.7%) in the efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) group, and 6 subjects (1.7%) in the ATV/r+FTC/TDF group.* *In a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in BMD of the hip and spine were observed in both treatment groups. Decreases in BMD of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in BMD of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.* *Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy (see section 4.8). If bone abnormalities are suspected then appropriate consultation should be obtained.*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		HIV-1 infected pediatric patients Retrospective analyses of pediatric BMD Z-scores adjusted by height (GS-US-174-0115, GS-US-104-0321, GS-US-104-0352) In vitro nonclinical studies on intestinal phosphate absorption	**Statements and Adverse Reactions in Section 4.8 of the STB SmPC:** *Summary of the safety profile* *In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Stribild (see section 4.4).* *Tabulated summary of adverse reactions* *Musculoskeletal and connective tissue disorders:* *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,3,5]* *[1] This adverse reaction was not observed in the Phase 3 clinical studies for Stribild but identified from clinical studies or post marketing experience for emtricitabine or tenofovir disoproxil fumarate when used with other antiretrovirals.* *[3] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* *[5] This adverse reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical studies in adults or paediatric HIV clinical studies for emtricitabine or in randomised controlled clinical studies or the tenofovir disoproxil fumarate expanded access program for tenofovir disoproxil fumarate. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical studies (n = 1,563) or tenofovir disoproxil fumarate in randomised controlled clinical studies and the expanded access program (n = 7,319).* Update of labeling as appropriate.
Post-treatment hepatic flares in HIV/HBV coinfected patients	FTC, TDF	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Statement in Section 4.2 of STB SmPC:** *If Stribild is discontinued in patients co-infected with HIV and hepatitis B virus (HBV), these patients should be closely monitored for evidence of exacerbation*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			of hepatitis (see section 4.4). **Warning in Section 4.4 of STB SmPC:** *<u>Patients with HIV and hepatitis B or C virus co infection</u>: Discontinuation of Stribild therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Stribild should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.* **Statements in Section 4.8 of STB SmPC:** *<u>Summary of the safety profile</u>* *Discontinuation of Stribild therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4).* *<u>Other special population(s)</u>* *<u>Exacerbations of hepatitis after discontinuation of treatment:</u> In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 4.4).* Update of labeling as appropriate.

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Interaction with didanosine	TDF	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Warning in Section 4.4 of STB SmPC**: *Co-administration of other medicinal products: Stribild is indicated for use as a complete regimen for the treatment of HIV-1 infection and must not be administered with other antiretroviral products.* **Statements in Section 4.8 of STB SmPC:** *Description of selected adverse reactions* *Interaction with didanosine: Stribild is not to be given with other antiretroviral agents. However, in case of initiation of Stribild in patients previously taking didanosine or discontinuation of Stribild and change to a regimen including didanosine there could be a short period when measurable plasma levels of didanosine and tenofovir occur. Note then that co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported.* Update of labeling as appropriate.
Pancreatitis	TDF	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Adverse Reactions in Section 4.8 of the STB SmPC:** *Tabulated summary of adverse reactions* *Gastrointestinal disorders:* *Uncommon: pancreatitis*[1] [1] *This adverse reaction was not observed in the Phase 3 clinical studies for Stribild but identified from clinical studies or post marketing experience for emtricitabine or tenofovir disoproxil fumarate when used with other antiretrovirals.* There is also a warning statement in Section 4.8 of the STB SmPC regarding the risk of pancreatitis associated with the interaction with didanosine (see above). Update of labeling as appropriate.

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Lactic acidosis and severe hepatomegaly with steatosis	FTC, TDF	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Boxed warning in Section 4.4 of STB SmPC:** *Lactic acidosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non-specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.* *Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.* *Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.* *Patients at increased risk should be followed closely.* **Statements and Adverse Reactions in Section 4.8 of the STB SmPC:** *Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate and emtricitabine (see sections 4.4 and 4.8 Description of selected adverse reactions).* *Tabulated summary of adverse reactions* *Metabolism and nutrition disorders:* *Rare: lactic acidosis*[1] [1] *This adverse reaction was not observed in the Phase 3 clinical studies for Stribild but identified from clinical studies or post marketing experience for emtricitabine or tenofovir disoproxil fumarate when used with other antiretrovirals.* *Description of selected adverse reactions*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels (see section 4.4). There is also a warning statement in Section 4.8 of the STB SmPC regarding the risk of lactic acidosis associated with the interaction with didanosine (see above). Update of labeling as appropriate.
Lipodystrophy	FTC, TDF	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Precautionary statements in Section 4.4 of STB SmPC:** *Lipodystrophy: CART has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate (see section 4.8).* *Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded. However, 144-week clinical data from antiretroviral-naïve patients indicate that the risk of lipodystrophy was lower with tenofovir disoproxil fumarate than with stavudine when administered with lamivudine and efavirenz.* **Statements in Section 4.8 of STB SmPC:** *Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate and emtricitabine (see sections*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			4.4 and 4.8 Description of selected adverse reactions). *<u>Description of selected adverse reactions</u>* *<u>Lipids, lipodystrophy and metabolic abnormalities:</u> CART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).* *CART has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4).* Update of labeling as appropriate.
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness	EVG	Routine pharmacovigilance activities Clinical studies (GS-US-236-0102, GS-US-236-0103)	**Adverse Reactions in Section 4.8 of the STB SmPC:** *<u>Tabulated summary of adverse reactions</u>* *Psychiatric disorders:* *Uncommon: suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness)* Update of labeling as appropriate.
Important Potential Risks			
Overdose (occurring through accidental concurrent use of STB with any of its marketed active components)	STB	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> **Statement in Section 4.4 of the STB SmPC:** *<u>Co-administration of other medicinal products:</u> Stribild is indicated for use as a complete regimen for the treatment of HIV-1 infection and must not be administered with other antiretroviral products.* *Stribild should not be administered concomitantly with other medicinal products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of hepatitis B virus infection.* *<u>Patients with HIV and hepatitis B or C virus co infection:</u> In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant Summary of Product Characteristics for these medicinal products. Stribild should not be*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			administered concomitantly with other medicinal products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of hepatitis B virus infection. **Statement in Section 4.5 of the STB SmPC:** *Stribild is indicated for use as a complete regimen for the treatment of HIV-1 infection and must not be administered with other antiretroviral products.*
Concurrent use of drugs whose coadministration with STB is contraindicated	COBI	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Statements in Section 4.3 of STB SmPC:** *Co-administration with the following medicinal products due to the potential for serious and/or life-threatening events or loss of virologic response and possible resistance to Stribild (see section 4.5):* • *alpha 1-adrenoreceptor antagonists: alfuzosin* • *antiarrhythmics: amiodarone, quinidine* • *anticonvulsants: carbamazepine, phenobarbital, phenytoin* • *antimycobacterials: rifampicin* • *ergot derivatives: dihydroergotamine, ergometrine, ergotamine* • *gastrointestinal motility agents: cisapride* • *herbal products: St. John's wort (Hypericum perforatum)* • *HMG Co-A reductase inhibitors: lovastatin, simvastatin* • *neuroleptics: pimozide* • *PDE-5 inhibitors: sildenafil for treatment of pulmonary arterial hypertension* • *sedatives/hypnotics: orally administered midazolam, triazolam* **Statements in Section 4.5 of STB SmPC:** *Concomitant use contraindicated: Co-administration of Stribild and some medicinal products that are primarily metabolized by CYP3A may result in increased plasma concentrations of these products, which are associated with the potential for serious and/or life-threatening reactions such as peripheral vasospasm or ischemia (e.g., dihydroergotamine, ergotamine, ergometrine), or myopathy, including rhabdomyolysis (e.g., simvastatin, lovastatin), or*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
			prolonged or increased sedation or respiratory depression (e.g., orally administered midazolam or triazolam). Co-administration of Stribild and other medicinal products primarily metabolised by CYP3A such as amiodarone, quinidine, cisapride, pimozide, alfuzosin and sildenafil for pulmonary arterial hypertension is contraindicated (see section 4.3). *Co-administration of Stribild and some medicinal products that induce CYP3A such as St. John's wort (Hypericum perforatum), rifampicin carbamazepine, phenobarbital and phenytoin may result in significantly decreased cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance (see section 4.3).* Update of labeling as appropriate.
Important Missing Information			
Long-term safety information	STB, EVG, COBI	Routine pharmacovigilance activities Clinical studies of STB (GS-US-236-0102, GS-US-236-0103, GS-US-236-0104) Clinical study in HIV-1 infected women (GS-US-236-0128) Clinical studies of COBI-boosted PI (GS-US-216-0105, GS-US-216-0114) Planned PK study of EVG in subjects with UGT1A1*28/*28 genotype administered STB The long-term safety of EVG/co will be addressed by STB studies	<u>Routine Risk Minimization Activities</u> Update of labeling as appropriate.

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Safety in children	EVG, COBI, TDF	Routine pharmacovigilance activities EVG: Planned clinical studies in HIV-1 infected children (EVG/co, GS-US-183-0154; EVG/r, GS-US-183-0160, GS-US-183-0155) COBI: Planned clinical studies in HIV-1 infected children (GS-US-216-0128) TDF: Clinical studies in HIV-1 infected children (GS-US-104-0321, GS-US-104-0352) TDF: Planned clinical study, including a PK substudy, in HBV infected children aged 2 to < 12 years (GS-US-174-0144) TDF: Planned PK bioavailability study of TDF granules in the fed state (GS-US-104-0427) TDF: Planned post-authorization safety study of HIV-1 infected pediatric patients TDF: Planned drug utilization study in HIV-1 infected pediatric patients	Routine Risk Minimization Activities **Statement in Section 4.2 of STB SmPC:** *Paediatric population: The safety and efficacy of Stribild in children aged 6 to less than 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.* *Stribild should not be used in children aged 0 to less than 6 years because of safety/efficacy concerns.* **Statement in Section 4.8 of STB SmPC:** *Paediatric population* *Insufficient safety data are available for children below 18 years of age. Stribild is not recommended in this population (see section 4.2).* Update of labeling as appropriate.

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Safety in pregnancy	EVG, COBI, FTC, TDF	Routine pharmacovigilance activities Epidemiological studies (EVG, COBI, FTC, TDF: Antiretroviral Pregnancy Registry; FTC, TDF: Cross-sectional study to assess the risk of mitochondrial disease in children exposed to NRTIs in utero [MITOC group])	Routine Risk Minimization Activities **Statements in Section 4.6 of STB SmPC:** *Pregnancy:* *There are no or limited clinical data with Stribild in pregnant women. However, a moderate amount of data in pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil fumarate.* *Animal studies do not indicate direct or indirect harmful effects of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).* *Stribild should be used during pregnancy only if the potential benefit justifies the potential risk.* Update of labeling as appropriate.
Safety in patients with renal impairment	STB, COBI, TDF	Routine pharmacovigilance activities Clinical study of STB and COBI in patients with renal impairment (eGFR between 50-89 mL/min) (GS-US-236-0118) Clinical study of TDF in HBV infected patients including patients with mild renal impairment (GS-US-174-0121) Planned clinical study of TDF in HBV infected patients with moderate to severe renal impairment (GS-US-174-0127)	Routine Risk Minimization Activities See Renal Safety Concern regarding warnings in the STB SmPC. Update of labeling as appropriate.

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Safety in elderly patients	EVG, COBI, FTC, TDF	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Statement in Section 4.2 of STB SmPC:** *Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years (see sections 4.4 and 5.1). Stribild should be administered with caution to elderly patients (see section 4.4).* **Warning in Section 4.4 of STB SmPC:** *Elderly: Stribild has limited data in patients over the age of 65 years. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with Stribild.* **Statements in Section 4.8 of STB SmPC:** *Other special population(s)* *Elderly: Stribild has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function, therefore caution should be exercised when treating elderly patients with Stribild (see section 4.4).* Update of labeling as appropriate.
Safety in lactation	EVG, COBI, FTC, TDF	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Statements in Section 4.6 of STB SmPC:** *Breast-feeding* *It is not known whether elvitegravir or cobicistat are excreted in human milk. Emtricitabine and tenofovir have been shown to be excreted in human milk. In animal studies it has been shown that elvitegravir, cobicistat and tenofovir are excreted in milk. There is insufficient information on the effects of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate in newborns/infants. Therefore Stribild should not be used during breast-feeding.* *In order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.* Update of labeling as appropriate.

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Safety in patients with severe hepatic impairment (CPT score C)	EVG, COBI	Routine pharmacovigilance activities	Routine Risk Minimization Activities **Statements in Section 4.2 of STB SmPC:** *Hepatic impairment: No dose adjustment of Stribild is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Stribild has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, Stribild is not recommended for use in patients with severe hepatic impairment (see sections 4.4 and 5.2).* **Statements in Section 4.4 of STB SmPC:** *Liver disease: The safety and efficacy of Stribild have not been established in patients with significant underlying liver disorders. The pharmacokinetics of emtricitabine have not been studied in patients with hepatic impairment. The pharmacokinetics of elvitegravir, cobicistat and tenofovir have been studied in patients with moderate hepatic impairment. Stribild has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). No dose adjustment of Stribild is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (see sections 4.2 and 5.2).* *Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.* Update of labeling as appropriate
Drug-drug interactions	STB, EVG, COBI, TDF	Clinical drug-drug interaction studies to evaluate the interaction of STB and antimycobacterials (GS-US-236-0125; planned), anticonvulsants (GS-US-236-0129; planned), and telaprevir (GS-US-236-0135; ongoing) In vitro studies to assess the potential for EVG to inhibit UGT1A1, UGT1A3 and UGT2B7 Planned PBPK simulations of the	Routine Risk Minimization Activities **Statements in Section 4.3 of STB SmPC:** *Co-administration with the following medicinal products due to the potential for serious and/or life threatening events or loss of virologic response and possible resistance to Stribild (see section 4.5):* • *anticonvulsants: carbamazepine, phenobarbital, phenytoin* • *antimycobacterials: rifampicin* **Statements in Section 4.5 of STB SmPC:** *The transporters that cobicistat inhibits include p-glycoprotein (P-gp), BCRP,*

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		effect of potent CYP3A4 inhibitors on COBI exposure In vitro studies to assess if MRP2 or BCRP contribute to the intestinal efflux transport of TDF	*OATP1B1 and OATP1B3.* *Co-administration of Stribild with medicinal products that are primarily metabolised by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1 or OATP1B3 may result in increased plasma concentrations of those products, which could increase or prolong their therapeutic effect and adverse reactions (see Concomitant use contraindicated and section 4.3).* *Co-administration of Stribild with medicinal products that inhibit CYP3A may decrease the clearance of cobicistat, resulting in increased cobicistat plasma concentrations.* *Elvitegravir is a modest inducer and may have the potential to induce CYP2C9 and/or inducible UGT enzymes; as such it may decrease the plasma concentration of substrates of these enzymes.* *<u>Concomitant use contraindicated</u>: Co-administration of Stribild and some medicinal products that induce CYP3A such as St. John's wort (Hypericum perforatum), rifampicin, carbamazepine, phenobarbital and phenytoin may result in significantly decreased cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance (see section 4.3).* *Table 1: Interactions between the individual components of Stribild and other medicinal products* ***Medicinal product by therapeutic areas*** / ***Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}[1]*** / ***Recommendation concerning co-administration with Stribild*** ***Antimycobacterials***

Safety Concern	Attributable Component(s) of STB	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)		
			Rifabutin (150 mg once daily)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)	*Co-administration of rifabutin, potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.* *Rifabutin:* *AUC: ↔* *C_{min}: ↔* *C_{max}: ↔* *25-O-desacetyl-rifabutin* *AUC: ↑525%* *C_{min}: ↑394%* *C_{max}: ↑384* *Elvitegravir:* *AUC: ↓21%* *C_{min}: ↓67%* *C_{max}: ↔*	*Co-administration of Stribild and rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to desacetyl-rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure.*
			HCV protease inhibitors		
			Boceprevir *Telaprevir*	*Interaction not studied with any of the components of Stribild.*	*Co-administration with Stribild is not recommended.*
			Update of labeling as appropriate		

Pharmacovigilance plans

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Table 81. Pharmacovigilance activities in addition to the routine pharmacovigilance

Description	Due date
PAM 1: PK study of EVG in subjects with UGT1A1*28/*28 genotype administered STB (information on EVG exposure in patients with UGT1A1 polymorphism associated with decreased activity of UGT1A1) (Long-term safety)	Q2 2015
PAM 2: Drug utilization study for STB (information on the effectiveness of the renal risk minimization measures for STB, factors potentially associated with the risk of proximal renal tubulopathy, and the reversibility of proximal renal tubulopathy). As part of this study to specifically seek out data in subjects with any of HBV or HCV co-infection, subjects of African heritage, low CD4 counts at ARV initiation, use of concomitant medications with nephrotoxic potential and any other factors that might potentially affect the risk of developing PRT. Where available from patient records, information on specific markers of tubular damage (e.g. urinary alpha- and/or beta-microglobulin, neutrophil gelatinase-associated lipocalin [NGAL]) and markers of glomerular damage (e.g. microalbuminuria) will be reported. (Renal toxicity)	Submission of protocol synopsis for review – mid May 2013 Protocol synopsis agreed - end June 2013 Data cut - 1 year post launch – Q3 2014 Submission of Study Report – 1Q 2015
PAM 3: Clinical study of STB, a TDF-containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected ARV treatment-naive patients to be conducted after an assessment of feasibility, and upon agreement on the study design with the CHMP (information on renal function and markers of renal tubular function) (Renal toxicity)	Submission of feasibility and proposed protocol - July 2013 Protocol agreed upon – Aug 2013 Completion of enrollment (9 months) - May 2014 On treatment & follow-up (6 months) – Nov 2014 Submission of Study Report – May 2015
PAM 4: Conduct of further studies to investigate the possible mechanism(s) that could lead to an additive or synergistic toxic effect of COBI + TDF on renal tubular function and/or a decrease in the aGFR during Stribild therapy: In vitro studies of the individual STB components on the cytotoxicity of TFV in HEK-293 cells co-transfected with OAT1 and MRP4	Q3 2013
PAM 5: In vitro studies to assess the potential for EVG to inhibit UGT1A1, UGT1A3 and UGT2B7 (Drug-drug interactions)	Q2 2013
PAM 6: Clinical study of STB in HIV-1 infected women (GS-US-236-0128) (information on BMD in HIV-1 infected women from a subset of subjects from Study GS US 236 0128 in which DEXA scans will be performed with up to 96 weeks of STB therapy)	Q4 2017 Submission of the Week 48 report by Q4 2016

Risk minimisation measures

The CHMP considers that the following additional risk minimisation measures are necessary for the safe and effective use of the product:

- Educational material for healthcare professionals to address the risk of renal toxicity

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The beneficial virological effects of Stribild are clearly demonstrated in two pivotal phase III randomized trials, comparing Stribild to Atripla and to the combination of ATZ/rtv plus Truvada, in HIV-1 infected adults without known mutations associated with resistance to the 3 antiretrovirals in Stribild. Both studies demonstrated non-inferiority of Stribild compared to the other regimens; at 48 weeks follow-up, the overall response rate (< 50 copies/mL) was 87.5% and 84.1% for Stribild and Atripla respectively (study -102) and 89.5% and 86.8% for Stribild and ATZ/rtv plus Truvada respectively (study -103).

Stribild exerts comparable antiviral effects, with associated increments in CD4 counts, vs. each of Atripla and ATV/rtv+TVD. While Atripla is not approved in the EU for use from the outset in ARV-naïve subjects and while ATV/rtv+TVD is not a favoured primary regimen, the actual virological response rates observed with Stribild and the comparators in the primary and sensitivity analyses compare very well with many other studies in the ARV-naïve.

Stribild is the first FDC including a INSTI to be taken once a day approved for use in adults. This provides a simplified treatment regimen.

Uncertainty in the knowledge about the beneficial effects

When assessing the possible benefits of the Stribild in ARV-naïve subjects (or in those with virus lacking any known RAMs for any of the three anti-HIV agents) the possible implications of initiating a regimen that incorporates two NRTIs with an integrase inhibitor must be considered. Since Stribild represents a complete treatment regimen, subjects who adhere to the once daily dosing regimen with food are automatically adherent to a triple combination regimen. This should also reduce the risk of selecting for virus resistant to one or more actives compared to regimens consisting of more than one formulation. However, omitting to take Stribild daily leaves the subject with intermittent periods without any anti-HIV agent. Results on development of resistance (pointed to co-selection of virus containing IN mutations along with resistance to FTC, with or without TFV) may reflect a relatively low genetic barrier to resistance to EVG. Therefore, failure of adherence enhances the risk of selecting for virus co-resistant to EVG, FTC and TFV, with additional implications for sequential use of RAL and 3TC.

Risks

Unfavourable effects

There is a known risk of adverse renal effects associated with TDF. The types of renal adverse reactions observed with Stribild were consistent with previous experience with tenofovir. However, there are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat. The apparent risk requires a careful appraisal before initiating treatment in light of the fact that other therapeutic alternative are available. There is also a need for careful monitoring of patients during therapy and detailed recommendations regarding pre- and on-treament monitoring of renal function as well as stopping treatment. The SmPC includes this information.

The data also indicate that rates of TEAEs including diarrhoea, nausea, headache, abnormal dreams, insomnia and depression may be more frequent with Stribild vs. Atripla or vs. ATV/rtv+TVD.

Uncertainty in the knowledge about the unfavourable effects

Estimation of the actual risk of Stribild-associated renal injury and its reversibility after discontinuation requires further clinical experience in terms of numbers and duration of exposure. The observed effects of Stribild on aGFR and renal plasma flow cannot be dismissed. The additional pharmacovigilance activities will allow to collect further data on these aspects.

Benefit-risk balance

Importance of favourable and unfavourable effects

The efficacy of the Stribild must be carefully weighed against the risk of renal injury in ARV-naïve subjects.

Benefit-risk balance

Discussion on the benefit-risk balance

The beneficial virological effects of Stribild are clearly demonstrated. The CHMP considers that provided patients are adequately screened pre-treatment for suitability to receive Stribild and are monitored on treatment for any evidence of renal toxicity as reflected in the SmPC the anti-viral efficacy of Stribild outweighs the risk of renal injury.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Stribild in the treatment of human immunodeficiency virus 1 (HIV 1) infection in adults aged 18 years and over who are antiretroviral treatment-naïve or are infected with HIV 1 without known mutations associated with resistance to the three antiretroviral agents in Stribild (see section 4.2, 4.4 and 5.1) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The Marketing Authorisation Holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Stribild are provided with a physician educational pack containing the following:

I. The Summary of Product Characteristics
II. Stribild renal educational brochure, including a creatinine clearance slide ruler.

The MAH must agree the content and format of the medical educational pack with the national competent authority in each Member State prior to its distribution in their territory.

The Stribild renal educational brochure shall contain the following key safety messages:

1. That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Stribild.

2. That patients who have previously discontinued treatment with tenofovir disoproxil fumarate due to renal toxicity should not be treated with Stribild.

3. That patients should have creatinine clearance calculated and urine glucose and urine protein determined prior to initiating Stribild therapy.

4. That Stribild should not be initiated in patients with creatinine clearance below 70 mL/min.

5. That it is recommended that Stribild is not initiated in patients with creatinine clearance < 90 mL/min unless, after review of the available treatment options, it is considered that Stribild is the preferred treatment for the individual patient.

6. The importance of regular monitoring of creatinine clearance, serum phosphate, urine glucose and urine protein during Stribild therapy.

7. The recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment.

8. That cobicistat inhibits the tubular secretion of creatinine and may cause modest increases in serum creatinine and modest declines in creatinine clearance without affecting renal glomerular function.

9. That patients who experience a confirmed increase in serum creatinine of greater than 26.5 µmol/L (0.3 mg/dL) from baseline should be closely monitored for renal safety.

10. That if serum phosphate is < 0.48 mmol/L (1.5 mg/dL) or creatinine clearance decreases during therapy to < 70 mL/min then renal function should be re-evaluated within one week.

11. That it is recommended that Stribild is discontinued in patients with creatinine clearance that falls to < 70 mL/min while on treatment unless it is considered that the potential benefit of this combination of antiretroviral agents for the individual patient outweighs the possible risks of continuing with therapy.

12. That if creatinine clearance is confirmed as < 50 mL/min or serum phosphate decreases to < 0.32 mmol/L (1.0 mg/dL) then Stribild should be discontinued.

13. That use of Stribild should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Stribild is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule .

14. Instructions on the use of the creatinine clearance slide ruler.

- **Obligation to complete post-authorisation measures**

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that cobicistat and elvitegravir are qualified as new active substances.