14 September 2017
EMA/642999/2017
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/II/0079

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
BHIVA	British HIV Association
BMD	bone mineral density
BMI	body mass index
CD4	cluster determinant 4
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COBI	cobicistat (Tybost®)
C-telopeptide	type 1 collagen C-telopeptide
CV	coefficient of variation
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
DXA	dual-energy x-ray absorptiometry
EACS	European AIDS Clinical Society
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EU	European Union
EVG	elvitegravir (Vitekta®)
FDC	fixed-dose combination
$FEPO_4$	fractional excretion of phosphate
FEUA	fractional excretion of uric acid
FTC	emtricitabine (Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HIV-1, HIV	human immunodeficiency virus, type 1
ICH	International Council on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INSTI	integrase strand-transfer inhibitor
N or n	number of subjects in a population (N) or subset (n)
NRTI	nucleoside reverse transcriptase inhibitor
N-telopeptide	type 1 collagen N-telopeptide
NtRTI	nucleotide reverse transcriptase inhibitor
M	module
M = E	missing = excluded
M = F	missing = failure
PENTA	Paediatric European Network for Treatment of AIDS
PK	pharmacokinetic(s)
PTH	parathyroid hormone
Q1, Q3	first quartile, third quartile
RBP	retinol binding protein
RNA	ribonucleic acid

RTV	ritonavir
SAE	serious adverse event
SD	standard deviation
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)
TBLH	total body less head
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TmP/GFR	renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate
UPCR	urine protein to creatinine ratio
US	United States

Background information on the procedure

Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Limited submitted to the European Medicines Agency on 1 February 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of HIV 1 infection in adolescents aged 12 to < 18 years weighing ⩾ 35 kg without known mutations associated with resistance to any of the three antiretroviral agents in Stribild, and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil fumarate (TDF); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on pharmacokinetics, safety and efficacy data through 48 weeks of treatment with Stribild in Study GS-US-236-0112.

The Package Leaflet and Risk Management Plan (v.12) are updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and Risk Management Plan (RMP).

In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor linguistic amendments

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0309/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0309/2016 was completed.

The PDCO issued an opinion on compliance for the PIP P/0309/2016.

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.

Derogation(s) of market exclusivity

Not applicable

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Joseph Emmerich

Timetable	Actual dates
Submission date	1 February 2017
Start of procedure:	18 February 2017
CHMP Rapporteur Assessment Report	12 April 2017
CHMP Co-Rapporteur Assessment Report	19 April 2017
PRAC Rapporteur Assessment Report	18 April 2017
PRAC members comments	26 April 2017
Updated PRAC Rapporteur Assessment Report	27 April 2017
PRAC Outcome	5 May 2017
CHMP members comments	8 May 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 May 2017
Request for supplementary information (RSI)	18 May 2017
CHMP Rapporteur Assessment Report	15 August 2017
PRAC Rapporteur Assessment Report	18 August 2017
PRAC members comments	23 August 2017
Updated PRAC Rapporteur Assessment Report	24 August 2017
PRAC Outcome	1 September 2017
CHMP members comments	4 September 2017
Updated CHMP Rapporteur Assessment Report	8 September 2017
Opinion	14 September 2017

Scientific discussion

Introduction

Stribild is a once-daily, fixed-dose combination (FDC) tablet that contains the integrase strand transfer inhibitor (INSTI) elvitegravir (EVG) co-formulated with the pharmaco-enhancer cobicistat (COBI) and the nucleoside/nucleotide reverse transcriptase inhibitor (N[t]RTI) backbone emtricitabine/tenofovir disoproxil fumarate (FTC/TDF; Truvada). Stribild was first approved in the European Union (EU) on 24 May 2013. The pivotal studies for the approval were 2 Phase 3 studies (**GS-US-236-0102** and **GS-US-236-0103**) in which the efficacy and safety of STB in antiretroviral (ARV) therapy (ART)-naïve was established and two Phase 3 studies (**GS-US-236-0115** and **GS-US-236-0121**) in which the efficacy and safety of virologically suppressed adult subjects was established.

This present application concerns an application to extend the use of Stribild to include the treatment of HIV-1 infected adolescent patients 12 to < 18 years of age and weighing ≥ 35 kg. The MAH considers that the pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of ART are similar between HIV-infected adult and paediatric patients. However, there are important and unique issues relating to HIV-infected infants, children, and adolescents. Treatment adherence is of particular issue. Therefore Stribild (STB) may be a potential option for adolescent patients. No specific clinical data were available for adolescent subjects at the time of the original approval of STB. In this submission, pharmacokinetic (PK), safety, and efficacy data through 48 weeks of treatment are presented for ART-naive, HIV-infected adolescent subjects in Study **GS-US-236-0112.** The MAH proposed the inclusion of data from study GS-US-236-0112 and supporting data from paediatric studies conducted with Emtriva and Viread, in the STB prescribing information to support the extension of indication to adolescents which is aligned with the indication approved for Viread and also with the indication proposed in the draft Truvada SmPC (EMEA/H/C/00594/II/0131).

Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

Clinical aspects

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.

Table 1. Tabular overview of clinical studies

Study	Study Design	Number of Subjects by Treatment Regimen	Data Presented	CSR and Narrative Locations
GS-US-236-0112	Phase 2/3, open-label, multicenter, 2-part, single-group study to evaluate the steady-state PK and confirm the dose of STB, and evaluate the safety and tolerability of STB through Week 48	STB: Enrolled: 50[a] Safety Analysis Set: 50	PK Week 48 safety and efficacy	**CSRs:** GS-US-236-0112 Week 24 CSR GS-US-236-0112 Week 48 CSR **Narrative:** m2.7.4, Section 1.1.3.1

CSR = clinical study report

a Of the 50 total subjects enrolled, 14 subjects were included in Part A, which was conducted primarily to evaluate PK and confirm the doses of STB, and 36 subjects were enrolled in Part B, which was conducted primarily to evaluate the safety and tolerability of STB.

Pharmacokinetics

The PK data from study GS-US-236-0112 are provided in support of the application.

GS-US-236-0112

This study was conducted to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) single-tablet regimen (Stribild, STB) in human immunodeficiency virus type 1 (HIV-1) infected, antiretroviral treatment (ART)-naive adolescents.

The study was conducted in two parts (part A and B) with part A being concerned primarily with the PK aspects.

Part A

Methodology

The primary objective of part A was to evaluate the steady state pharmacokinetics and confirm the dose of STB in HIV-1 infected, ART-naive adolescents.

Adolescent subjects 12 to < 18 years of age, of either sex, were enrolled in the study.

Subjects in Part A participated in an intensive pharmacokinetic (PK) evaluation on Day 10.

Subjects received 1 STB tablet daily, orally with food, at approximately the same time each day.

During the 9 days leading up to the intensive PK evaluation on Day 10, subjects were instructed to take their STB tablet with food at the same time each day in the morning (at breakfast). On Day 10, these subjects received their dose of study drug with food in the clinic, after an overnight fast of at least 8 hours.

A PK sub-study analysis set was defined separately for each of EVG, COBI, FTC, and TFV, and included all enrolled and treated subjects in Part A with any non-missing key PK parameter (AUCtau, Cmax, Ctrough) for the respective analyte from the intensive PK evaluation on Day 10. Other PK parameters estimated were Clast, Tlast, Tmax, t½, CL/F, Vz/F, and λz.

Pharmacokinetic parameters were estimated by application of a nonlinear model using standard Non-compartmental methods (WinNonlin® software, Version 6.3).

Plasma concentration data were listed for all subjects, and summarized by nominal time point.

Pharmacokinetic parameters were listed and summarized using descriptive statistics. For some

PK parameter data, the geometric mean, its 95% CI, and the mean and standard deviation (SD) of the natural log-transformed values were presented.

14 subjects were enrolled in Part A of the study and participated in the intensive PK evaluation on Day 10. Each of the 14 subjects had non-missing key PK parameter data (AUCtau, Cmax, and Ctrough) and was included in the PK sub-study analysis set for each analyte of interest.

Results

Elvitegravir Pharmacokinetic Parameters

Elvitegravir PK parameters were determined in the 14 subjects who participated in the intensive PK evaluation.

Table 2. GS-US-236-0112: Elvitegravir Pharmacokinetic Parameters (EVG PK Substudy Analysis Set)

EVG PK Parameter	Mean (%CV) (N = 14)
AUC_{tau} (ng•h/mL)[a]	31,620.9 (44.2)
C_{max} (ng/mL)	2624.3 (47.2)
C_{trough} (ng/mL)[b]	579.3 (78.6)
T_{max} (h)[c]	4.25 (3.88, 5.00)
CL/F (mL/h)	5029.7 (65.2)
Vz/F (mL)	55,869.6 (43.1)

a The predose concentration was used as a surrogate for the 24-hour postdose concentration for the purpose of estimating AUC_{tau}
b The predose trough concentration (C_{trough}) represents C_{tau}
c Median (Q1, Q3)

The primary EVG PK parameters AUCtau, Cmax, and Ctrough were compared in adolescents administered STB in this study (test) versus combined data from HIV-1 infected adult subjects who received STB in historical studies GS-US-236-0103 and GS-US-236-0104, and STB-treated subjects who participated in the PK sub-study in Study GS-US-236-0102 (see table below).

Elvitegravir AUCtau, Cmax, and Ctrough were increased by 30.29%, 41.5%, and 5.85%, respectively, in adolescents in this study compared with adults in historical studies. The 90% CIs of the GLSM ratios for each of the PK parameters extended above the predefined equivalence boundaries of 70% to 143%.

Table 3. GS-US-236-0112: Statistical Comparisons of Elvitegravir Plasma Pharmacokinetic Parameter Estimates Following Administration of Stribild to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies (EVG PK Substudy Analysis Set)

EVG PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	Test (Study GS-US-236-0112) (N = 14)	Reference (Historical Control) (N = 419)	
AUC_{tau} (ng•h/mL)[a]	28,529.11	21,896.87	130.29 (104.79, 162.00)
C_{max} (ng/mL)	2390.01	1689.04	141.50 (116.06, 172.52)
C_{trough} (ng/mL)[b]	410.08	387.42	105.85 (69.99, 160.09)

GLSM = geometric least squares mean

The 95% CI of the geometric mean of CL/F extended slightly above the pre-specified boundaries of 60% to 140%, while that of Vz/F was contained within the boundaries (Table 4).

Table 4. GS-US-236-0112: Elvitegravir CL/F and Vz/F (EVG PK Substudy Analysis Set

		CL/F (mL/h)	Vz/F (mL)
EVG (n = 14)	Mean (%CV)	5029.7 (65.2)	55,869.6 (43.1)
	Geomean (95% CI / Geomean)	4181.6 (0.694, 1.440)	51,677.4 (0.792, 1.262)

Cobicistat Pharmacokinetic Parameters

Table 5. GS-US-236-0112: Cobicistat Pharmacokinetic Parameters (COBI PK Substudy Analysis Set)

COBI PK Parameter	Mean (%CV) (N = 14)
AUC_{tau} (ng•h/mL)[a]	11,884.8 (94.4)
C_{max} (ng/mL)	1500.4 (65.0)
C_{trough} (ng/mL)[b]	39.7 (172.5)
T_{max} (h)[c]	4.00 (2.00, 4.98)
CL/F (mL/h)	19,099.4 (55.1)
Vz/F (mL)	92,824.1 (62.9)

The primary COBI PK parameters AUCtau, Cmax, and Ctrough were compared in adolescents administered STB in this study (test) versus combined data from HIV-1 infected adult subjects who received STB in historical studies GS-US-236-0103 and GS-US-236-0104, STB-treated subjects who participated in the PK substudy in Study GS-US-236-0102, and subjects who received COBI-boosted ATV plus TVD in Studies GS-US-216-0105 and GS-US-216-0114.

The 90% CIs of the GLSM ratios for COBI AUCtau and Cmax were contained within the predefined equivalence boundaries of 70% to 143%. Cobicistat Ctrough was slightly higher, and the 90% CI of the GLSM ratio extended beyond the predefined equivalence boundaries of 70% to 143% (Table 6).

Table 6. GS-US-236-0112: Statistical Comparisons of Cobicistat Plasma Pharmacokinetic Parameter Estimates Following Administration of Stribild to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies (COBI PK Substudy Analysis Set)

COBI PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	Test (Study GS-US-236-0112) (N = 14)	Reference (Historical Control) (N = 483)	
AUC_{tau} (ng•h/mL)[a]	9200.48	8728.69	105.41 (78.12, 142.22)
C_{max} (ng/mL)	1275.17	1178.59	108.20 (84.00, 139.36)
C_{trough} (ng/mL)[b]	18.93	17.72	106.86 (65.92, 173.21)

Emtricitabine Pharmacokinetic Parameters

Emtricitabine PK parameters were determined in the 14 subjects who participated in the intensive PK evaluation.

Table 7. GS-US-236-0112: Emtricitabine Pharmacokinetic Parameters (FTC PK Substudy Analysis Set)

FTC PK Parameter	Mean (%CV) (N = 14)
AUC_{tau} (ng•h/mL)[a]	15,136.5 (31.1)
C_{max} (ng/mL)	2217.4 (30.0)
C_{trough} (ng/mL)[b]	102.6 (30.1)
T_{max} (h)[c]	3.94 (2.00, 4.08)
CL/F (mL/h)	13,516.9 (27.4)
Vz/F (mL)	107,931.4 (38.7)

The primary FTC PK parameters AUCtau, Cmax, and Ctrough were compared in adolescents administered STB in this study (test) versus combined data from HIV-1 infected adult subjects who received STB and participated in the PK substudy in historical studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104. The 90% CIs of the GLSM ratios for FTC AUCtau, Cmax, and Ctrough were contained within the predefined equivalence boundaries of 70% to 143%.

Table 8. GS-US-236-0112: Statistical Comparisons of Emtricitabine Plasma Pharmacokinetic Parameter Estimates Following Administration of Stribild to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies (FTC PK Substudy Analysis Set)

FTC PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	Test (Study GS-US-236-0112) (N = 14)	Reference (Historical Control) (N = 61)[a]	
AUC_{tau} (ng•h/mL)[b]	14,508.95	12,106.32	119.85 (103.27, 139.08)
C_{max} (ng/mL)	2124.40	1813.97	117.11 (100.69, 136.21)
C_{trough} (ng/mL)[c]	98.48	104.44	94.29 (78.77, 112.88)

Tenofovir Pharmacokinetic Parameters

Tenofovir PK parameters were determined in the 14 subjects who participated in the intensive PK evaluation.

Table 9. GS-US-236-0112: Tenofovir Pharmacokinetic Parameters (TFV PK Substudy Analysis Set)

TFV PK Parameter	Mean (%CV) (N = 14)
AUC_{tau} (ng•h/mL)[a]	4450.7 (29.5)
C_{max} (ng/mL)	438.5 (38.9)
C_{trough} (ng/mL)[b]	86.6 (27.2)
T_{max} (h)[c]	2.00 (2.00, 4.00)
CL/F (mL/h)	23,947.1 (24.2)
Vz/F (mL)	433,934.9 (37.1)

The primary TFV PK parameters AUCtau, Cmax, and Ctrough were compared in adolescents administered STB in this study (test) versus combined data from healthy and HIV-1 infected adult subjects who received STB in historical studies GS-US-236-0103 and GS-US-236-0104, and STB-treated subjects who participated in the PK substudy in Study GS-US-236-0102. Tenofovir AUCtau and Cmax were modestly increased by 37.46% and 30.78%, respectively, in adolescents in this study compared with adults in historical studies; the 90% CIs of the GLSM ratios for AUCtau and Cmax extended beyond the predefined equivalence boundaries of 70% to 143%, while that for Ctrough was contained within the boundaries.

Table 10. GS-US-236-0112: Statistical Comparisons of Tenofovir Plasma Pharmacokinetic Parameter Estimates Following Administration of Stribild to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies (TFV PK Substudy Analysis Set)

TFV PK Parameter	GLSM		%GLSM Ratio (90% CI) Test / Reference
	Test (Study GS-US-236-0112) (N = 14)	Reference (Historical Control) (N = 419)	
AUC_{tau} (ng•h/mL)[a]	4281.03	3114.36	137.46 (121.01, 156.14)
C_{max} (ng/mL)	409.41	313.05	130.78 (110.31, 155.05)
C_{trough} (ng/mL)[b]	83.83	68.21	122.89 (109.33, 138.14)

Pharmacodynamics

There are no new data since the efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate Stribild for treatment of HIV-1 is well established.

Clinical efficacy

Dose response studies

No clinical dose response studies are provided to support the proposed use in HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years and weighing ≥ 35 kg.

Main study

GS-US-236-0112

Study Title: *"A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents conducted in two parts (Parts A and B) ".*

Methods

Adolescent subjects 12 to < 18 years of age, of either sex, were enrolled in the study as follows:

Part A: An initial group of subjects was enrolled to evaluate the steady-state pharmacokinetics and confirm the dose of STB. Subjects in Part A participated in an intensive pharmacokinetic (PK) evaluation on Day 10.

Part B: Following the confirmation of EVG exposure in Part A, and independent data monitoring committee review of preliminary safety and efficacy data, subjects were enrolled in Part B to evaluate the safety, tolerability, and antiviral activity of STB.

Subjects returned for study visits at Weeks 1, 2, 4, 8, 12, 16, and 24, and then every 8 weeks through Week 48.

Subjects who complete 48 weeks of study treatment are given the option to continue to receive STB in an extension phase of the study, during which study visits are scheduled every 12 weeks, until: a) the subject turns 18 and STB is commercially available for adults in the country in which the subject is enrolled; b) STB becomes commercially available for adolescents in the country in which the subject is enrolled; or c) Gilead Sciences elects to terminate development of STB in that country.

Study participants

Subjects who met all of the following criteria were eligible for participation in the study:

- 12 years to < 18 years of age at baseline
- Able to give written assent prior to any screening evaluation
- Parent or guardian able to give written informed consent prior to any screening evaluation and willing to comply with study requirements
- Plasma HIV-1 RNA > 1,000 copies/mL at screening (Roche COBAS TaqMan v2.0)
- CD4 cell count > 100 cells/µL
- Weight ≥ 35 kg (77 lb)
- Screening HIV-1 genotype report provided by Gilead Sciences must have shown sensitivity to FTC and TDF using the GenoSure RT/PR assay
- Able to swallow oral tablets
- Adequate renal function: estimated glomerular filtration rate (eGFR) □ 90 mL/min/1.73m2
- eGFR using Schwartz formula (mL/min/1.73m2) = k x L/Scr, where k is a proportionality constant of 0.55 for adolescent females ≥ 12 years old and 0.70 for adolescent males ≥ 12 years old; L is height in cm; and Scr is serum creatinine (mg/dL)
- Clinically normal electrocardiogram (ECG) (or if abnormal, determined by the investigator to be not clinically significant)
- Documented screening for active pulmonary tuberculosis per local standard of care within 6 months of a screening visit
- Hepatic transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) ≤ 5 ≤ upper limit of normal (ULN)
- Total bilirubin≤1.5 mg/dL, or normal direct bilirubin
- Subjects with a positive hepatitis B virus surface antigen (HBsAg) screening test could participate in the study, providing that alternative therapy (other than TDF) for chronic hepatitis B infection was available as part of the local standard of care
- Adequate hematologic function (absolute neutrophil count [ANC] ≥ 500/mm3; platelets

≥50,000/mm3; hemoglobin ≥8.5 g/dL)

- Subjects with chronic neutropenia, defined as an ANC < 500/mm3 documented at least twice within 6 months of screening, and in whom, according to the investigator, there was no evidence of active opportunistic or serious infection, could enroll in the study contingent upon approval from the Gilead study medical monitor

- Negative serum pregnancy test (female subjects only)

- Male and female subjects of childbearing potential had to agree to utilize highly effective contraception methods while on study treatment, or to abstain from heterosexual intercourse throughout the study period and for 30 days following the last dose of study drug; highly effective methods normally utilize 2 separate forms of contraception, 1 of which had to be an effective barrier contraceptive method. Pre-pubertal females (Tanner Stages 1 and 2) were not considered to be of childbearing potential, unless onset of menarche had occurred.

- Female subjects who utilized a hormonal contraceptive as one of their birth control methods must have used the same method for at least 3 months prior to study dosing. It was recommended that an oral contraceptive contain ≥ 30 µg of ethinyl estradiol if administered with STB.

- Male subjects had to agree to utilize a highly effective method of contraception during heterosexual intercourse throughout the study period and for 30 days following discontinuation of study drug. A highly effective method of contraception was defined as 2 separate forms of contraception, 1 of which had to be an effective barrier method.

  Alternatively, a male subject had to be non-heterosexually active, or practice sexual abstinence.

- Willing and able to comply with all study requirements

- Life expectancy ≥ 1 year

Exclusion criteria

Subjects with any of the following were not eligible for participation in the study:

- A new AIDS-defining condition (with the exception of CD4 cell count and percentage criteria) diagnosed within the 30 days prior to screening

- Prior treatment with any approved or investigational or experimental anti-HIV-1 drug for anylength of time (other than that given for prevention of mother-to-child transmission)

- Evidence of active pulmonary or extrapulmonary tuberculosis disease within 3 months of the screening visit

- Anticipated to require rifamycin treatment for mycobacterial infection while participating in the study. (Prophylactic isoniazid therapy for latent tuberculosis treatment was allowed.)

- Experiencing decompensated cirrhosis (eg, ascites, encephalopathy)

- Pregnant or lactating

- Any serious or active medical or psychiatric illness which, in the opinion of the investigator, would have interfered with subject treatment, assessment, or compliance with the protocol. This included uncontrolled renal, cardiac, haematological, hepatic, pulmonary (including chronic asthma), endocrine (eg, diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that were clinically significant or required treatment within 30 days prior to study dosing

- Current alcohol or substance abuse judged by the investigator to potentially interfere with subject

compliance

- A history of significant drug sensitivity or drug allergy
- Known hypersensitivity to the study drug, its metabolites, or formulation excipients
- Treatment with immunosuppressant therapies or chemotherapeutic agents within 3 months of screening, or expected to receive these agents (eg, immunoglobulins, and other immune- or cytokine-based therapies) during the study
- A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with cutaneous KS were eligible, but must not have received any systemic therapy for KS within 30 days of baseline, and must not have been anticipated to require systemic therapy during the study
- Had previously participated in an investigational trial involving administration of any investigational agent within 30 days prior to study dosing
- Participation in any other clinical trial without prior approval from the sponsor was prohibited while participating in this trial
- Receiving ongoing therapy with any of the medications in the table below, including drugs not to be used with EVG, COBI, FTC, and TDF (refer to individual agent Prescribing information or the STB Investigator Brochure); or subjects with any known allergies to the excipients of STB tablets

Treatments

Stribild tablets containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF were administered orally, with food, at approximately the same time each day.

Objectives

Primary

- To evaluate the safety and tolerability of STB through Week 48 in HIV-1 infected, ART-naive adolescents

The secondary objective of this study is as follows:

- To evaluate the antiviral activity of STB through Week 48 in HIV-1 infected, ART-naïve adolescents

Outcomes/endpoints

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm
- The percentage of subjects with plasma HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm
- The change from baseline in plasma HIV-1 RNA (log10 copies/mL) at Weeks 24 and 48
- The change from baseline in CD4 cell count (cells/µL) and percentage at Weeks 24 and 48
- The percentage of subjects with HIV-1 RNA < 50 and < 400 copies/mL at Weeks 24 and 48 (M = F and missing = excluded [M = E] analyses)
- The percentage of subjects with HIV-1 RNA <20, < 50, and < 400 copies/mL at Weeks 24 and 48 (missing = failure [M = F] and missing = excluded [M = E] analyses)
- Pure virologic failure (PVF) with HIV-1 RNA cut-off at 50 copies/mL by Week 48

Sample size

Part B
A total of 50 treatment-naive adolescents (including the first 12 to 16 subjects from Part A plus an additional 34 to 38 subjects from Part B) were planned to study the safety of STB in adolescents. With this sample size, the study would have 87% to 99.8% chance to observe at least 1 SAE, assuming an SAE incidence rate of 4% (observed in Study GS-US-236-0104) to 12% (observed in Study GS-US-236-0102).

Randomisation

Not applicable.

Blinding (masking)

Not applicable as the study was open-label

Statistical methods

The Week 48 analysis window was defined as from Study Day 308 to Study Day 377 (inclusive). All on-treatment HIV-1 RNA data collected (up to 1 day after the last dose date of study drug for subjects who prematurely discontinued study drug) were used in the FDA-defined snapshot algorithm. Virologic outcome was defined as the following categories: virologic success, virologic failure, and no virologic data in the Week 48 visit window.

The analyses for all the efficacy endpoints were conducted using the FAS. The number and percentage of subjects with HIV-1 RNA < 50 copies/mL and < 400 copies/mL based on the FDA-defined snapshot algorithm, and the numbers and percentages of subjects with HIV-1 RNA <20, < 50, and < 400 copies/mL M = F analysis, and M = E analysis were summarized. The 95% CIs for the percentage estimates were constructed using an exact method.

For the FDA-defined snapshot algorithm, the number and percentage of subjects with virologic success, virologic failure (including subcategories), and no virologic data (including reasons) were summarized. For the M = F analysis, results were summarized for all visits up to the Week 48 visit. For the M = E analysis, results were summarized at all visits through the data cut. Time to PVF was analyzed using the Kaplan-Meier method.

Log10 HIV-1 RNA data were summarized using observed data. CD4 cell count and CD4% data were summarized using observed, on-treatment data (ie, up to 1 day after the last dose date of study drug). Baseline and change from baseline values in log10 HIV-1 RNA (copies/mL), CD4 cell count (cells/µL), and CD4% at all visits through the Week 48 analysis data cut date were summarized using descriptive statistics. The means and 95% CI of changes from baseline over time were plotted.

Results

Participant flow

Of the 56 subjects screened, 50 were enrolled into the study and received at least 1 dose of study drug: 14 in Part A and 36 in Part B. Subjects were enrolled at 19 sites in 3 countries (7 in the US, 7 in South Africa, and 5 in Thailand.

As of the data cut date for the interim Week 48 analysis, 96.0% (48 subjects) had completed study treatment in the main phase of the study, and 98.0% (49 subjects) had completed the main phase of the study. 1 subject (2.0%) prematurely discontinued study treatment due to pregnancy and 1 subject (2.0%) discontinued both study treatment and study due to noncompliance with study drug.

Of the 49 subjects who completed the main phase of the study, 40 subjects entered into the extension phase. Of those 40 subjects, 35 were still receiving study treatment in the extension phase; 2 subjects had prematurely discontinued study treatment because of noncompliance with study drug, and 3 subjects were no longer receiving study treatment because they turned 18 and STB is commercially available for adults in the country in which the subject was enrolled.

Table 11. GS-US-236-0112: Disposition of Subjects (All Screened Subjects)

Subject Disposition[a,b,c]	STB
Subjects Screened	56
Screened Subjects Who Were Not Enrolled	6
Screen Failure Subjects Who Were Not Enrolled	6
Subjects Enrolled	50
Enrolled in Part A	14
Enrolled in Part B	36
Subjects in Safety Analysis Set	50
Subjects in Full (FAS) Analysis Set	50
MAIN PHASE	
Subjects Still on Study Treatment	0
Subjects Completing Study Treatment	48 (96.0%)
Subjects Not Entering the Extension Phase	8 (16.0%)
Subjects Prematurely Discontinuing Study Treatment	2 (4.0%)
Reasons for Prematurely Discontinuing Study Treatment	
Pregnancy	1 (2.0%)
Non-Compliance with Study Drug	1 (2.0%)
Subjects Still on Study	0
Subjects Completing Study	49 (98.0%)
Subjects Prematurely Discontinuing from Study	1 (2.0%)
Reasons for Prematurely Discontinuing from Study	
Non-Compliance with Study Drug	1 (2.0%)
EXTENSION PHASE	
Subjects Entering Extension Phase	40 (80.0%)
Subjects Still on Study Treatment	35 (87.5%)
Subjects No Longer on Study Treatment - Subject is 18 Years Old and Study Drug is Commercially Available	3 (7.5%)
Subjects Prematurely Discontinuing Study Treatment	2 (5.0%)
Reasons for Prematurely Discontinuing Study Treatment	
Non-Compliance with Study Drug	2 (5.0%)
Subjects Still on Study	35 (87.5%)
Subjects No Longer on Study - Subject is 18 Years Old and Study Drug is Commercially Available	3 (7.5%)
Subjects Prematurely Discontinuing from Study	2 (5.0%)
Reasons for Prematurely Discontinuing from Study	
Non-Compliance with Study Drug	2 (5.0%)

Recruitment

Conduct of the study

Baseline data

The majority of subjects in the safety analysis set were male (70.0%), with a mean age of 15 years (range: 12 to 17); most were black (68.0%) or Asian (28.0%) and not Hispanic or Latino (94.0%), which generally represents the paediatric HIV epidemics in the US and globally, see table below

The mean value for BMI at baseline was 21.1 kg/m^2 (range: 15.9 to 28.5). Mean (SD) baseline eGFR values calculated using the Schwartz formula and the modified Schwartz formula were 145.7 (24.64) mL/min/1.73 m2 and 102.1 (12.12) mL/min/1.73 m2, respectively. Most of the male subjects were Tanner Stage 5 (62.9%) or 2 (17.1%) for pubic hair and Stage 5 (65.7%) or 2 (17.1%) for genitalia. Most female subjects were Tanner Stage 3 (46.7%) or 4 (20.0%) for pubic hair and Stage 4 (33.3%) or 3 (26.7%) for breasts.

Baseline Disease Characteristics

The mean (SD) baseline HIV-1 RNA value was 4.60 (0.551) log10 copies/mL; 80.0% of subjects had baseline HIV-1 RNA >100,000 copies/mL and 20.0% of subjects had baseline HIV-1 RNA > 100,000 copies/mL. The mean (SD) baseline CD4 cell count was 399 (127.6) cells/µL; 4% of subjects had a baseline CD4 cell count ≤ 199 cells/µL, 36.0% of subjects had a baseline CD4 cell count ≤ 349 cells/µL, and 80.0% of subjects had a baseline CD4 cell count ≤ 499 cells/µL. The mean (SD) baseline CD4% was 20.9% (7.19%). The most common HIV modes of infection were homosexual sex (38.0%), vertical transmission (34.0%), and heterosexual sex (24.0%). The majority of subjects (74.0%) had asymptomatic HIV-1 infection. One subject was HBsAg positive, and no subject was HCV antibody positive.

Table 12. GS-US-236-0112: Baseline Disease Characteristics (Safety Analysis Set)

Characteristic[a]	STB (N=50)
HIV-1 RNA (log10 copies/mL)	
N	50
Mean (SD)	4.60 (0.551)
Median	4.55
Q1, Q3	4.32, 4.85
Min, Max	3.18, 5.73
HIV-1 RNA Categories (copies/mL)	
<= 100,000	40 (80.0%)
> 100,000	10 (20.0%)
CD4 Cell Count (/uL)	
N	50
Mean (SD)	399 (127.6)
Median	402
Q1, Q3	298, 486
Min, Max	133, 734
CD4 Cell Count Categories (/uL)	
<= 199	2 (4.0%)
>= 200 and <= 349	16 (32.0%)
>= 350 and <= 499	22 (44.0%)
>= 500	10 (20.0%)
CD4 Percentage (%)	
N	50
Mean (SD)	20.9 (7.19)
Median	20.2
Q1, Q3	16.9, 24.8
Min, Max	4.5, 41.1
Years Since Subject Diagnosed with HIV	
N	50
Mean (SD)	1.6 (2.72)
Median	1.0
Q1, Q3	0.0, 2.0
Min, Max	0.0, 11.0
Mode of Infection (HIV Risk Factors)[b]	
Heterosexual Sex	12 (24.0%)
Homosexual Sex	19 (38.0%)
IV Drug Use	0
Transfusion	0
Vertical Transmission	17 (34.0%)
Unknown	2 (4.0%)
Other	2 (4.0%)
HIV Disease Status	
Asymptomatic	37 (74.0%)
Symptomatic HIV Infection	12 (24.0%)
AIDS	1 (2.0%)
HBV Surface Antigen	
Negative	49 (98.0%)
Positive	1 (2.0%)
HCV Antibody	
Negative	50 (100.0%)

a. The denominator for percentages is the number of subjects in the safety analysis set

Numbers analysed

All of the 50 enrolled subjects were included in the safety analysis set and the FAS. Forty-seven subjects (94.0%) were included in the spine DXA analysis set, and 49 subjects (98.0%) were included in the TBLH DXA analysis set.

Table 13. GS-US-236-0112: Analysis Sets at Week 24 (All Enrolled Analysis Set)

Analysis Set[a]	STB
Subjects Enrolled	50
Subjects in Safety Analysis Set	50 (100.0%)
Subjects in FAS	50 (100.0%)
Subjects in Spine DXA Analysis Set	47 (94.0%)
Subjects in TBLH DXA Analysis Set	49 (98.0%)

o

Outcomes and estimation

Virologic Outcome at Week 24 and 48 Using the FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL

At Week 24, 88.0% of subjects (44 of 50) in the FAS had virologic success (HIV-1 RNA < 50 copies/mL, FDA-defined snapshot algorithm. Of the 6 subjects who did not achieve virologic success, 5 subjects (10.0%) had virologic failure at Week 24, with HIV-1 RNA ≥ 50 copies/mL, and 1 subject (2.0%, 1 of 50) had no virologic data in the Week 24 window; this subject prematurely discontinued study drug due to pregnancy, with last available HIV-1 RNA < 50 copies/mL while on study drug.

Table 14. GS-US-236-0112: Virologic Outcome at Week 24 (HIV-1 RNA Cutoff at 50 copies/mL, FDA-Defined Snapshot Algorithm- FAS)

HIV-1 RNA Category	STB (N = 50)
Virologic Success at Week 24	
HIV-1 RNA < 50 copies/mL	44 (88.0%)
Virologic Failure at Week 24	5 (10.0%)
HIV-1 RNA >= 50 copies/mL	5 (10.0%)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	0
Added New ARV	0
No Virologic Data in Week 24 Window	1 (2.0%)
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	1 (2.0%)
Missing Data during Window but on Study Drug	0

At Week 48, 88.0% of subjects (44 of 50) in the FAS had virologic success (HIV-1 RNA < 50 copies/mL, FDA-defined snapshot algorithm. Of the 6 subjects who did not achieve virologic success, 5 subjects (10%, 5 of 50) had virologic failure at Week 48; 4 of these subjects had HIV-1 RNA ≥ 50 copies/mL at Week 48, and 1 subject discontinued study drug due to noncompliance, with last available HIV-1 RNA ≥

50 copies/mL. One subject (2.0%, 1 of 50) had no virologic data in the Week 48 window (the subject who prematurely discontinued study drug due to pregnancy, as described above).

Table 15. GS-US-236-0112: Virologic Outcome at Week 48 (HIV-1 RNA Cut-off at 50 copies/mL, FDA-Defined Snapshot Algorithm, FAS)

HIV-1 RNA Category	STB (N = 50)
Virologic Success at Week 48	
HIV-1 RNA < 50 copies/mL	44 (88.0%)
Virologic Failure at Week 48	5 (10.0%)
HIV-1 RNA >= 50 copies/mL	4 (8.0%)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	1 (2.0%)
Added New ARV	0
No Virologic Data in Week 48 Window	1 (2.0%)
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	1 (2.0%)
Missing Data during Window but on Study Drug	0

Virologic Outcome at Week 24 and 48 Using the FDA-Defined Snapshot Algorithm and HIV-1 RNA < 400 copies/mL

At Week 24, using the FDA-defined snapshot algorithm with a cut-off of HIV-1 RNA < 400 copies/mL, 94.0% of subjects (47 of 50) in the FAS had virologic success, see table below. Of the 3 subjects who did not achieve virologic success, 2 subjects (4.0%, 2 of 50) had virologic failure at Week 24, with HIV-1 RNA ≥ 400 copies/ mL, and 1 subject (2.0%, 1 of 50) had no virologic data in the Week 24 window (the subject who prematurely discontinued study drug due to pregnancy.

Table 16. GS-US-236-0112: Virologic Outcome at Week 24 (HIV-1 RNA Cut-off at 400 copies/mL, FDA-Defined Snapshot Algorithm, FAS)

HIV-1 RNA Category	STB (N = 50)
Virologic Success at Week 24	
HIV-1 RNA < 400 copies/mL	47 (94.0%)
Virologic Failure at Week 24	2 (4.0%)
HIV-1 RNA >= 400 copies/mL	2 (4.0%)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 400 copies/mL	0
Added New ARV	0
No Virologic Data in Week 24 Window	1 (2.0%)
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 400 copies/mL	1 (2.0%)
Missing Data during Window but on Study Drug	0

At Week 48, using the FDA-defined snapshot algorithm with a cut-off of HIV-1 RNA < 400 copies/mL, 92.0% of subjects (46 of 50) in the FAS had virologic success. Of the 4 subjects who did not achieve virologic success, 3 subjects (6.0%, 3 of 50) had virologic failure at Week 48; 2 of these subjects had HIV-1 RNA ≥ 400 copies/mL at Week 48, and 1 subject discontinued study drug due to noncompliance, with last available HIV-1 RNA ≥ 50 copies/mL. One subject (2.0%, 1 of 50) had no virologic data in the

Week 48 window; this subject prematurely discontinued study drug due to pregnancy, with last available HIV-1 RNA < 400 copies/mL (and < 50 copies/mL), as described for Week 24 in Table 16..

Table 17. GS-US-236-0112: Virologic Outcome at Week 48 (HIV-1 RNA Cut-off at 400 copies/mL, FDA-Defined Snapshot Algorithm, FAS)

HIV-1 RNA Category	STB (N = 50)
Virologic Success at Week 48	
HIV-1 RNA < 400 copies/mL	46 (92.0%)
Virologic Failure at Week 48	3 (6.0%)
HIV-1 RNA >= 400 copies/mL	2 (4.0%)
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 400 copies/mL	1 (2.0%)
Added New ARV	0
No Virologic Data in Week 48 Window	1 (2.0%)
Discontinued Study Drug Due to AE/Death	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 400 copies/mL	1 (2.0%)
Missing Data during Window but on Study Drug	0

Percentage of Subjects with HIV-1 RNA < 20 copies/mL at Weeks 24 and 48 (M = F and M = E Analyses)

The percentage of subjects with HIV-1 RNA < 20 copies/mL at Week 24 in the FAS, using both the M = F and M = E analysis, was 80.0% (40 of 50 subjects). The percentage of subjects with HIV-1 RNA < 20 copies/mL at Week 48 in the FAS, using both the M = F and M = E analysis, was 86.0% (43 of 50 subjects)

Percentage of Subjects with HIV-1 RNA < 50 and < 400 copies/mL at Weeks 24 and 48 (M = F and M = E Analyses)

At Week 24, using both the M = F and M = E analyses (FAS), the percentage of subjects with HIV-1 RNA < 50 copies/mL was 88.0% (44 of 50 subjects). The percentage of subjects with HIV-1 RNA < 400 copies/mL, at Week 24, was 94.0% (47 of 50 subjects).

At Week 48, using both the M = F and M = E analyses (FAS), the percentage of subjects with HIV-1 RNA < 50 copies/mL was 90.0% (45 of 50 subjects). The percentage of subjects with HIV-1 RNA < 400 copies/mL, at Week 48, was 94.0% (47 of 50 subjects).

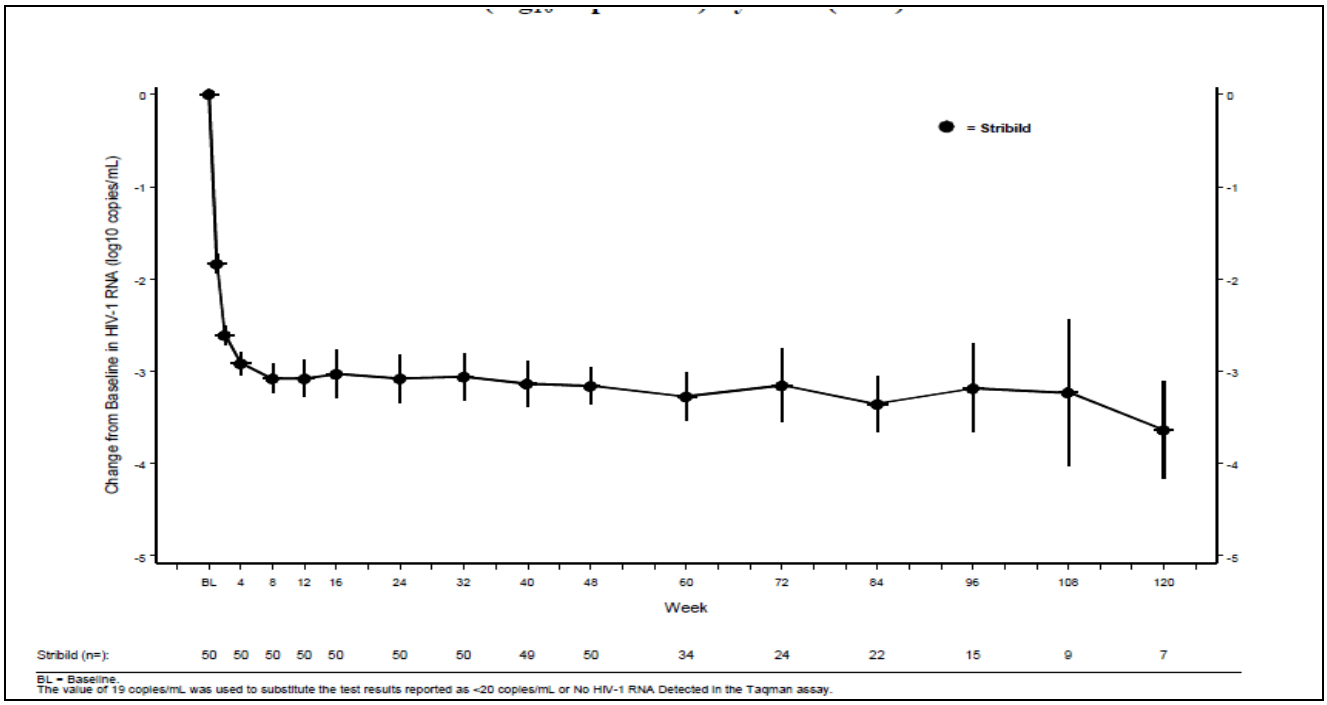
Table 18. GS-US-236-0112: Subjects with HIV-1 RNA < 50 and < 400 copies/mL at Week 48 (M = F and M = E Analyses, FAS)

HIV-1 RNA	STB (N = 50)
< 50 copies/mL	
Missing = Failure[a]	
HIV-1 RNA at Week 48	
< 50 copies/mL	45/50 (90.0%)
95% CI[c]	78.2% to 96.7%
< 20 copies/mL	43/50 (86.0%)
< 20 Not Detectable	27/50 (54.0%)
< 20 Detectable	16/50 (32.0%)
20 to < 50 copies/mL	2/50 (4.0%)
50 to < 400 copies/mL	2/50 (4.0%)
400 to < 1000 copies/mL	1/50 (2.0%)
>= 1000 copies/mL	2/50 (4.0%)
Missing	0/50
Missing = Excluded[b]	
HIV-1 RNA at Week 48	
< 50 copies/mL	45/50 (90.0%)
95% CI[c]	78.2% to 96.7%
< 20 copies/mL	43/50 (86.0%)
< 20 Not Detectable	27/50 (54.0%)
< 20 Detectable	16/50 (32.0%)
20 to < 50 copies/mL	2/50 (4.0%)
50 to < 400 copies/mL	2/50 (4.0%)
400 to < 1000 copies/mL	1/50 (2.0%)
>= 1000 copies/mL	2/50 (4.0%)
< 400 copies/mL	
Missing = Failure[a]	
HIV-1 RNA at Week 48	
< 400 copies/mL	47/50 (94.0%)
95% CI[c]	83.5% to 98.7%
400 to < 1000 copies/mL	1/50 (2.0%)
>= 1000 copies/mL	2/50 (4.0%)
Missing	0/50
Missing = Excluded[b]	
HIV-1 RNA at Week 48	
< 400 copies/mL	47/50 (94.0%)
95% CI[c]	83.5% to 98.7%
400 to < 1000 copies/mL	1/50 (2.0%)
>= 1000 copies/mL	2/50 (4.0%)

Change from Baseline in HIV-1 RNA at Weeks 24 and 48

The mean (SD) baseline HIV-1 RNA level (FAS) was 4.60 (0.551) log10 copies/mL. Mean HIV-1 RNA levels decreased over the first 8 weeks following initiation of STB, and decreases were maintained through Weeks 24 and 48. At Weeks 24 and 48, the mean (SD) change from baseline in HIV-1 RNA was −3.08 (0.922) log10 copies/mL and −3.16 (0.705) log10 copies/mL, respectively.

Figure 1. GS-US-236-0112: Mean and 95% CI of Change from Baseline in HIV-1 RNA (log10 copies/mL) by Visit (FAS)



Change from Baseline in CD4 Cell Count at Weeks 24 and 48

The mean (SD) baseline CD4% (FAS; based on observed data) was 20.9% (7.19%). Mean CD4% increased following initiation of study drug, and continued to increase with increased duration of exposure to study drug through 48 weeks. At Weeks 24 and 48, the mean (SD) increase from baseline in CD4% was 7.4% (4.70%) and 8.1% (5.34%), respectively

Ancillary analyses

None

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19. Summary of Efficacy for trial GS-US-236-0112

Title: A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents conducted in two parts (Parts A and B)				
Study identifier	GS-US-236-0112			
Design	A Phase 2/3, Open-Label Study in adolescents			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks not applicable From 48 weeks until subjects turn 18 (therefore ongoing)	
Hypothesis	To explore safety and efficacy in adolescents			
Treatments group	STR		Stribild tablets containing 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of TDF for 48 weeks with 50 subjects randomised into the study	
Endpoints and definitions	Efficacy endpoint	Percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm		
	Efficacy endpoint:	Change from baseline in plasma HIV-1 RNA (log10 copies/mL) at Weeks 24 and 48		
	Efficacy endpoint:	Change from baseline in CD4 cell count (cells/µL) and percentage at Weeks 24 and 48		
Database lock				
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat and Per protocol After 24 and 48 weeks of treatment			
Descriptive statistics and estimate variability	Treatment group	Stribild tablets	N/A	N/A
	Number of subject	50		
	Percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24	88.0% of subjects		
	Percentage of	88.0% of		

	subjects with plasma HIV-1 RNA < 50 copies/mL at week 48	subjects		
	Change from baseline in plasma HIV-1 RNA (log10 copies/mL) at Week 24	−3.08 (0.922) log10 copies/mL		
	Change from baseline in plasma HIV-1 RNA (log10 copies/mL) at Week 48	−3.16 (0.705) log10 copies/mL		
	Change from baseline in CD4 cell count (cells/µL) and percentage at Week 24	7.4% (4.70%)		
	Change from baseline in CD4 cell count (cells/µL) and percentage at Week 48	8.1% (5.34%),		
Notes				
Analysis description	**None**			

Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH presents the results of study **GS-US-236-0112** which was conducted in ART naïve adolescents to evaluate the efficacy of Stribild in the achievement of HIV-1 RNA <50 copies/ml. The study was conducted open-label for 48 weeks.

The study was conducted primarily to investigate the safety and tolerability of STB through Week 48 in HIV-1 infected, ART-naive adolescents and secondarily to evaluate the antiviral activity of STB through Week 48 in HIV-1 infected, ART-naïve adolescents. This is considered acceptable.

Efficacy data and additional analyses

50 were enrolled and 48 subjects completed the study. The results of the study demonstrate that 88% of the subjects achieved virological success using the FDA-defined snap-shot algorithm. 6 subjects did not achieve virologic success with 5 subjects confirmed as virologic failures at Week 48; 4 of these subjects had HIV-1 RNA ≥ 50 copies/mL at Week 48, and 1 subject discontinued study drug due to noncompliance. The mean increase from baseline in CD4% count was 7.4% at week 24 and 8.1% at week 48.

Overall therefore the results of the study are indicative of the efficacy of Stribild in the treatment of HIV-1 infected, ART-naïve adolescents.

Additional expert consultation

None

Assessment of paediatric data on clinical efficacy

As above: The study was conducted in a paediatric subgroup.

Conclusions on the clinical efficacy

A limited number of subjects were included in GS-US-236-0112. However, the results are indicative of efficacy of Stribild in the treatment of HIV-1 infected, ART-naïve adolescents.

Clinical safety

Introduction

Data from study **GS-US-236-0112** is provided in support.

Safety assessments included monitoring of AEs and concomitant medications, clinical laboratory tests (chemistry, haematology, urinalysis, and pregnancy testing), 12-lead electrocardiograms (ECGs), Tanner stage assessments, and vital signs.

Blood was collected for analysis of serum bone biomarkers (collagen type 1 N- and C-telopeptides [N-telopeptide and C-telopeptide, respectively], osteocalcin, bone-specific alkaline phosphatase, parathyroid hormone (PTH), and 25-OH vitamin D). Dual-energy x-ray absorptiometry (DXA) of the spine and total-body-less-head (TBLH) was conducted to assess bone mineral density (BMD) because bone toxicity has been associated with TDF use.

The following renal laboratory parameters were assessed: serum creatinine, eGFR calculated using the Schwartz and modified Schwartz formulae, serum phosphorus, serum glucose, proteinuria by dipstick, urine protein to creatinine ratio (UPCR), urine retinol binding protein (RBP) to creatinine ratio, beta-2-microglobulin to creatinine ratio, ratio of maximum renal tubular phosphate reabsorption rate to glomerular filtration rate (TmP/GFR), fractional excretion of phosphate (FEPO4), and fractional excretion of uric acid (FEUA) because renal toxicity has been associated with TDF, and because COBI inhibits tubular secretion of creatinine, leading to an increase in serum creatinine and a decrease in eGFR without an effect on actual glomerular filtration rate in adults.

Neuropsychiatric events were evaluated as psychiatric disorders, such a depression, insomnia, abnormal dreams, suicidal ideation, suicide attempt, headache, and dizziness, are common in HIV-infected patients and have been associated with ART.

Patient exposure

The median (Q1, Q3) duration of exposure to study drug was 61.6 weeks (52.1, 96.3). At the time of the data cut for the interim Week 48 analysis, 30.0% of subjects had received STB for ≥ 96 weeks.

Adverse events

Most subjects (90.0%, 45 of 50 subjects) had at least 1 AE, the majority of which were Grade 1 or Grade 2 in severity. Grade 3 or Grade 4 AEs were reported for 2 subjects (4.0%). Ten subjects (20.0%) had an AE considered related to study drug by the investigator. A Grade 2 study drug-related AE was reported for 1 subject (2.0%). None of the study drug-related AEs were reported as Grade 3 or above.

The most common AEs were upper respiratory infection (28.0%, 14 subjects), headache (24.0%, 12 subjects), vomiting (18.0%, 9 subjects).

Adverse events related to study drug were reported for 10 subjects (20.0%). All study drug-related AEs were reported as Grade 1 in severity, except a Grade 2 study drug-related AE reported for 1 subject (2.0%). Nausea (6.0%, 3 subjects) and headache (8.0%, 4 subjects) were the most common study drug-related AEs, reported for at least 5% of subjects.

Table 20. GS-US-236-0112: Study Drug-Related Adverse Events (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term[a,b]	STB (N=50)
Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug	10 (20.0%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug by System Organ Class And Preferred Term	
Gastrointestinal disorders	6 (12.0%)
Nausea	3 (6.0%)
Diarrhoea	2 (4.0%)
Vomiting	2 (4.0%)
Abdominal pain	1 (2.0%)
Nervous system disorders	6 (12.0%)
Headache	4 (8.0%)
Dizziness	2 (4.0%)

Serious adverse event/deaths/other significant events

Four subjects (8.0%) had an SAE. No subject had a study drug-related SAE or an AE that led to study drug discontinuation, and there were no deaths. Acute kidney injury in 1 subject was noted as a clinically significant renal event, and disseminated tuberculosis in another subject, treated with ethambutol, isoniazid, levofloxacin, and pyrazinamide was noted as a (CDC) Class C AIDS-defining event. No SAE occurred in more than 1 subject, and none was considered related to study drug by the investigator.

Bone safety

No fracture events were reported.

Body Height

At baseline, the body-height Z-score of the safety analysis set was below that of the reference population: mean (SD) −0.85 (1.225); median (Q1, Q3) -0.82 (−1.76, −0.05). There were no notable changes in these values during the course of the study. At Week 48, changes from baseline in the safety analysis set (N = 48) were: mean (SD) −0.02 (0.230); median (Q1, Q3) −0.01 (−0.14, 0.09).

Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD

Table 21. GS-US-236-0112: Percentage Changes from Baseline in Spine and Total-Body-Less Head BMD (Spine and TBLH DXA Analysis Sets)

	Percentage Change from Baseline in BMD					
	Spine			TBLH		
Time Point	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Week 24	47	-0.964 (3.6551)	-0.985 (-3.571, 0.945)	49	-0.141 (2.1251)	-0.488 (-1.448, 0.852)
Week 48	46	0.676 (4.5255)	1.067 (-2.284, 3.341)	48	0.771 (2.6462)	0.431 (-0.817, 2.175)

Percentages of subjects with ≥ 4% decrease from baseline in spine and TBLH BMD at Weeks 24 and 48 were as follows:

- Spine: 10 of 47 subjects (21.3%) at Week 24 and 7 of 46 subjects (15.2%) at Week 48 (6 subjects had ≥ 4% decrease at both Weeks 24 and 48). (6 subjects had ⩾ 4% decrease at both Weeks 24 and 48). 3 of whom shifted from BMD status within the expected range for age to low BMD status (BMD Z-score ⩽ -2.0)

- TBLH: 1 of 49 subjects (2.0%) at Week 24 and 2 of 48 subjects (4.2%) at Week 48 (1 subject had ≥ 4% decrease at both Weeks 24 and 48). (1 subject had ⩾ 4% decrease at both Weeks 24 and 48).

Change from Baseline in Bone Mineral Density Z-scores

Table 22. GS-US-236-0112: Spine and Total-Body-Less-Head Height-age BMD Z-Scores at Baseline, and Change from Baseline at Weeks 24 and 48 (Spine and TBLH DXA Analysis Sets)

	Spine BMD Z-Score (Height-age[a])			TBLH BMD Z-Score (Height-age[a])		
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Baseline	38	0.00 (1.240)	0.09 (−0.97, 0.98)	39	−0.52 (1.027)	−0.67 (−1.36, 0.29)
Change from Baseline at:						
Week 24	38	−0.15 (0.290)	−0.14 (−0.31, −0.02)	39	−0.11 (0.139)	−0.10 (−0.21, 0.00)
Week 48	37	−0.09 (0.384)	−0.02 (−0.28, 0.14)	38	−0.12 (0.291)	−0.10 (−0.37, 0.07)

Five subjects showed a worsening from baseline (change from > -2 to ≤ -2) in their spine and/or

TBLH height-age BMD Z-scores at Week 24 and/or Week 48, as follows:

- Height-age TBLH BMD Z-score: 2 subjects at Week 24 and 3 subjects at Week 48 (1 subject had a worsening from baseline at both Weeks 24 and 48)

- Height-age spine BMD Z-score: 1 subject at both Weeks 24 and 48

Serum Bone Biomarkers

There were median percentage increases (> 10%) from baseline at Weeks 24 and 48 in N-telopeptide (15.9% and 19.2%), osteocalcin (31.74% and 25.53%), bone-specific alkaline phosphatase (13.22% and 15.59%), and PTH (14.6% and 40.8%).

Table 23. GS-US-236-0112: Change from Baseline in Serum Bone Biomarkers (Safety Analysis Set)

	STB		
	N	Median	Q1, Q3
N-telopeptide (nmol BCE/L)			
Baseline	49	27.7	20.5, 46.2
% Change at Week 24	46	15.9	-7.8, 36.4
% Change at Week 48	46	19.2	-14.8, 37.9
C-telopeptide (µg/L)			
Baseline	49	9.3	7.3, 11.1
% Change at Week 24	48	6.4	-13.1, 22.0
% Change at Week 48	46	-2.6	-17.3, 19.7
Osteocalcin (ng/mL)			
Baseline	50	45.89	32.06, 78.58
% Change at Week 24	48	31.74	9.17, 58.46
% Change at Week 48	47	25.53	-0.56, 45.05
Bone-Specific Alkaline Phosphatase (µg/L)			
Baseline	50	29.16	19.74, 44.75
% Change at Week 24	49	13.22	1.92, 41.17
% Change at Week 48	47	15.59	-9.74, 44.17
PTH (pg/mL)			
Baseline	48	32.0	24.0, 42.6
% Change at Week 24	46	14.6	-5.5, 66.9
% Change at Week 48	46	40.8	-4.7, 98.7
25-OH Vitamin D (ng/mL)			
Baseline	50	23.3	21.1, 28.4
% Change at Week 24	49	5.0	-13.1, 34.5
% Change at Week 48	47	0.0	-11.1, 18.6

Renal Safety

There were no reported cases of proximal renal tubulopathy or Fanconi syndrome. One clinically significant renal SAE was reported. This was acute kidney injury secondary to dehydration from Shigella dysentery, with onset on Day 275 and duration of 6 days. The event was considered unrelated to study drug by the investigator, and study drug dosing continued. Serum creatinine at baseline was 0.90 mg/dL; values on Days 282, 337, and 366, were 1.19, 1.23, and 0.92 mg/dL, respectively. Estimated GFR (Schwartz) at baseline was 121 mL/min/1.73 m2; values at Days 282, 337, and 366 were 92, 89, and 119 mL/min/1.73 m2, respectively. No graded abnormality of serum creatinine was reported. Intermittent Grade 1 proteinuria was noted at Days 113, 144, 170, 282, 337 (Week 48), and 366. Serum phosphate and urine glucose were within normal reference ranges at all visits. The absence of persistent renal abnormalities suggested no proximal renal tubulopathy.

Neuropsychiatric Events

Seventeen subjects had neuropsychiatric events, all of which were Grade 1 or 2 in severity, and non-serious. The most common neuropsychiatric event was headache (12 subjects). The remaining events

were: dizziness (4 subjects), affective disorder (1 subject), sleep disorder (1 subject), depression (1 subject), and somnolence (1 subject). Additionally, 1 subject, with a medical history of suicide attempt, had an SAE of suicidal behaviour.

Laboratory findings

All 50 subjects had at least 1 treatment-emergent laboratory abnormality reported during the study. The majority of abnormalities were Grade 1 or Grade 2 in severity. Excluding Grade 3 hematuria detected by non-quantitative dipstick analysis and hematuria following quantitative analysis reported for female subjects, Grade 3 or Grade 4 laboratory abnormalities were reported for 2 subjects.

Transient Grade 3 increased aspartate aminotransferase (AST) and Grade 4 increased creatine kinase at Week 40 were reported for 1 subject, who had a tendency toward increased creatine kinase values from screening onward. Grade 3 increased creatine kinase at Weeks 16 and 40 were reported for 1 subject, who also had Grade 1 increased AST at the same time points. The abnormalities were not reported as AEs.

Liver-Related Laboratory Tests

No subjects had elevations > 3 × ULN in AST or ALT in addition to > 2 × ULN in total bilirubin and < 2 × ULN in alkaline phosphatase. No Hy's Law cases were identified.

Renal Laboratory Parameters

Serum Creatinine

Increases in median values for serum creatinine were noted as early as Week 2 (after which they generally stabilised and were non-progressive through Week 48. Median (Q1, Q3) baseline serum creatinine and changes from baseline were as follows:

- Baseline: 0.77 (0.62, 0.89) mg/dL
- Week 2 change from baseline: 0.08 (0.02, 0.14) mg/dL
- Week 24 change from baseline: 0.08 (0.01, 0.14) mg/dL
- Week 48 change from baseline: 0.11 (0.05, 0.16) mg/dL

One subject had a Grade 1 serum creatinine laboratory abnormality

Estimated Glomerular Filtration Rate

Decreases in eGFR using the Schwartz formula were noted as early as Week 2, after which they generally stabilised and were non-progressive through Week 48. Median (Q1, Q3) baseline eGFR using the Schwartz formula and changes from baseline were as follows:

- Baseline: 139.5 (128.0, 161.0) mL/min/1.73 m2
- Week 2 change from baseline: −15.0 (−21.0, −3.0) mL/min/1.73 m2
- Week 24 change from baseline: −14.0 (−25.0, −1.0) mL/min/1.73 m2
- Week 48 change from baseline: −15.0 (−29.5, −8.0) mL/min/1.73 m2

When eGFR was calculated using the modified Schwartz formula, a decrease from baseline was also seen at Week 2, which subsequently stabilized and was nonprogressive, although the absolute values for baseline eGFR and the magnitude of the median of change from baseline at Week 2 were numerically smaller than for the Schwartz formula. Median (Q1, Q3) baseline eGFR using the modified Schwartz formula and changes from baseline were as follows:

- Baseline: 97.8 (94.5, 111.2) mL/min/1.73 m2
- Week 2 change from baseline: -7.4 (−11.9, −0.7) mL/min/1.73 m2
- Week 24 change from baseline: −4.2 (−9.9, 0.8) mL/min/1.73 m2
- Week 48 change from baseline: -3.6 (−9.2, 2.7) mL/min/1.73 m2

Glycosuria
The only urine glucose abnormality reported was Grade 2 urine glucose in 1 subject. The subject had Grade 1 urine glucose on Day 225, which increased to Grade 2 on Day 421 and was ongoing at Day 684 (trace), all while normo-glycemic. The subject also had concurrent Grade 1 to 2 proteinuria

Treatment-Emergent Proteinuria by Urinalysis (Dipstick)

At baseline, 4 of 50 subjects (8.0%) had proteinuria as assessed by dipstick analysis (all Grade 1). Post-baseline, Grade 1 or Grade 2 proteinuria, generally isolated and transient, was reported for 22 subjects (44%; 15 subjects Grade 1, 7 subjects Grade 2).

Proteinuria by Quantitative Assessment

Generally, there was an increase from baseline in proteinuria, as assessed by UPCR. Median (Q1, Q3) baseline UPCR and percentage changes from baseline were as follows:

- Baseline: 51.20 (30.94, 80.36) mg/g
- Percentage change from baseline at Week 48: 8.70% (−20.64%, 52.06%)

Urine Retinol Binding Protein to Creatinine Ratio and Beta-2 Microglobulin to Creatinine Ratio

There was an increase from baseline in urine RBP to creatinine ratio. Median (Q1, Q3) baseline urine RBP to creatinine ratio and percentage changes from baseline were as follows:
- Baseline: 65.94 (44.35, 90.67) µg/g
- Percentage change from baseline at Week 48: 14.21% (−15.12%, 61.13%)

Generally, urine beta-2 microglobulin to creatinine ratio decreased from baseline. Median (Q1, Q3) baseline urine beta-2 microglobulin to creatinine ratio and percentage changes from baseline were as follows:

- Baseline: 114.7 (94.3, 214.5) µg/g
- Percentage change from baseline at Week 48: −23.7% (−38.7%, 51.3%)

Discontinuation due to adverse events

No subject discontinued due to an adverse event.

Post marketing experience

The MAH did a cumulative search up to 31 May 2016 of the Gilead Drug Safety and Public Health (DSPH) safety database for STB and paediatric (age < 18 years) cases to assess the safety profile of STB in paediatric patients. A total of 11 post-marketing paediatric cases were retrieved:

7 adolescent cases (age 12 to 18 years), 2 child cases (age < 12 years), and 2 non-valid cases (missing identifiers and no reported event, respectively). One of the non-valid cases described a child (age and gender unspecified) with non-serious events of renal disorder and unspecified abnormal laboratory test.

A total of 18 events (3 serious, 15 non-serious) were reported in the 9 medically confirmed, spontaneous cases. One case included serious events of blood creatinine increased and glomerular filtration rate decreased. Another case reported neutropenia (serious) and off-label use (non-serious); the reporting physician noted that neutropenia was from STB. The remaining 7 spontaneous cases reported the following non-serious events: off-label use (n = 4), neutropenia (n = 1), transaminases increased (n = 1), rash (n = 1), vomiting (n = 1), intentional product misuse (n = 1), musculoskeletal pain (n = 1), eye swelling (n = 1), pyrexia (n = 1), pruritis (n = 1), and drug interaction (n = 1).

Overall, the majority of reported events among STB paediatric cases were non-serious (83%). Events of blood creatinine increased, glomerular filtration rate decreased, neutropenia, transaminases increased, rash, vomiting, and pruritis were consistent with the safety profile of STB in adults and are referenced in the STB core safety information document. The reported events of eye swelling, musculoskeletal pain, and pruritus in 1 patient were confounded by the patient's underlying syphilis and concomitant medications (Bactrim and penicillin). No safety issues specific to paediatric patients were identified for STB based on post-marketing data from the Gilead DSPH safety database.

Discussion on clinical safety

The safety data in this application are derived from study GS-US-236-0112. It would appear that most subjects (90.0%, 45 of 50 subjects) reported one or more adverse events the majority of which were Grade 1 or Grade 2 in severity. Ten subjects (20.0%) had an AE considered related to study drug by the investigator. There were no serious treatment adverse events. The most commonly reported treatment related AEs were headache (24.0%, 12 subjects), and vomiting (18.0%, 9 subjects). No subject discontinued study drug due to an AE and there were no deaths.

Adverse events of special interest for STB were renal events, bone fractures, and neuropsychiatric events. There were no reported cases of proximal renal tubulopathy or Fanconi's syndrome. One subject had acute kidney injury of 6 days duration secondary to dehydration from Shigella dysentery which was considered to be a serious adverse event unrelated to study drug by the investigator; study drug dosing continued. No subject had a fracture. The most common neuropsychiatric event was headache.

Renal laboratory assessments showed changes consistent with the inhibitory effects of COBI on renal tubular secretion of creatinine. An increase from baseline in serum creatinine and a reduction in eGFR calculated using the Schwartz formula was noted as early as Week 2. These changes subsequently stabilised. Only one subject had a Grade 1 serum creatinine laboratory abnormality. There was no adverse event related and no AEs of decreased eGFR were reported. However Proteinuria (Grade 1 or Grade 2) was reported in 22 subjects (44%).

Seven subjects (15.2%) at Week 48 had a $\geq$ 4% decrease from baseline in spine BMD. Two subjects (4.2%) at Week 48 had a $\geq$ 4% decrease from baseline in TBLH BMD (1 subject had $\geq$ 4% decrease at both Weeks 24 and 48). There were median percentage increases (> 10%) from baseline at Weeks 24 and 48 in N-telopeptide (15.9% and 19.2%), osteocalcin (31.74% and 25.53%), bone-specific alkaline

phosphatase (13.22% and 15.59%), and PTH (14.6% and 40.8%). These results suggest that no significant change occurred from baseline in height-age spine and TBLH BMD Z-scores at Week 48.

The most common neuropsychiatric event was headache which occurred in 12 subjects.

Overall, there are no new safety concerns regarding use in the paediatric population when compared to adults

Additional expert consultations

None

Assessment of paediatric data on clinical safety

As above

Conclusions on clinical safety

The safety profile of the single entities for Stribild and Stribild as a FDC have previously been characterised and are well-known. The main concerns relate to renal and bone events associated with TDF use and neuropsychiatric events are associated with HIV-infected patients and ART use. Renal and bone safety were specifically studied. The results showed an increase from baseline in serum creatinine and a reduction in eGFR in terms of renal events. 44% of subjects had Grade 1 or Grade 2 proteinuria. A decrease from baseline in mean spine and TBLH BMD was seen at Week 24 but at week 48, it appeared that there was an increase from baseline. Notably the BMD status for 3 subjects shifted from within the expected range for age to low BMD status (BMDZ-score $\leq$ -2.0).

Overall the results are considered to be consistent with what is known regarding the single entities in particular TDF and also for COBI which is known to inhibit tubular excretion of creatinine. There does not appear to be any new issue concerning use in adolescents when compared to adults. It should however be emphasised that the number of adolescents studied to date is limited; a fact reflected in the RMP.

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Direct Healthcare Professional Communication

Not applicable.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be

submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

Safety concerns

Modifications are highlighted in bold.

	Safety Concerns for STB	Attributable Component(s) of STB
Important Identified Risks	Renal toxicity	TDF
	Bone events due to proximal renal tubulopathy/loss of BMD	TDF
	Post-treatment hepatic flares in HIV/HBV coinfected patients	FTC, TDF
	Interaction with didanosine	TDF
	Pancreatitis	TDF
	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness	EVG
	Concurrent use of drugs whose coadministration with STB is contraindicated	COBI, EVG
Important Potential Risks	Overdose (occurring through accidental concurrent use of STB with any other TDF-containing product)	TDF
Missing Information	Long-term safety information	STB
	Safety in children **<12 years of age**	EVG, COBI, TDF
	Safety in elderly patients	EVG, COBI, FTC, TDF
	Safety in pregnancy	EVG, COBI, FTC, TDF
	Safety in lactation	EVG, COBI, FTC, TDF
	Safety in patients with renal impairment	STB (as a STR), COBI, TDF
	Safety in patient with severe hepatic impairment (CPT score C)	EVG, COBI
	Drug-drug interactions	COBI
	Safety in patients with cardiac conduction disorders	COBI

Pharmacovigilance plan

Modifications are highlighted in bold.

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Interventional clinical studies (Category 3)				
GS-US-236-0128 A Randomized, Double-Blind, Phase 3B Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/ Emtricitabine/ Tenofovir Disoproxil Fumarate Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/ Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Women	To evaluate the safety of STB in HIV-1 infected women To evaluate changes in BMD from baseline in in a substudy.	*Important identified risks*: Renal toxicity (TDF) Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Started	Final Week 96 report submitted 22 December 2016
GS-US-236-0112 **A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine /Tenofovir Disoproxil Fumarate Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents**	**To evaluate the safety and antiviral activity in pediatric subjects from 12 to <18 years of age**	***Important missing information:*** **Long-term safety**	**Started**	**Final report Q2 2018**
Non-interventional studies (Category 3)				
GS-EU-236-0141 A Prospective, Observational Drug Utilization Study of Stribild® in Adults With HIV-1 Infection	To collect 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	*Important identified risks*: Renal toxicity (TDF)	Started	March 2016 (Interim report; submitted) October 2017 (Final report)
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to EVG, COBI, FTC and TDF during pregnancy	*Missing information*: Safety in pregnancy (EVG, COBI, FTC, TDF)	Started	In the STB PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)
Other data (Category 3)				
Monitoring of reversibility of renal tubulopathy in clinical trials	To collect information on the reversibility of renal tubulopathy following the discontinuation of tenofovir DF in adult and pediatric patients	*Important identified risk*: Renal toxicity (TDF)	Ongoing activity	Ongoing activity

Risk minimisation measures

There were no major changes in the RMM table apart the below:

Safety in children **<12 years of age.**

The Stribild renal brochure has been updated to include key safety messages for adolescents aged 12 to < 18 years. (see below, section recommendations, additional RMMs)

Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated as shown below (inserted text underlined in blue and deleted text as strike-through). The full SmPC with annotated changes include revisions requested by the CHMP. The Package Leaflet has been updated accordingly, together with Annex II.

In addition, the CHMP considered acceptable to include supportive data from paediatric studies conducted with Emtriva and Viread in the Stribild SmPC. The data included are in line with the approved Truvada SmPC (EMEA/H/C/000594/II/0131) and affect sections 4.4, 4.8 and 5.1.

SmPC

4.1 Therapeutic indications

Stribild is indicated for 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 any of the three antiretroviral agents in Stribild (see sections 4.2, 4.4 and 5.1).

Stribild is also indicated for the treatment of HIV-1 infection in adolescents aged 12 to < 18 years weighing ≥ 35 kg who are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil fumarate (TDF) (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

~~One tablet to be taken once daily with food (see section 5.2)~~

Adults and adolescents aged 12 years and older weighing at least 35 kg: One tablet, once daily with food

If the patient misses a dose of Stribild within 18 hours of the time it is usually taken, the patient should take Stribild with food as soon as possible and resume the normal dosing schedule. If a patient misses a dose of Stribild by more than 18 hours and it is almost time for the next dose, the patient should not take the missed dose and simply resume the usual dosing schedule.

If the patient vomits within 1 hour of taking Stribild another tablet should be taken.

Special populations

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).

Adults with r~~R~~enal 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.

Paediatric patients with renal impairment

Use of Stribild is not recommended in paediatric patients under the age of 18 years with renal impairment (see section 4.4).

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).

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 of hepatitis (see section 4.4).

Paediatric population

The safety and efficacy of Stribild in children ~~aged 6 to less than 18~~ under the age of 12 years or weighing < 35 kg have not ~~yet~~ been established (see section 5.2). ~~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~~

Method of administration

Stribild should be taken orally, once daily with food (see section 5.2). The film-coated tablet should not be chewed or crushed.

4.4 Special warnings and precautions for use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

~~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 (see section 4.5).~~

~~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, or with other medicinal products containing tenofovir alafenamide.~~

~~Contraception requirements~~

~~Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 µg ethinylestradiol and containing norgestimate as the progestagen or should use an alternative reliable method of contraception (see sections 4.5 and 4.6). Co-administration of Stribild with oral contraceptives containing progestagens other than norgestimate has not been studied and, therefore, should be avoided.~~

~~Opportunistic infections~~

~~Patients receiving Stribild or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.~~

~~Effects on r~~Renal and bone effects ~~function~~ in adults

Renal effects

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.

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).

Renal monitoring

Before initiating treatment with Stribild

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.

During treatment with Stribild

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 a more frequent monitoring of renal function is required.

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.

See also under *Co-administration of other medicinal products* below.

Renal management

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. Interrupting treatment with Stribild should also be considered in case of progressive decline of renal function when no other cause has been identified.

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, vancomycin, cidofovir or interleukin 2 (also called aldesleukin) (see section 4.5).If concomitant use of Stribild and nephrotoxic agents is unavoidable, renal function must be monitored weekly.~~

~~Cases of acute renal failure after initiation of high dose or multiple non steroidal anti inflammatory drugs~~

~~(NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If Stribild is co-administered with an NSAID, renal function should be monitored adequately.~~

~~Treatment switching~~

~~When switching patients who are CYP2B6 poor metabolisers from an efavirenz containing regimen to Stribild, there is a potential for lower elvitegravir exposure due to prolonged CYP3A induction by efavirenz. Monitoring of viral load is recommended for these patients during the first month after switching treatment to Stribild.~~

[…]

Renal and bone effects in the paediatric population

There are uncertainties associated with the long-term effects of tenofovir disoproxil fumarate bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.

Renal effects
Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to < 12 years in a clinical study of tenofovir disoproxil fumarate (GS-US-104-0352) (see sections 4.8 and 5.1).

Renal monitoring
Renal function (creatinine clearance and urine glucose and urine protein) should be evaluated prior to treatment initiation, and creatinine clearance, serum phosphate, urine glucose and urine protein should be monitored during treatment as in HIV-1 infected adults (see above).

Renal management
If serum phosphate is confirmed to be < 0.96 mmol/L (3.0 mg/dL) in any paediatric patient receiving Stribild, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of treatment. Interrupting treatment with Stribild should also be considered in case of progressive decline of renal function when no other cause has been identified. As in adults, adolescents 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 (see above).

Co-administration and risk of renal toxicity
The same recommendations apply as in adults (see Co-administration of other medicinal products below).

Renal impairment
The use of Stribild is not recommended in paediatric patients with renal impairment (see section 4.2). Stribild should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during Stribild therapy.

Bone effects
Tenofovir disoproxil fumarate may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).

In a clinical study of HIV-1-infected, treatment-naïve patients aged 12 to <18 years (N=50), small decreases in mean BMD Z-scores were observed following treatment with Stribild (see section 4.8).

If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.

Patients with HIV and hepatitis B or C virus co infection

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for

severe and potentially fatal hepatic adverse reactions.

Physicians should refer to current HIV treatment guidelines for the optimal management of HIV infection in patients co infected with hepatitis B virus (HBV).

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 administered concomitantly with other medicinal products containing tenofovir disoproxil (as fumarate), lamivudine or adefovir dipivoxil used for the treatment of hepatitis B virus infection.

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.

~~Use with certain hepatitis C virus antiviral agents~~

~~Co-administration of tenofovir disoproxil fumarate with ledipasvir/sofosbuvir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of ledipasvir/sofosbuvir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir with Stribild should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving Stribild concomitantly with ledipasvir/sofosbuvir should be monitored for adverse reactions related to tenofovir disoproxil fumarate.~~

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).

[…]

Opportunistic infections

Patients receiving Stribild or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to CART. Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

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 (see section 4.5).

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, or with other medicinal products containing tenofovir alafenamide.

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, vancomycin, cidofovir or interleukin 2 (also called aldesleukin) (see section 4.5). If concomitant use of Stribild and nephrotoxic agents is unavoidable, renal function must be monitored weekly.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If Stribild is co-administered with an NSAID, renal function should be monitored adequately.

Contraception requirements

Female patients of childbearing potential should use either a hormonal contraceptive containing at least 30 µg ethinylestradiol and containing norgestimate as the progestagen or should use an alternative reliable method of contraception (see sections 4.5 and 4.6). Co-administration of Stribild with oral contraceptives containing progestagens other than norgestimate has not been studied and, therefore, should be avoided.

Use with certain hepatitis C virus antiviral agents

Co-administration of tenofovir disoproxil fumarate with ledipasvir/sofosbuvir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil fumarate and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil fumarate in the setting of ledipasvir/sofosbuvir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir with Stribild should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving Stribild concomitantly with ledipasvir/sofosbuvir should be monitored for adverse reactions related to tenofovir disoproxil fumarate.

~~Treatment switching in adults and paediatric patients~~

~~When switching patients who are CYP2B6 poor metabolisers from an efavirenz containing regimen to Stribild, there is a potential for lower elvitegravir exposure due to prolonged CYP3A induction by efavirenz. Monitoring of viral load is recommended for these patients during the first month after switching treatment to Stribild.~~

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions considered possibly or probably related to Stribild in clinical studies of treatment-naïve adult patients were nausea (16%) and diarrhoea (12%) (pooled data from Phase 3 clinical studies GS US 236 0102 and GS US 236 0103, through 144 weeks).

The safety profile of Stribild in virologically-suppressed adult patients derived from Studies GS US 236 0115, GS US 236 0121 and GS US 236 0123 is consistent with the safety profile of Stribild in treatment-naïve adult patients through Week 48. The most frequently reported adverse reactions to Stribild in clinical studies of virologically-suppressed adult patients were nausea (3% in Study GS US 236 0115 and 5% in Study GS US 236 0121) and fatigue (6% in Study GS US 236 0123).

[…]

Paediatric population

Studies with Stribild

The safety of Stribild in 50 HIV-1-infected, treatment-naïve paediatric patients aged 12 to <18 years was evaluated through 48 weeks in an open-label clinical study (GS-US-236-0112, see section 5.1). In this study, the safety profile of Stribild was similar to that in adults (see section 4.8, *Tabulated summary of adverse reactions*). Among the 50 paediatric patients receiving Stribild, mean BMD increased from baseline to Week 48, +0.68% for lumbar spine and +0.77% for total body less head. Mean changes from baseline BMD Z-scores (height-age adjusted) were −0.09 for lumbar spine and −0.12 for total body less head at Week 48.

Studies with emtricitabine

Assessment of adverse reactions related to emtricitabine is based on experience in three paediatric studies (n = 169) where treatment-naïve (n = 123) and treatment-experienced (n = 46) paediatric HIV

infected patients aged 4 months to 18 years were treated with emtricitabine in combination with other antiretroviral agents. In addition to the adverse reactions reported in adults, anaemia (9.5%) and skin discolouration (31.8%) occurred more frequently in clinical trials in paediatric patients than in adults (see section 4.8, *Tabulated summary of adverse reactions*).

Studies with tenofovir disoproxil fumarate

Assessment of adverse reactions related to tenofovir disoproxil fumarate is based on two randomised trials (studies GS-US-104-0321 and GS-US-104-0352) in 184 HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks (see section 5.1). The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 *Tabulated summary of adverse reactions* and 5.1).

Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents (aged 12 to <18 years), the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children (aged 2 to 15 years), the BMD Z-scores observed in subjects who switched to tenofovir disoproxil fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).

In study GS-US-104-0352, 89 paediatric patients with a median age of 7 years (range 2 to 15 years) were exposed to tenofovir disoproxil fumarate for a median of 313 weeks. Four of the 89 patients discontinued due to adverse reactions consistent with proximal renal tubulopathy. Seven patients had estimated glomerular filtration rate (GFR) values between 70 and 90 mL/min/1.73 m^2. Among them, two patients experienced a clinically meaningful decline in estimated GFR during therapy which improved after discontinuation of tenofovir disoproxil fumarate.

Insufficient safety data are available for children below 12 ~~18~~years of age. Stribild is not recommended in this population (see section 4.2).

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).

Patients with renal impairment

Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any adult ~~patient~~ with renal impairment treated with Stribild (see sections 4.2, 4.4 and 5.2). The use of Stribild is not recommended in paediatric patients with renal impairment (see sections 4.2 and 4.4).

[…]

5.1 Pharmacodynamic properties

[…]

Clinical experience
The efficacy of Stribild in HIV-1 infected treatment-naïve adult patients is based on the analyses of 144-week data from 2 randomised, double-blinded, active-controlled, Phase 3 studies, GS-US-236-0102 and GS-US-236-0103 (n = 1,408). The efficacy of Stribild in HIV-1 infected virologically-suppressed adult patients is based on the analyses of 48-week data from two randomised, open-label studies (Studies GS-US-236-0115 and GS-US-236-0121) and a single group open-label study (Study GS-US-236-0123) (n = 910; 628 receiving Stribild).

Treatment-naïve HIV-1 infected adult patients

[…]

Paediatric population

Studies with Stribild

The efficacy and safety of Stribild in HIV-1-infected, treatment-naïve paediatric patients aged 12 to less than 18 years is based on the analyses of 48-week data from the single-group, open-label study GS-US-236-0112 (N=50).Mean age was 15 years (range, 12−17), 70% were male, 68% black, 28% Asian. At baseline, mean plasma HIV-1 RNA was 4.60 $\log_{10}$ copies/mL, mean CD4+ cell count 399 cells/mm^3 (range, 133−734), and mean CD4+% 20.9% (range, 4.5%−41.1%). Twenty percent had baseline plasma HIV-1 RNA >100,000 copies/mL.

At Week 48, 44 of 50 (88%) adolescent patients treated with Stribild achieved HIV-1 RNA <50 copies/mL and 4 achieved HIV-1 RNA ≥50 copies/mL; 1 patient discontinued study drug, and 1 had no virologic data at Week 48. The mean decrease in HIV-1 RNA was −3.16 $\log_{10}$ copies/mL, and the mean increase in CD 4+ cell count was 229 cells/mm^3. No emergent resistance to Stribild was detected through Week 48.

Studies with emtricitabine

In infants and children older than 4 months, the majority of patients taking emtricitabine achieved or maintained complete suppression of plasma HIV-1 RNA through 48 weeks (89% achieved ≤ 400 copies/ml and 77% achieved ≤ 50 copies/ml).

Studies with tenofovir disoproxil fumarate

In study GS-US-104-0321, 87 HIV-1-infected treatment experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks. Due to limitations of the study, a benefit of tenofovir disoproxil fumarate over placebo was not demonstrated based on plasma HIV-1 RNA levels at week 24.

In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.

In study GS-US-104-0352, 97 treatment experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks. At week 48, 83% of patients in the tenofovir disoproxil fumarate treatment group and 92% of patients in the stavudine or zidovudine treatment group had HIV 1 RNA concentrations < 400 copies/mL. The difference in the proportion of patients who maintained < 400 copies/mL at week 48 was mainly influenced by the higher number of discontinuations in the tenofovir disoproxil fumarate treatment group. When missing data were excluded, 91% of patients in the tenofovir disoproxil fumarate treatment group and 94% of patients in the stavudine or zidovudine treatment group had HIV 1 RNA concentrations < 400 copies/mL at week 48.

Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.

In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil fumarate discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil fumarate exposure 104 weeks).

~~The European Medicines Agency has deferred the obligation to submit the results of studies with Stribild in one or more subsets of the paediatric population in treatment of HIV-1 infection~~

The safety and efficacy of Stribild in children under the age of 12 years have not been established (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

[…]

Paediatric population

Exposures of elvitegravir and tenofovir in paediatric patients aged 12 to <18 years who received Stribild in GS-US-236-0112 were increased by 30% and 37% respectively, when compared with historical adult controls. Tenofovir exposures were in the range of those observed in TDF-containing boosted-protease inhibitor regimens. Exposures of cobicistat and emtricitabine in paediatric patients aged 12 to <18 years were similar to exposures achieved in adults.
The pharmacokinetics of elvitegravir or cobicistat in paediatric subjects <12 years of age have not been fully established.

~~In general, elvitegravir pharmacokinetics in paediatric patients (12 to < 18 years of age) and emtricitabine pharmacokinetics in children (aged 4 months to 18 years of age) are similar to those seen in adults. Tenofovir exposure achieved in 8 paediatric patients (12 to < 18 years of age) receiving oral daily doses of tenofovir disoproxil fumarate 300 mg (tablet) was similar to exposures achieved in adults receiving once daily doses of 300 mg.~~

The Package Leaflet has been updated accordingly.

User consultation

Not applicable.

Benefit-Risk Balance

Therapeutic Context

Disease or condition

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 37 million people infected worldwide, including more than 3.2 million children under 15 years of age (Joint United Nations Programme on HIV/AIDS [UNAIDS] 2014, UNAIDS 2016). In the US, an estimated 7352 diagnoses of HIV-1 infection were reported in 2013, of which an estimated 2095 were in individuals ≤ 19 years of age (91% in adolescents 13 to 19 years), indicating a continuous prevalence of HIV-1 infection in US pediatric and adolescent populations (Centers for Disease Control [CDC] 2015). In the EU and European Economic Area, 29,381 newly diagnosed cases of HIV-1 infection were reported in 2012, 10.6% of which were in young people 15 to 24 years of age (European Centre for Disease Prevention and Control et al 2013).

Available therapies and unmet medical need

Standard of care for the treatment of HIV-1 infection uses combination ART to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. Current treatment guidelines from the European AIDS Clinical Society suggest that initial therapy for ART-naive HIV-infected patients consist of 2 N[t]RTIs and either a nonnucleoside reverse transcriptase inhibitor (rilpivirine), a boosted protease inhibitor (darunavir),or an INSTI (COBI-boosted EVG, raltegravir or dolutegravir).

The pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of ART are similar between HIV-infected adult and pediatric patients. Adult guidelines for ART are usually appropriate for post-pubertal adolescents because the majority of adolescents are infected with HIV-1 sexually or through injection drug use during adolescence, and follow a clinical course that is more similar to that of adults than to that of adolescents infected earlier in life. However, there are some important and unique issues for HIV-infected infants, children and adolescents. Importantly, it needs to be considered that processes involved in growth and development during childhood and adolescence can affect the adverse event (AE) profile of drugs, and that developmental changes associated with aging and growth are often not linear. Treatment adherence is often particularly problematic for adolescents. Specific adherence challenges include pill burden, lifestyle issues (e.g. not carrying medication; change in schedule), denial and fear of their HIV-1 infection, distrust of healthcare workers, misinformation about HIV-1, and a lack of knowledge about the availability and effectiveness of ART. Poor adherence to HIV-1 treatment regimens can lead to sub-therapeutic ARV drug levels, which can increase the risk of drug resistance and virologic failure. Once-daily, single-tablet regimens have been shown to provide increased adherence and improved clinical and virologic outcomes in adults.

Main clinical study

Stribild is a fixed dose combination of EVG, COBI and TDF which offers convenience in terms of reduced pill burden. This variation concerns an application to extend the use of Stribild to include the treatment of HIV-1 infected adolescent patients 12 to < 18 years of age and weighing ≥ 35 kg. The MAH acknowledges the important and unique issues relating to HIV-infected infants, children, and adolescents; in particular with reference to treatment adherence. The MAH considers therefore that STB may be a potential option for adolescent patients. For this current application, pharmacokinetic (PK), safety, and efficacy data through 48 weeks of treatment have been presented for ART-naive, HIV-infected adolescent subjects in Study **GS-US-236-0112.**

Subjects enrolled in this study were HIV-1 infected, ART-naive adolescents, 12 to < 18 years of age, weight ≥ 35 kg, with plasma HIV-1 RNA levels ≥ 1,000 copies/mL, CD4 cell counts > 100 cells/µL, and estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73m2 (as calculated using the Schwartz formula) at screening, with no prior use of any approved or experimental anti-HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission), and sensitivity to FTC and TDF as demonstrated by HIV-1 genotyping at screening. Subjects received open-label treatment for 48 weeks. Of 56 screened subjects, 50 were enrolled into the study and received at least 1 dose of STB.

As of the data cut date for the interim Week 48 analysis, 96.0% (48 subjects) had completed study treatment in the main phase of the study, and 98.0% (49 subjects) had completed the main phase of the study.

Favourable effects

The results of study **GS-US-236-0112** demonstrate that the virologic success rate was 88.0% (44 of 50 subjects) at both Weeks 24 and 48 in adolescent subjects receiving STB, when assessed using the FDA-defined snapshot algorithm with a cut-off of HIV-1 RNA < 50 copies/mL

Six subjects did not achieve virologic success, with 5 subjects confirmed as virologic failures at Week 48; 4 of these subjects had HIV-1 RNA ≥50 copies/mL at Week 48, and 1 subject discontinued study drug due to noncompliance. The mean increase from baseline in CD4% count was 7.4% at week 24 and 8.1% at week 48. These results are indicative of the efficacy of Stribild in the treatment of HIV-1 infected, ART-naïve adolescents.

Uncertainties and limitations about favourable effects

Study **GS-US-236-0112** was an open-label, non-comparative study which included a limited number of subjects. However, this is not considered to be a significant issue as the data from the study are indicative of efficacy in adolescents and the studies conducted with adults are also demonstrative of efficacy and it is known that the pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of ART are similar between HIV-infected adult and paediatric patients.

Unfavourable effects

Stribild was well tolerated by the 50 HIV-infected, ART-naive adolescents in this study, through a median duration of exposure of 61.6 weeks. The most commonly reported treatment related AEs were headache in 24.0% of subjects and vomiting in 18.0% of subjects.

There is a known risk of adverse renal effects associated with TDF. An increase from baseline in serum creatinine and a reduction in eGFR calculated using the Schwartz formula was noted as early as Week 2. However, these changes subsequently stabilised. Proteinuria (Grade 1 or Grade 2) was reported for 22 subjects (44%).

In terms of bone effects, ten of 47 subjects (21.3%) at Week 24 and 7 of 46 subjects (15.2%) at Week 48 had a ≥ 4% decrease from baseline in spine BMD (6 subjects had ≥ 4% decrease at both Weeks 24 and 48). One of 49 subjects (2.0%) at Week 24 and 2 of 48 subjects (4.2%) at Week 48 had a ≥ 4% decrease from baseline in TBLH BMD (1 subject had ≥ 4% decrease at both Weeks 24 and 48).

Overall, among the paediatric patients receiving Stribild, mean BMD increased from baseline to Week 48, +0.68% for lumbar spine and +0.77% for total body less head. Mean changes from baseline BMD Z-scores (height-age adjusted) were −0.09 for lumbar spine and −0.12 for total body less head at Week 48.

These effects are consistent with previous experience with tenofovir.

Uncertainties and limitations about unfavourable effects

The unfavourable effects are considered to be consistent with what is known regarding the single entities in particular TDF and also for COBI which is known to inhibit tubular excretion of creatinine. There does not appear to be any new issue concerning use in adolescents when compared to adults. It is considered however that the uncertainty regarding the estimation of the actual risk of Stribild-associated renal injury and its reversibility after discontinuation in adults is the same for adolescents.

It is also pertinent to note that the number of adolescents studied to date is limited.

Effects Table

Table 1. Effects Table for Stribild (extension of indication):

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Efficacy endpoint	Percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at week 48	%	Stribild 88%	Uncontrolled	Open-labelled study	Study **GS-US-236-0112**
Efficacy endpoint	Change from baseline in plasma HIV-1 RNA (log10 copies/mL) at Week 48	log10 copies/mL	−3.16 (0.705) log10 copies/mL	Uncontrolled	Open-labelled study	Study **GS-US-236-0112**
Efficacy endpoint	Change from baseline in CD4 cell count (cells/µL) and percentage at Week 48	log10 copies/mL	8.1% (5.34%)	Uncontrolled	Open-labelled study	Study **GS-US-236-0112**
Unfavourable Effects						
Safety	Mean changes (SD) from baseline in spine BMD at week 48	Height-age adjusted Z-score	-0.09 (0.385)			
	Mean changes (SD) from baseline in TBLH BMD at week 48	Height-age adjusted Z-score	-0.12 (0.291)			
	Proteinuria (Grade 1 or 2)	%	44% of subjects			

Benefit-risk

This submission provides PK, safety and efficacy data for ART-naive, HIV-infected adolescent subjects in Study **GS-US-236-0112** through 48 weeks of treatment with STB.

These data collectively support an extension to the approved prescribing information for STB to include adolescent patients 12 to < 18 years of age weighing ≥ 35 kg and demonstrate a favourable benefit: risk profile for STB for the treatment of HIV-1 infection in adolescents.

Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include the treatment of HIV 1 infection in adolescents aged 12 to < 18 years weighing ⩾ 35 kg without known mutations associated with resistance to any of the three antiretroviral agents in Stribild, and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil fumarate (TDF); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on pharmacokinetics, safety and efficacy data through 48 weeks of treatment with Stribild in Study GS-US-236-0112.

The Package Leaflet, Annex II and Risk Management Plan (v.12.1) are updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor linguistic amendments.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and Risk Management Plan (RMP).

This CHMP recommendation is subject to the following amended conditions:

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk management plan (RMP)

The 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.

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

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

6. 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.

7. 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.

8. 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.

For prescribers of adult patients:

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

10. 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.

11. 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.

12. 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.

13. 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.

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

For prescribers of adolescent patients:

15. That a multidisciplinary approach is recommended for the management of adolescent patients.

16. That Stribild is not recommended for use in adolescent patients with renal impairment.

17. That if serum phosphate is confirmed to be < 3.0 mg/dl (0.96 mmol/l) in any adolescent patient receiving Stribild, renal function should be re-evaluated within one week. If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of Stribild treatment.

18. That tenofovir disoproxil fumarate may cause a reduction in BMD and the effects of tenofovir disoproxil fumarate associated changes in BMD on long term bone health and future fracture risk are currently unknown in adolescent patients.

19. That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0309/2016 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include the treatment of HIV 1 infection in adolescents aged 12 to < 18 years weighing ⩾ 35 kg without known mutations associated with resistance to any of the three antiretroviral agents in Stribild, and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil fumarate (TDF); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on pharmacokinetics, safety and efficacy data through 48 weeks of treatment with Stribild in Study GS-US-236-0112. The Package Leaflet, Annex II and Risk Management Plan (v.12.1) are updated in accordance.

Summary

Please refer to the Scientific Discussion - Stribild II-79.