HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

6 November 2013

STRIBILD 150 mg/150 mg/200 mg/245 mg, film-coated tablet

B/30 (CIP: 34009 274 264 5 2)

Applicant: GILEAD SCIENCES

INN	emtricitabine, cobicistat, elvitegravir and tenofovir disoproxil fumarate
ATC Code (2012)	**J05AR09 (**Antivirals for treatment of HIV infections, combinations**)**
Reason for the request	**Inclusion**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"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."**

Actual Benefit	- **Substantial for patients who are "antiretroviral treatment-naïve and infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD."** - **Inadequate for previously treated patients, including those *"infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD,"* given the absence of clinical data in this patient population.**
Improvement in Actual Benefit	**Despite the simplification of the dose regimen, given the absence of a demonstration of superiority in terms of immuno-virological efficacy compared with first-line triple-therapies, the low genetic barrier to resistance for elvitegravir and the need for increased renal monitoring and possible cobicistat-related interactions, which are all potential limitations, the Committee considers that STRIBILD does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of antiretroviral treatment-naïve patients infected with HIV-1.**
Therapeutic use	**- For treatment-naive patients, due to the simplicity of use (1 tablet/day) and the demonstration of immuno-virological efficacy comparable to those of standard treatments, with good short- and medium-term safety, STRIBILD is a satisfactory alternative as long as renal function monitoring is carried out and the treatment regimen followed due to the low genetic barrier. These last two points, combined with the possible cobicistat-related interactions, limit its use as a first-line treatment.** **STRIBILD is proposed as a new treatment method, as an alternative to ISENTRESS + TRUVADA triple-therapy, when a treatment strategy with an integrase inhibitor is suggested, but only for antiretroviral treatment-naïve patients.** **- For patients who have received prior treatment (Marketing Authorisation wording "*patients infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD*"), in the absence of clinical data, the Committee considers that STRIBILD is of no current therapeutic use.**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	24 May 2013 (centralised procedure)
Prescribing and dispensing conditions / special status	List I Medicine for initial hospital prescription

ATC Classification	2012	
	J	Antiinfectives for systemic use
	J05	Antivirals for systemic use
	J05A	Direct acting antivirals
	J05AR	Antivirals for treatment of HIV infections, combinations
	J05AR09	emtricitabine, cobicistat, elvitegravir and tenofovir disoproxil fumarate

02 BACKGROUND

STRIBILD is a triple-therapy against the HIV-1 infection made up of a fixed combination of four substances, in a tablet to be taken daily:

- two nucleo(side)/(tide) reverse transcriptase inhibitors (NRTIs): emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), already marketed in France since 2003 and 2002 individually, and in the combined form TRUVADA (TDF/FTC) since 2005,
- a new substance from the integrase inhibitor category: elvitegravir (EVG),
- a new pharmacokinetic potentiator (with no antiretroviral activity), cobicistat (COBI), which enables the half-life of the elimination of elvitegravir to be increased and a single daily dose to be possible.

The indication approved by EMA is wider than that forming the subject of the application for reimbursement:

"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-naive* or *are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD*."

However, the applicant indicates that given the limited amount of data available to support assessment by the Transparency Committee for non-treatment-naive patients, but who are "*infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD,*" the reimbursement of STRIBILD is not requested in this second part of the indication. Clinical trials are currently in progress and will form the subject of a new application.

03 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-naive or are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD."

04 DOSAGE

"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 of the SPC).

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 of the SPC). STRIBILD should be administered with caution to elderly patients (see section 4.4 of the SPC).

Renal impairment
STRIBILD should not be initiated in patients with creatinine clearance below 70 ml/min (see sections 4.4 and 5.2 of the SPC). See section 4.4 of the SPC 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 of the SPC). See section 4.4 of the SPC regarding patients with creatinine clearance that falls below 70 ml/min while on treatment with STRIBILD.

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 of the SPC).

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 of the SPC).

Paediatric population
The safety and efficacy of STRIBILD in children aged 6 to less than 18 years have not yet been established. Currently available data are described in section 5.2 of the SPC, 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 of the SPC). The film-coated tablet should not be chewed or crushed."

05 THERAPEUTIC NEED[1]

HIV infection is a serious and life-threatening condition.

The aim of an antiretroviral treatment, depending on the situation (first-line treatment and beyond, including after multiple treatment failures), should be to achieve and maintain a plasma viral load of < 50 copies/ml and a CD4 lymphocytes count of > 500/mm^3.

Six categories of anti-HIV medication with different mechanisms of action are available to treat patients infected with HIV: nucleo(side)/(tide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), integrase inhibitors (INIs) and CCR5 receptor antagonists.
Currently, therapeutic combinations combining at least three highly active agents are recommended. These treatment regimens enable an increase in survival, reduce opportunistic infections and HIV-related complications and improve quality of life. *First-line triple-therapy is still a combination of two NRTIs with a 3rd agent* (1 PI or 1 NNRTI). Fusion inhibitors, integrase inhibitors and CCR5 receptor antagonists are not the preferred choice of first-line treatments.
STRIBILD is a fixed combination of two NRTIs (emtricitabine and tenofovir) and two new substances (1 integrase inhibitor [elvitegravir] plus 1 "potentiator" [cobicistat]). The two NRTIs in the combination are currently marketed in France in the treatment of HIV-1 infection in combination with other antiretrovirals, and exist as their individual forms (EMTRIVA [emtricitabine]; VIREAD [tenofovir]) or in a fixed combination (TRUVADA [emtricitabine/tenofovir]). They are also included in two 1 tablet/day triple-therapies, currently on the market: ATRIPLA (emtricitabine/tenofovir/efavirenz) and COMPLERA (emtricitabine /tenofovir /rilpivirine).

The only other triple-therapy, combining substances from the same therapeutic class as STRIBILD (2 NRTIs + 1 integrase inhibitor), is ISENTRESS (raltegravir) co-administered with the fixed combination TRUVADA [emtricitabine/tenofovir], which is the product it is combined with in the registration studies.

ISENTRESS (raltegravir) is the first representative in the integrase inhibitors class currently marketed in France. This product is of benefit when used as a combination for patients resistant to other antiretrovirals. However, for treatment-naive patients, due to *the rapid development of mutations in cases of persistent viral replication (weak genetic barrier)* and the absence of demonstrated immuno-virological superiority compared with treatment alternatives, its use is restricted to a small number of patients for whom the use of other first-line treatments is not possible, *especially for high cardiovascular risk patients or to reduce the risk of interactions with other medicines for patients receiving other treatments.*[2]

[1] Prise en charge médicale des personnes vivant avec le VIH. Recommandation du groupe d'experts. Rapport 2013. Under the management of Professor Philippe Morlat and with the guidance of CNNS and ANRS. http://www.sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf
[2] See the Transparency Committee Opinion of 3 November 2010 for ISENTRESS. Available at: http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-11/isentress_-_ct-8568.pdf

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

For treatment-naive patients the comparator medicine for STRIBILD is ISENTRESS in combination with TRUVADA, which is the product it is combined with in registration studies.

Proprietary Medicinal Product (INN) - Company	Indication	Transparency Committee Opinion
ISENTRESS (raltegravir) MSD	ISENTRESS is indicated, in combination with other antiretroviral agents, in the treatment of human immunodeficiency virus infection (HIV-1) in adult patients. This indication is based on safety and efficacy data from two double-blind, placebo-controlled studies conducted in treatment-experienced patients and one double-blind study versus an active comparator control, in treatment-naïve patients.	Opinions of 02/02/2008 and 03/11/2010 (**previously treated patients**) AB: substantial IAB: On the one hand, given: - the benefit of submitting a medicinal product in a new class of antiretrovirals: integrase inhibitors, - the virological efficacy of ISENTRESS + TO, demonstrated in the reduction in viral load superior to comparator investigated (placebo + TO), and on the other hand: - uncertainties concerning the safety profile of the medicinal product (possible increase in the risk of cancer and biological abnormalities: ALAT, ASAT, CPK), - a potential weak genetic barrier, the Committee considers that ISENTRESS, in association with an optimised antiretroviral treatment, provides a moderate improvement in actual benefit (level III) in terms of virological efficacy in the treatment of a limited population of previously treated adult patients who have a detectable viral load under their current antiretroviral treatment and who have been confirmed by genotype and phenotype tests to be resistant to at least one nucleoside inhibitor (NI), one non-nucleoside inhibitor (NNI) and more than one protease inhibitor (PI). Opinion of 03/11/2010 (**previously treated patients**: long-term data) AB: substantial IAB: IAB III retained Opinion of 03/11/2010 (**treatment-naive patients**) AB: substantial IAB: "as superiority has not been demonstrated in terms of immuno-virological efficacy compared with alternative treatments available and given the relatively low genetic barrier to the development of resistance (risk of selection of resistant variants) which would limit its use as a first-line treatment in this population, the Committee considers that ISENTRESS does not provide an improvement in actual benefit (IAB V) in the management of treatment-naïve adult patients with HIV-1 infection."
TRUVADA (tenofovir disoproxil / emtricitabine) Gilead	TRUVADA is a fixed dose combination of emtricitabine and tenofovir disoproxil (in the fumarate form). It is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults.	Opinion of 21/09/2005 AB: substantial IAB: Absence of IAB (level V) for adult patients not requiring dosage adjustment, compared with taking the different components of the fixed combination separately. Opinion 6 July 2011 (re-assessment of IAB: Submission of new data) Absence of IAB versus KIVEXA

➢ Medicinal products recommended as first-line therapies for treatment-naive patients

Currently, therapeutic combinations combining at least three highly active agents are recommended as first-line treatments: 2 NRTIs + a third agent (1 PI or 1 NNRTI):

- 2 NRTIs (tenofovir / emtricitabine) + 1 NNRTI (efavirenz),
- 2 NRTIs (tenofovir / emtricitabine) + 1 NNRTI (rilpivirine),
- 2 NRTIs (abacavir / lamivudine) + 1 NNRTI (efavirenz),

- 2 NRTIs (tenofovir / emtricitabine) + 1 PI / ritonavir (atazanavir / ritonavir or darunavir / ritonavir),
- 2 NRTIs (abacavir / lamivudine) + 1 PI/ritonavir (atazanavir/ritonavir).

(INN) Company	Indication (treatment-naive patients)
3rd agents (PIs or NNRTIs)	
PREZISTA (darunavir) Janssen-Cilag	PREZISTA 400 mg, co-administered with low dose ritonavir, is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) in adults who are antiretroviral treatment-naive (ART-naive).
REYATAZ (atazanavir) BMS	REYATAZ is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.
SUSTIVA (efavirenz) BMS	SUSTIVA is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 years of age and older.
EDURANT (rilpivirine) JANSSEN-CILAG	EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naive adult patients with a viral load ≤100,000 HIV-1 RNA copies/ml.
Joint combinations of preferentially recommended NRTIs (combined forms)	
KIVEXA (lamivudine / abacavir) GSK	KIVEXA is a fixed-dose combination of two nucleoside analogues (abacavir and lamivudine). It is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection in adults and adolescents from 12 years of age.
TRUVADA (tenofovir disoproxil / emtricitabine) Gilead Sciences	TRUVADA is a fixed dose combination of emtricitabine and tenofovir disoproxil (in the fumarate form). It is indicated in antiretroviral combination therapy for the treatment of HIV-1 infected adults.
Pharmacokinetic potentiator	
NORVIR (ritonavir) Abbott	NORVIR is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infected patients (adults and children of 2 years of age and older). For patients who have already been treated with protease inhibitors, treatment with ritonavir should be based on the results from individual viral resistance tests and the treatment history of the patients.

➢ Other treatments available

Other antiretrovirals used in the treatment of HIV-infection are also available.

- Protease inhibitors (PIs)
  - fosamprenavir: TELZIR, film-coated tablet and oral solution
  - indinavir: CRIXIVAN, hard capsule
  - lopinavir/ritonavir: KALETRA, tablet and oral solution
  - saquinavir mesylate: INVIRASE, hard capsule
  - tipranavir: APTIVUS, soft capsule
- Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
  - nevirapine: VIRAMUNE, tablet and oral solution
  - etravirine: INTELENCE, tablet
- Nucleotide Reverse Transcriptase Inhibitor (NRTI)
  - tenofovir disoproxil fumarate: VIREAD, film-coated tablet
- Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
  - abacavir: ZIAGEN, tablet and oral solution
  - didanosine: VIDEX, hard capsule and powder for oral suspension
  - emtricitabine: EMTRIVA, hard capsule and oral solution
  - lamivudine: EPIVIR, tablet and oral solution
  - stavudine: ZERIT, hard capsule and oral solution
  - zidovudine: RETROVIR, hard capsule, oral solution and solution for injection
  - abacavir / lamivudine / zidovudine: TRIZIVIR, film-coated tablet

    - zidovudine / lamivudine: COMBIVIR, film-coated tablet
- Nucleoside, nucleotide and non-nucleoside reverse transcriptase inhibitors
    - rilpivirine / emtricitabine / tenofovir disoproxil: EVIPLERA, film-coated tablet
- Fusion inhibitor
    - enfuvirtide: FUZEON, powder and solvent for suspension for injection
- CCR5 inhibitor
    - maraviroc: CELSENTRI, film-coated tablets

Conclusion

The most relevant comparator is the ISENTRESS (raltegravir) + the fixed combination TRUVADA (emtricitabine + tenofovir) triple-therapy, which combines antiretrovirals from the same therapeutic categories.
The other recommended treatments for treatment-naive patients are also relevant comparators.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Reimbursement, or not, of the medicinal product in Europe and North America

COUNTRY	Reimbursement		
	Date reimbursement started	Yes/No/Assessment in progress	Scope (indications) and specific condition(s)
Unites States	August 2012	Yes	Scope of the Marketing Authorisation
Canada	December 2012	Yes	Scope of the Marketing Authorisation
Germany	June 2012	Yes	Scope of the Marketing Authorisation
United Kingdom	June 2012	Yes	Scope of the Marketing Authorisation

08 ANALYSIS OF AVAILABLE DATA

The dossier includes two controlled phase III studies carried out on treatment-naive adult patients:

- Study GS-US-236-0102: controlled study versus the fixed combination emtricitabine/tenofovir/efavirenz (ATRIPLA) lasting 192 weeks. It should be noted that the comparator chosen (ATRIPLA) does not have Marketing Authorisation in Europe for the treatment of HIV-1 infection in treatment-naive patients. The European Marketing Authorisation for this medicinal product is restricted to "*adults patients in whom the disease has been under virological control (with an RNA HIV load of < 50 copies/ml) through a combination of antiretrovirals for three months or longer.*" Therefore, the results from this study are presented as an indication only.
- Study GS-US-236-0103: controlled study versus a triple-therapy combining two NRTIs (fixed combination emtricitabine + tenofovir [TRUVADA]) + one PI (atazanavir potentiated by ritonavir) lasting 192 weeks.

There is no study that compared STRIBILD with the triple-therapy ISENTRESS (raltegravir) + TRUVADA (emtricitabine/tenofovir), combining treatments from the same therapeutic categories. The absence of this comparison is justified by the applicant due to the fact that "when these studies started in 2010, ISENTRESS (the only other treatment in the integrase inhibitor category) had only just obtained its Marketing Authorisation for the treatment of treatment-naive patients and was not considered as a standard treatment in this population."

08.1 Efficacy

➢ Study methods

The study method of both trials is described in Table 1.

Table 1: Methodologies for studies GS-US-236 102 and 103

Study	GS-US-236-0102	GS-US-236-0103
Date and location of study	• from 16 March 2010 to 10 August 2011 • 102 centres: 97 in USA and 5 in Puerto Rico	• from 06 April 2010 to 13 September 2011 • 146 centres: 88 in the USA and Puerto Rico, 11 in France, 8 in Germany, 8 in Australia
Aim and method	Controlled, randomised, double-blind non-inferiority study (delta threshold 12%) comparing the efficacy and safety of STRIBILD (fixed combination of elvitegravir [EVG], cobicistat [COBI], emtricitabine [FTC] and tenofovir disoproxil fumarate[TDF]) with that of: • the fixed combination of emtricitabine / tenofovir / efavirenz (ATRIPLA) in study GS-US-236-0102; • atazanavir potentiated by ritonavir (ATV/r) + the fixed combination of emtricitabine / tenofovir (TRUVADA) in study GS-US-236-0103.	
Population	Antiretroviral treatment-naive adult patients with HIV-1 infection.	
Study design	• randomised, double-blind treatment phase lasting 96 weeks (follow-up visits scheduled at 2, 4, 8, 12, 16, 24, 32, 40 and 48 weeks, then every 12 weeks up to 96 weeks) then patients continued their treatment double-blind and were evaluated every 12 weeks up to when the blind period ended (at 192 weeks). • open-label extension phase up to commercialisation or the end of development.	
Treatments	• STRIBILD (EVG 150 mg / COBI 150 mg / FTC 200 mg / TDF 300 mg) + ATRIPLA placebo (2 tablets) • ATRIPLA (EFV 600 mg / FTC 200 mg / TDF 300 mg) + STRIBILD placebo (2 tablets)	• STRIBILD (EVG 150 mg / COBI 150 mg / FTC 200 mg / TDF 300 mg) + ATV+r + FTC / TDF placebo (4 tablets) • Atazanavir / ritonavir (ATV 300 mg + RTV 100 mg) + TRUVADA (FTC 200 mg / TDF 300 mg) and STRIBILD placebo (4 tablets)

Patient recruitment	***Inclusion criteria*** • Patients aged 18 years or over, male or female who accept to use an appropriate method of contraception; • Plasma viral load (HIV-1 RNA) ≥ 5,000 copies/ml; • who have never received an anti-HIV treatment; • genotype sensitivity to FTC, TDF, ATV and EFV during recruitment; • normal renal function, with an estimated glomerular filtration rate ≥ 70 ml/min according to the Cockcroft-Gault formula. ***Non-inclusion criteria*** • active HIV-related disease (AIDS) diagnosed in the 30 days prior to randomisation; • treatment for hepatitis C (HCV) virus during the study; • decompensated cirrhosis (ascites, encephalopathy, etc.); • women who are pregnant or breastfeeding; • patients with a history of malignant diseases during the five years prior to randomisation, or those with a malignant disease other than Kaposi's sarcoma (SK), basal cell carcinoma or non-invasive resectionable squamous-cell carcinoma. Patients with a Kaposi's skin sarcoma were eligible, but should not have received systemic treatment in the 30 days prior to inclusion and not likely to receive treatment during the study; • severe active infection (other than HIV-1 infection) requiring parenteral antibiotic or antifungal treatment in the 30 days prior to inclusion.
Endpoints	***Primary efficacy endpoint*** Virological response, defined as the proportion of patients with a HIV-1 RNA viral load < 50 copies/ml at 48 weeks, according to the snapshot statistical analysis (analysis corresponding to taking into account the last VL value observed between Weeks 44 and 54). *Non-inferiority of STRIBILD compared with the comparator was established if the lower limit of the 95% confidence interval of the difference in virological response (STRIBILD – comparator) was greater than -12%.* ***Secondary endpoints, in particular:*** • *virological response at 96 weeks* • *immune response: change in the absolute value and the T CD4+ lymphocyte level at 48 and 96 weeks compared with baseline* • *Analysis of resistance and Safety*
Number of patients needed	In each of the two studies, 700 patients were scheduled to be included, randomised according to a 1:1 ratio (350 patients in each of the two groups) to establish non-inferiority in terms of responder rate at 48 weeks, with a power of at least 95%, by estimating a response rate of 79.5%, a non-inferiority limit of 12% and a unilateral significance limit of 0.025.
Populations analysed	• *ITT (*Intention-to-Treat*) population: all patients randomised in the study, who received at least one dose of treatment;* • *PP (*Per Protocol*) population: all patients randomised, who received at least one dose of treatment and who participated in the study without a major violation of the protocol (including not contravening any of the inclusion criteria);* • *Safety analysis population: all patients randomised who received at least one dose of treatment. All data collected 30 days after premature and definitive discontinuation of the study were included in the safety data.*

➢ Study results

Characteristics of patients included

In total, 700 patients were included in study 102 (348 in the STRIBILD group versus 352 in the ATRIPLA group) and 708 patients in study 103 (353 in the STRIBILD group versus 353 in the atazanavir / ritonavir + TRUVADA group).
At inclusion, the demographic and clinical characteristics of patients were similar in both treatment groups (Table 2). The mean age of patients was 38 years (the majority were male, 90%) and the majority (>90%) were infected with sub-type B of the HIV-1 virus. The median HIV-1 RNA plasma viral load was approximately 4.8 $\log_{10}$ copies/ml (including 60% with a low viral load ≤ 100,000 copies/ml) and the median baseline CD4+ level was approximately 370 x 10^6 cells/l. The

majority (>80%) of patients were at stage A (asymptomatic) of the infection. Very few patients (<5%) were co-infected with HBV or HCV.

Table 2: Clinical characteristics of patients included in studies 102 and 103 (ITT population)

	Study 102		Study 103	
	STRIBILD (N=348)	**ATRIPLA (N=352)**	**STRIBILD (N=357)**	**Atazanavir/ritonavir + TRUVADA (N=358)**
Viral stage				
Viral load (log$_{10}$ HIV-1 RNA copies/ml)				
Median (Min-Max)	*4.73 (2.64-6.42)*	*4.78 (3.03-6.54)*	*4.88 (1.69-6.58)*	*4.86 (2.98-6.63)*
Viral load (copies/ml)				
≤ 100 000	*66.1%*	*67.0%*	*57.5%*	*60.3%*
> 100 000	*33.9%*	*33.0%*	*42.5%*	*39.7%*
Absolute CD4+ value (cells/µl)				
Median (Min-Max)	*376 (276-487)*	*383 (268-479)*	*351 (262-454)*	*366 (274-466)*
T CD4+ lymphocytes level (%)				
Median (Min-Max)	*22.6 (1.9-49.00)*	*22.8 (0.6-56.0)*	*20.2 (1.9-49.00)*	*21.3 (0.9-46.1)*
Clinical stage				
Asymptomatic	*83.3%*	*83.8%*	*80.7%*	*82.5%*
Symptomatic	*8.6%*	*9.4%*	*10.2%*	*10.7%*
AIDS	*8.0%*	*6.8%*	*9.1%*	*6.8%*
Hepatitis B co-infection	*1.4%*	*2.6%*	*1.4%*	*2.0%*
Hepatitis C co-infection	*4.9%*	*4.3%*	*5.1%*	*2.8%*

Efficacy

In both studies, the results for the PP analysis demonstrated the non-inferiority of STRIBILD compared with the active comparator groups (ATRIPLA or atanazavir / ritonavir + TRUVADA) for the primary efficacy endpoint defined as the virological response (viral load < 50 copies/ml) at 48 weeks:

- study 102: STRIBILD vs. ATRIPLA (94.9% vs. 96.0%, difference of -1.0%, 95% CI: [-4.4%; 2.4%]),
- study 103: STRIBILD vs. atanazavir / ritonavir + TRUVADA (97.5% *vs.* 97.7%, difference of -0.1%, 95% CI: [-2.6%; 2.4%]).

These results were confirmed in the ITT analysis (Table 3). Sensitivity analyses for the primary efficacy endpoint (including different populations and different imputation methods for virological response) confirm the non-inferiority of STRIBILD compared with the comparators, with virological response rates for STRIBILD of between 83% and 93% depending on the analysis and the population investigated.

Table 3: results at 48 and 96 weeks for studies 102 and 103 (ITT analysis)

	Study 102		Study 103	
n (%)	**STRIBILD (N=353)**	**ATRIPLA (N=354)**	**STRIBILD (N=357)**	***Atazanavir / ritonavir + TRUVADA* (N=358)**
Virological response at 48 weeks (HIV-RNA < 50 copies/ml)	**87.6%**	**84.1%**	**89.5%**	**86.8%**
Difference [95% CI]	3.6% [-1.6%; 8.8%]		3.0% [-1.9%; 7.8%]	
Virological failure at 48 weeks	7.2%	7.1%	5.4%	5.4%
Virological response at 96 weeks (HIV-RNA < 50 copies/ml)	84.2%	81.5%	83.3%	82.3%
Difference [95% CI]	2.7% [−2.9%; 8.3%]		1.1%[−4.5%; 6.7%]	
Virological failure at 96 weeks	6.3%	7.7%	6.8%	7.3%
Immune response (increase in CD4+ (cells/µl) at 96 weeks				
Mean (SD)	295 (213.3)	273 (189.7)	256 (167.1)	261 (188.0)
Difference [95% CI]	22 [−10; 54]		−8 [−35; 19]	

08.2 Resistance data

Data from studies GS-US-236-0102 and 103

In study 102, 40 patients (5.7%) in virological failure met the criteria for a resistance investigation to be carried out at 96 weeks:

- of the 17 patients treated with STRIBILD who were evaluated, 10 (which is 2.9% of the population treated with STRIBILD) developed a mutation with resistance to one or several of its components,
- of the 23 patients treated with ATRIPLA who were evaluated, 10 (which is 2.8% of the population treated with ATRIPLA) developed a resistance mutation to one or several of its components (efavirenz / emtricitabine / tenofovir).

In study 103, 35 patients (4.9%) in virological failure met the criteria for a resistance investigation to be carried out at 96 weeks:

- of the 19 patients treated with STRIBILD who were evaluated, 6 (which is 1.7% of the population treated with STRIBILD) developed a mutation with resistance to one or several of its components,
- of the 16 patients treated with atanazavir / ritonavir + TRUVADA who were evaluated, none of them developed a mutation with resistance to any of the components of the triple-therapy (atanazavir / ritonavir + emtricitabine / tenofovir).

Table 4: Studies 102 and 103: resistance analyses at 48 and 96 weeks

	Study 102				**Study 103**			
	STRIBILD (n=348)		**ATRIPLA (n=352)**		**STRIBILD (n=353)**		***Atazanavir/r + TRUVADA* (n=355)**	
	at 48 weeks	**at 96 weeks**	**at 48 weeks**	**at 96 weeks**	**at 48 weeks**	**at 96 weeks**	**at 48 weeks**	**at 96 weeks**
Patients analysed for resistance, n (%)	14 (4.0)	17 (4.9)	17 (4.8)	23 (6.5)	12 (3.4)	19 (5.4)	8 (2.3)	16 (4.5)
Patients with resistance, n (%)*	**8 (2.3)**	**10 (2.9)**	**8 (2.3)**	**10 (2.8)**	**5 (1.4)**	**6 (1.7)**	**0**	**0**
≥ 1 primary resistance mutation to INIs, n	7	9	0	0	4	4	0	0
E92Q	7	7	0	0	1	2	0	0
T66I	1	1	0	0	1	1	0	0
Q148R	1	1	0	0	2	2	0	0
N155H	1	3	0	0	2	2	0	0
≥ 1 primary resistance mutation to NNRTIs, n	0	0	8	10	0	0	0	0
K103N	0	0	7	9	0	0	0	0
K101E	0	0	3	3	0	0	0	0
V108I	0	0	2	2	0	0	0	0
Y188Y/F/H/L	0	0	1	2	0	0	0	0
G190A	0	0	1	1	0	0	0	0
≥ 1 primary resistance mutation to NRTIs, n	**8**	**10**	**2**	**3**	**4**	**5**	0	0
M184V/I	8	10	2	3	4	5	0	0
K65R	3	4	2	3	1	1	0	0
A62V	1	2	0	0	1	2	0	0
≥ 1 primary resistance mutation to PIs, n	0	0	0	0	0	0	0	0

*INIs = integrase inhibitors; NNRTIs = Non-nucleoside reverse transcriptase inhibitors; NRTIs = nucleo(side)/(tide) reverse transcriptase inhibitors; PIs = protease inhibitors.

Data from the SPC

"In cell culture

Resistance to emtricitabine or tenofovir has been seen *in vitro* and in some patients with HIV-1 due to the development of the M184V or M184I emtricitabine resistance substitution in reverse transcriptase or the K65R tenofovir resistance substitution in reverse transcriptase. Emtricitabine-resistant viruses with the M184V/I mutation were cross-resistant to lamivudine, but retained sensitivity to didanosine, stavudine, tenofovir and zidovudine. The K65R mutation can also be selected by abacavir, stavudine or didanosine and results in reduced susceptibility to these agents plus lamivudine, emtricitabine and tenofovir. Tenofovir disoproxil fumarate should be avoided in patients with HIV-1 harbouring the K65R mutation.

In patients, HIV-1 expressing three or more thymidine analogue associated mutations (TAMs) that included either the M41L or L210W reverse transcriptase mutation showed reduced susceptibility to tenofovir disoproxil fumarate.

HIV-1 isolates with reduced susceptibility to elvitegravir have been selected in cell culture. Reduced susceptibility to elvitegravir was most commonly associated with the integrase mutations T66I, E92Q and Q148R. Additional integrase mutations observed in cell culture selection included H51Y, F121Y, S147G, S153Y, E157Q, and R263K. HIV-1 with the raltegravir-selected mutations T66A/K, Q148H/K, and N155H showed cross-resistance to elvitegravir.

No development of resistance to cobicistat can be demonstrated in HIV-1 *in vitro* due to its lack of antiviral activity.

Substantial cross-resistance was observed between most elvitegravir-resistant HIV-1 isolates and raltegravir, and between emtricitabine-resistant isolates and lamivudine. Patients who failed treatment with STRIBILD and who had HIV-1 with emergent STRIBILD resistance mutations harboured virus that remained susceptible to all PIs, NNRTIs, and most other NRTIs.

In treatment-naive patients
In a pooled analysis of antiretroviral-naïve patients receiving STRIBILD in phase 3 studies GS-US-236-0102 and GS-US-236-0103, genotyping and phenotyping were performed on plasma HIV-1 isolates from all patients who had HIV-1 RNA > 400 copies/ml at virologic failure, at week 48, or at the time of early study drug discontinuation. As of week 48, the development of one or more primary elvitegravir, emtricitabine, or tenofovir resistance-associated mutations were observed in 13 of the 25 patients with evaluable genotypic data from paired baseline and STRIBILD treatment-failure isolates (1.9%, 13/701 patients). The most common mutations that emerged were M184V/I (n = 12) and K65R (n = 4) in reverse transcriptase and E92Q (n = 8), Q148R (n = 3), N155H (n = 3) and T66I (n = 2) in integrase. Other mutations in integrase that occurred in addition to a primary INSTI resistance mutation each in single cases were H51Y, L68V, G140C, E157Q, and S153A. HIV-1 isolates patients who did not respond to treatment and presented with emerging elvitegravir resistance (10 of the 12 patients with data available for both genes) developed emtricitabine and elvitegravir resistance. In phenotypic analyses of HIV-1 from the 25 patients in the resistance analysis population, 11 patients (44%) had HIV-1 isolates with reduced susceptibility to elvitegravir, 12 patients (48%) had reduced susceptibility to emtricitabine, and 2 patients (8%) had reduced susceptibility to tenofovir.

In study GS-US-236-0103, 27 patients treated with STRIBILD had HIV-1 with the NNRTI-associated K103N mutation in reverse transcriptase at baseline. They had a virologic success rate similar to the overall population (89%), and no emergent resistance to elvitegravir, emtricitabine, or tenofovir in their HIV-1."

08.3 Safety/Adverse effects

8.3.1 Safety data from clinical studies

The safety data presented are from an analysis of pooled data from phase III studies (102 and 103, date of analysis at 48 weeks) and a phase II study (104, date of analysis at 60 weeks), in which 749 patients received treatment with STRIBILD, 375 with ATRIPLA and 355 with atanazavir / ritonavir (ATV+r) + TRUVADA (FTC / TDF).
In these three studies, the incidence of adverse events was similar in all three treatment groups (92.7% with STRIBILD versus 94.7% with ATRIPLA and 93.8% in the atanazavir / ritonavir + TRUVADA group). The incidence of adverse events considered as being potentially related to the study treatment was lower with STRIBILD (45.8%) than with ATRIPLA (66.7%) and atanazavir / ritonavir + TRUVADA (57.2%); the most commonly observed AEs were (Table 5):

- with STRIBILD: gastrointestinal disorders (nausea: 15.1% and diarrhoea: 11.5%) and abnormal dreams (8.7%),
- with ATRIPLA: abnormal dreams (26.1%), dizziness (20.0%) and diarrhoea (10.7%),
- with atanazavir / ritonavir + TRUVADA: diarrhoea (16.1%), ocular jaundice (13.2%) and nausea (13.2%).

Table 5: Adverse events considered as being potentially treatment-related (incidence > 5%) in studies 102, 103 and 104 (Pooled analysis, safety analysis population)

Including all grades of treatment-related AEs, (%)	**STRIBILD 102, 103, 104** (N=749)	**ATRIPLA 102, 104** (N=375)	***Atazanavir/r + TRUVADA* 103** (N=355)
% patients who presented with an AE (all grades, all incidences), considered as being treatment-related	**45.8%**	**66.7%**	**57.2%**
Eye disorders	**0.7%**	**1.9%**	**14.4%**
Ocular jaundice	0.3%	-	13.2%
Gastrointestinal disorders	**27.4%**	**24.0%**	**31.2%**
Diarrhoea	11.5%	10.7%	16.1%
Flatulence	2.0%	0.3%	7.3%
Nausea	15.1%	8.3%	13.2%
General disorders	**7.5%**	**12.0%**	**9.0%**
Asthenia	4.9%	7.7%	5.6%
Hepatobiliary disorders	**0.1%**	**0.5%**	**9.6%**
Jaundice	-	0.3%	8.5%
Nervous system disorders	**12.1%**	**29.6%**	**12.1%**
Dizziness	2.8%	20.0%	4.2%
Headaches	7.1%	4.0%	6.2%
Somnolence	1.2%	6.9%	1.1%
Psychiatric disorders	**14.0%**	**36.3%**	**8.2%**
Abnormal dreams	8.7%	26.1%	3.4%
Insomnia	2.9%	7.7%	1.4%
Skin and subcutaneous tissue disorders	**5.2%**	**16.3%**	**9.3%**
Rash	1.9%	7.5%	2.8%

The majority of adverse events were of mild to moderate intensity. Serious adverse events were reported for 69 (9.2%) patients in the STRIBILD group versus 25 (6.7%) in the ATRIPLA group and 31 (8.1%) in the atanazavir / ritonavir + TRUVADA group. Five (0.7%) patients reported a serious adverse event considered as being related to the study treatment in the STRIBILD group (depression, hypersensitivity, hepatic lesions, Burkitt's lymphoma and headaches) versus 7 (1.9%) in the ATRIPLA group and 2 (0.6%) in the atanazavir / ritonavir + TRUVADA group. Discontinuation of the study treatment due to adverse effects was not common (3.7% of patients receiving STRIBILD versus 5.1% in each of the comparator groups). The most common adverse events that led to treatment discontinuation were: in the STRIBILD group, psychiatric disorders (0.7%) and gastrointestinal disorders (0.7%); in the ATRIPLA group, psychiatric disorders (1.7%), skin and subcutaneous tissue disorders (1.4%); and in the atanazavir / ritonavir + TRUVADA group, gastrointestinal disorders (1.4%), skin and subcutaneous tissue disorders (1.1%) and eye disorders (1.1%). Musculoskeletal adverse events resulted in discontinuation of the study treatment for two patients (weakness and muscle degradation) in the STRIBILD group, however this was not the case in either of the two other treatment groups.

Tenofovir (a component of STRIBILD, ATRIPLA and TRUVADA), can lead to renal toxicity[3] Pharmacokinetic analyses have shown that the levels of exposure to tenofovir are increased by approximately 30% after the administration of STRIBILD compared with tenofovir alone. In the studies, renal events (Fanconi syndrome, renal impairment or increase in serum creatinine) with the results from relevant laboratory analyses of proximal renal tubular lesions (mainly hypophosphataemia, with an increase in fractional urinary phosphorus excretion, glycosuria and proteinuria) resulted in discontinuation of the use of STRIBILD for eight patients (renal impairment:

[3] Cases of renal impairment, renal failure, increase in creatinine level, hypophosphataemia and proximal tubulopathy (which includes Fanconi syndrome) have been reported within the context of the use of tenofovir disoproxil fumarate in clinical practice (see. SPC for VIREAD).

3 patients; Fanconi syndrome: 1 patient; increase in serum creatinine levels: 4 patients). Abnormalities seen in laboratory tests were reversed when the study treatment was discontinued and did not appear to have any clinical consequences.
Due to these known risks, precautions for use were included in the SPC for STRIBILD regarding its use in patients with or at risk of renal impairment.

Assessment of bone mineral density (BMD) is included in the monitoring recommendations for patients being treated with tenofovir. Tenofovir may lead to a slight reduction in BMD. BMD was monitored in study 103. Mean reductions in BMD, expressed as a percentage, between the start of treatment and Week 48, were comparable in the STRIBILD group (n = 54) and the atanazavir / ritonavir + TRUVADA group (n = 66) to the lumbar spine (-2.6% versus -3.3%) and hip regions (-3.1% versus -3.9%). In the various studies, the percentage of patients who had had a fracture during the study was comparable between the different treatments (1.3% with STRIBILD; 1.6% with ATRIPLA and 1.7% with atanazavir / ritonavir + TRUVADA).

Analysis of data at 96 weeks for the phase III studies (studies 102 and 103) did not highlight any new safety concerns compared with the effects reported at 48 weeks.

8.3.2 Summary of the safety profile (according to the SPC)

"The most frequently reported adverse reactions considered possibly or probably related to STRIBILD were nausea (16%) and diarrhoea (12%) (pooled data from Phase 3 clinical studies GS-US-236-0102 and GS-US-236-0103 taken at 48 weeks).

In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving STRIBILD (see section 4.4 of the SPC).

Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate and emtricitabine (see sections 4.4 and 4.8 of the SPC, Description of selected adverse reactions).

Discontinuation of STRIBILD therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis (see section 4.4 of the SPC).

Tabulated summary of adverse effects
Adverse reactions to STRIBILD from Phase 3 clinical studies GS-US-236-0102 and GS-US-236-0103, and adverse reactions to treatment with emtricitabine and tenofovir disoproxil fumarate from clinical studies and post-marketing experience, when used with other antiretrovirals, are listed in the table below, by body system organ class and highest frequency observed. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10 cases reported), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100) or rare (≥ 1/10,000, < 1/1,000).

Table 6: Tabulated summary of adverse reactions associated with STRIBILD based on experience from Phase 3 studies GS-US-236-0102 and GS-US-236-0103 and adverse reactions to treatment with emtricitabine and tenofovir disoproxil fumarate from clinical studies and post-marketing experience, when used with other antiretrovirals.

Frequency	Adverse reaction
Blood and lymphatic system disorders:	
Common:	neutropenia[1]
Uncommon:	anaemia[1,2]
Immune system disorders:	
Common:	allergic reaction[1]

Metabolism and nutrition disorders:	
Very common:	hypophosphataemia[1,3]
Common:	hyperglycaemia, [1] hypertriglyceridaemia, [1] decreased appetite
Uncommon:	hypokalaemia [1,3]
Rare:	lactic acidosis [1,4]
Psychiatric disorders:	
Common:	insomnia, abnormal dreams
Uncommon:	depression, suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness)
Nervous system disorders:	
Very common:	headache, dizziness
Gastrointestinal disorders:	
Very common:	diarrhoea, vomiting, nausea
Common:	elevated amylase including elevated pancreatic amylase, [1] elevated serum lipase, [1] abdominal pain, dyspepsia, constipation, abdominal distension,[1] flatulence
Uncommon:	pancreatitis[1,4]
Hepatobiliary disorders:	
Common:	increased transaminases, [1] hyperbilirubinaemia[1]
Rare:	hepatic steatosis, [1,4] hepatitis[1]
Skin and subcutaneous tissue disorders:	
Very common:	Rash
Common:	vesiculobullous rash, [1] pustular rash, [1] maculopapular rash, [1] pruritus, [1] urticaria, [1] skin discolouration (increased pigmentation)[1,2]
Uncommon:	angioedema[1]
Musculoskeletal and connective tissue disorders:	
Very common:	elevated creatine kinase[1]
Uncommon:	rhabdomyolysis[1,3], muscular weakness[1,3]
Rare:	osteomalacia (manifested as bone pain and infrequently contributing to fractures), [1,3,5] myopathy[1,3]
Renal and urinary disorders:	
Uncommon:	renal failure, [4] proximal renal tubulopathy including Fanconi syndrome acquired, [4] increased blood creatinine[4], proteinuria
Rare:	acute tubular necrosis, [1] nephritis (including acute interstitial nephritis), [1,5] nephrogenic diabetes insipidus[1]
General disorders and administration site conditions:	
Very common:	asthenia[1]
Common:	Pain, [1] fatigue

[1] This adverse reaction was not observed in the Phase 3 clinical studies for STRIBILD but identified from clinical studies or post-marketing experience for emtricitabine or tenofovir disoproxil fumarate when used with other antiretrovirals.

[2] Anaemia was common and skin discolouration (increased pigmentation) was very common when emtricitabine was administered to paediatric patients.

[3] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.

[4] See section 4.8, Description of selected adverse reactions for more details.

[5] This adverse reaction was identified through post-marketing surveillance for emtricitabine or tenofovir disoproxil fumarate but not observed in randomised, controlled clinical studies in adults or paediatric HIV clinical studies for emtricitabine or in randomised controlled clinical studies or the tenofovir disoproxil fumarate expanded access program for tenofovir disoproxil fumarate. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in randomised controlled clinical studies (n = 1,563) or tenofovir disoproxil fumarate in randomised controlled clinical studies and the expanded access program (n = 7,319).

Description of selected adverse reactions

Renal impairment

In the clinical studies of STRIBILD over 48 weeks (n = 701), 6 (0.9%) subjects in the STRIBILD group and 1 (0.3%) subject in the atazanavir boosted by ritonavir (ATV/r) plus the fixed combination of emtricitabine / tenofovir disoproxil fumarate (FTC/TDF) group discontinued study drug due to a renal adverse reaction. The types of renal adverse reactions seen with STRIBILD were consistent with previous experience with tenofovir disoproxil fumarate. Four (0.6%) of the subjects who received STRIBILD developed laboratory findings consistent with proximal tubulopathy leading to discontinuation of STRIBILD. Two of the four subjects had renal impairment

(i.e. estimated creatinine clearance less than 70 ml/min) at baseline. The laboratory findings in these four subjects with evidence of proximal tubulopathy improved without clinical consequence upon discontinuation of STRIBILD. However, they did not completely resolve in any of the subjects (see section 4.4 of the SPC).

The cobicistat component of STRIBILD has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In studies GS-US-236-0102 and GS-US-236-0103, decreases in estimated creatinine clearance occurred early in treatment with STRIBILD, after which they stabilised. At the end of 48 weeks of treatment, the mean change in estimated glomerular filtration rate (eGFR) by -Cockcroft-Gault method was -13.9 ± 14.9 ml/min for STRIBILD, -1.6 ± 16.5 ml/min for EFV/FTC/TDF and -9.3 ± 15.8 ml/min for ATV/r+FTC/TDF.

Interaction with didanosine
STRIBILD is not to be given with other antiretroviral agents. However, in case of initiation of STRIBILD in patients previously taking didanosine or discontinuation of STRIBILD and change to a regimen including didanosine there could be a short period when measurable plasma levels of didanosine and tenofovir occur. Note then that co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, cases of pancreatitis and lactic acidosis, sometimes fatal, have been reported.

Lipids, lipodystrophy and metabolic abnormalities
Combined antiretroviral treatment has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4 of the SPC).

Combined antiretroviral treatment has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see section 4.4 of the SPC).

Immune Reactivation Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of combined antiretroviral treatment, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease) have also been reported. However, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4 of the SPC).

Osteonecrosis
Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term combined antiretroviral treatment. The frequency of this is unknown (see section 4.4 of the SPC*).*

Lactic acidosis and severe hepatomegaly with steatosis
Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels (see section 4.4 of the SPC*)*.

<u>Paediatric population</u>
Insufficient safety data are available for children below 18 years of age. STRIBILD is not recommended in this population (see section 4.2 of the SPC).

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 of the SPC).

Patients with renal impairment

Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with STRIBILD (see sections 4.2, 4.4 and 5.2 of the SPC).

Exacerbations of hepatitis after discontinuation of treatment

In HIV infected patients co-infected with HBV, clinical and laboratory evidence of hepatitis have occurred after discontinuation of treatment (see section 4.4 of the SPC)."

08.4 Risk management plan

A summary of the various pharmacovigilance and risk minimisation activities stated in the risk management plan is presented in the table below.

		Pharmacovigilance		Risk minimisation	
	Compound concerned*	**Routine PV**	**Additional studies**	**Stated in SPC**	**Additional action**
Identified risks					
Renal safety	TDF	X	X	X	X
Proximal tubulopathy-related bone event / loss of BMD	TDF	X	X	X	
Risk of hepatitis flare in HIV/HBV co-infected patients	FTC/TDF	X		X	
Interaction with didanosine	TDF	X		X	
Pancreatitis	TDF	X		X	
Lactic acidosis and severe hepatomegaly / steatosis	FTC/TDF	X		X	
Lipodystrophy	FTC/TDF	X		X	
Suicidal ideation or suicide attempt in patients with a pre-existing history of psychiatric illness	EVG	X	X	X	
Potential risks					
Accidental overdose (use of STB with one of its components)	**STB**	**X**		**X**	
Use of medicines contraindicated with STB	COBI	X		X	
Missing information					
Long-term safety data	**STB, EVG, COBI**	**X**	**X**		
Data on paediatric patients	EVG, COBI, TDF	X	X	X	
Data on pregnant women	EVG, COBI, FTC, TDF	X	X	X	
Data on patients with renal impairment	STB, COBI, TDF	X	X		
Data on elderly patients	EVG, COBI, FTC, TDF	X		X	
Data while breast-feeding	EVG, COBI, FTC, TDF	X		X	

Data on patients with severe hepatic impairment	EVG, COBI	X		X	
Interaction with other medicinal products	STB, EVG, COBI, TDF	X	X	X	

* STB = STRIBILD; EVG = elvitegravir; COBI = cobicistat; FTC = emtricitabine; TDF = tenofovir;

08.5 Summary & discussion

STRIBILD (fixed combination of elvitegravir / cobicistat / emtricitabine / tenofovir) was evaluated in two randomised, double-blind, active comparator-controlled studies (GS-US-236-0102 [study 102] and GS-US-236-0103 [study 103]), in HIV-1 infected, antiretroviral treatment-naive patients with an estimated creatinine clearance (CrCl) greater than 70 ml/min.
In study 102, patients received STRIBILD (n = 348) or ATRIPLA (fixed combination of efavirenz / emtricitabine / tenofovir, N = 352) once daily. In study 103, patients received STRIBILD (N = 353) or atazanavir potentiated by ritonavir combined with TRUVADA (emtricitabine / tenofovir, N = 355) once daily.

Patients included had a mean age of 38 years, were male (90%), infected with sub-type B HIV-1 (90%), were asymptomatic (80%), had a median plasma HIV-1 RNA viral load of 4.8 log10 copies/ml (60% ≤ 100,000 copies/ml) and a median CD4+ count of 370 x 106 cells/l and were not co-infected with HBV or HCV (95%).

The primary efficacy endpoint was virological response, defined as the proportion of patients with a HIV-1 RNA viral load < 50 copies/ml at 48 weeks. The non-inferiority of STRIBILD compared with the comparator was established if the lower limit of the 95% confidence interval for the difference in virological response (STRIBILD – comparator) was greater than -12%.

The Per Protocol virological response demonstrated the non-inferiority of STRIBILD compared with the comparators. It was:
- with STRIBILD vs. ATRIPLA: 94.9% vs. 96.0%, which is a difference of -1.0%; 95% CI [-4.4%; 2.4%]
- with STRIBILD vs. TRUVADA + atazanavir / ritonavir: 97.5% vs. 97.7%, which is a difference of -0.1% [-2.6%; 2.4%]

These results were confirmed in the ITT analysis:
- with STRIBILD vs. ATRIPLA: 87.6% vs. 84.1%
- with STRIBILD vs. TRUVADA + atazanavir / ritonavir: 89.5% vs. 86.8%

Virological response was maintained at 96 weeks (ITT analysis):
- with STRIBILD vs. ATRIPLA: 84.2% vs. 81.5%
- with STRIBILD vs. TRUVADA + atazanavir / ritonavir: 83.3% vs. 82.3%

Immune response (increase of CD4+ in cells/µl) at 96 weeks was also comparable between STRIBILD and the comparators (ITT analysis):
- with STRIBILD vs. ATRIPLA: 295 vs. 273
- with STRIBILD vs. TRUVADA + atazanavir / ritonavir: 256 vs. 261

In terms of resistance, the results from the in vitro and clinical studies with STRIBILD suggest that the genetic barrier to resistance of elvitegravir (a component of STRIBILD) is relatively low, as is that of raltegravir (another integrase inhibitor).
STRIBILD vs. ATRIPLA:
- of the patients in virological failure and included in the resistance analysis at 48 weeks, 8/14 (which is 2.3% of all the patients treated with STRIBILD) developed at least one mutation with resistance to one or several of the STRIBILD components versus 8/17 in the ATRIPLA group (2.3% of the total population treated with ATRIPLA). These figures change at 96 weeks, to 10/17 (2.9% of all the patients treated with STRIBILD) versus 10/23 in the ATRIPLA group (2.8% of the total population treated with ATRIPLA).

- in addition, for patients in virological failure, mutations associated with a resistance to NRTIs (M184V/I, k65R and A62V mutations)[4] were more common with STRIBILD than with ATRIPLA, both at 48 weeks (8/14 versus 2/17) and at 96 weeks (10/17 versus 3/23).

STRIBILD vs. TRUVADA + atazanavir / ritonavir:

- of the patients in virological failure and included in the resistance analysis at 48 weeks, 5/12 (1.4% of all patients treated with STRIBILD) developed a mutation with resistance to one or several of the STRIBILD components, however this did not occur in any of the patients in the TRUVADA + atazanavir / ritonavir group. These figures change at 96 weeks, to 6/19 (1.7% of all the patients treated with STRIBILD) versus no patients in the TRUVADA + atazanavir / ritonavir group.
- for the patients in virological failure in the STRIBILD group, the mutations associated with a resistance to NRTIs (M184V/I, k65R and A62V mutations) were observed for 4/12 patients at 48 weeks and 5/19 patients at 96 weeks.

These results reflect the relatively low genetic barrier to resistance of elvitegravir, with a higher and faster risk of selection of the resistant variants in cases of virological failure than with treatments combining a protease inhibitor with ritonavir, or even an NNRTI such as efavirenz. In addition, there is crossed-resistance between elvitegravir and raltegravir.

STRIBILD was generally well tolerated in these studies, with a safety profile comparable to that of its comparators. The most commonly reported adverse effects with STRIBILD were nausea (16%) and diarrhoea (12%). Serious adverse events were reported for 9.2% of patients treated with STRIBILD versus 6.7% in the ATRIPLA group and 8.1% in the TRUVADA + atanazavir / ritonavir group. Discontinuation of the study treatment due to adverse effects was not very common (3.7% versus 5.1% in each of the comparator groups). The most common adverse events that led to treatment discontinuation were: in the STRIBILD group, psychiatric disorders (0.7%) and gastrointestinal disorders (0.7%); in the ATRIPLA group, psychiatric disorders (1.7%), skin and subcutaneous tissue disorders (1.4%); and in the TRUVADA + atanazavir / ritonavir group, gastrointestinal disorders (1.4%), skin and subcutaneous tissue disorders (1.1%) and eye disorders (1.1%). Musculoskeletal adverse events resulted in the discontinuation of the study treatment for two patients (weakness and muscle degradation) in the STRIBILD group; however this was not the case with the comparator groups.

Tenofovir (a component of STRIBILD) can lead to renal toxicity.[5] Pharmacokinetic analyses have shown that the levels of exposure to tenofovir are increased by approximately 30% after the administration of STRIBILD compared with tenofovir alone. In the studies, renal events (Fanconi syndrome, renal impairment or increase in serum creatinine) with the results from relevant laboratory analyses of proximal renal tubular lesions (mainly hypophosphataemia, with an increase in fractional urinary phosphorus excretion, glycosuria and proteinuria) resulted in discontinuation of the use of STRIBILD for eight patients (renal impairment: 3 patients; Fanconi syndrome: 1 patient; increase in serum creatinine levels: 4 patients). Abnormalities seen in laboratory tests were reversed when the study treatment was discontinued and do not appear to have any clinical consequences. Due to these known risks, precautions for use were included in the SPC for STRIBILD regarding its use in patients with or at risk of renal impairment (in particular the concomitant use of nephrotoxic medication and for patients over 65 years of age, etc.). Furthermore, tenofovir may lead to a slight reduction in bone mineral density (BMD). Therefore its assessment is included in the monitoring recommendations for patients treated with tenofovir. Strict monitoring of patients is required before and during treatment with STRIBILD (see special warnings and precautions for use section of the SPC). Overall, the known renal and musculoskeletal effects with tenofovir alone appear slightly increased with the STRIBILD tablet, probably due to the potential effect of cobicistat, and should be the subject of new evaluations within the scope of the risk management plan (RMP).

[4] These cumulative mutations may reduce the sensitivity of the virus to nearly all medicines in the NRTI category (emtricitabine, abacavir, stavudine, didanosine and tenofovir).

[5] Cases of renal impairment, renal failure, increase in creatinine levels, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported within the scope of the use of tenofovir disoproxil fumarate in clinical practice (See SPC for VIREAD).

Data for women (only 10% of the participants in the studies) and the elderly over 65 years of age is very limited, as is that for patients in an advanced stage of HIV-1 infection (the AIDS stage or symptomatic patients) and those patients with non-sub-type B HIV-1 infection or co-infected with HBV/HCV, which limits the conclusions that can be made in these patient populations.

08.6 Study programmes

A list of post-marketing studies requested by EMA within the context of the Marketing Authorisation of STRIBILD:

Description of the studies	Progress of the discussions with EMA on 04/07/2013
Pharmacokinetic study of elvitegravir on patients with UGT1A1*28/*28 genotype receiving STRIBILD	In the process of being prepared. Study report to be delivered Q2 2015.
A prospective, observational follow-up study of the use of STRIBILD in adult HIV-1 infected patients (in particular evaluation of the effectiveness of the risk minimisation measures for renal safety, the monitoring of patients co-infected with HBV or HCV, the monitoring of patients with low CD4 levels and the monitoring of patients with a co-prescription for a potentially renal toxic medicinal product).	In the process of being approved by EMA. Study report to be delivered Q1 2015.
A randomised, open-label phase IV study evaluating the impact of STRIBILD and the combination of atazanavir + ritonavir + TRUVADA versus atazanavir + ritonavir + KIVEXA on the kidneys of adult patients with normal renal function.	Protocol should be submitted to EMA in July 2013. Study report to be delivered in May 2015
Evaluation of the effect of cobicistat and the components of STRIBILD on the in vitro cytotoxicity of tenofovir on human embryonic kidney cells.	To be delivered Q3 2013
In vitro evaluation of the potential inhibition of UGT2B7, UGT1A1 and UGT1A3 by elvitegravir.	To be delivered Q2 2013
A randomised, double-blind phase IIIb clinical study, evaluating the efficacy and safety of STRIBILD vs. atazanavir + ritonavir + TRUVADA in treatment-naive women infected with HIV-1.	To be delivered Q4 2016

09 THERAPEUTIC USE

Therapeutic strategy:

According to the 2013 report of the clinical management of patients infected with HIV, headed by Professor MORLAT:[1]

- *In treatment-naive patients*

1.1.1. Management of those infected with HIV

Numerous antiretrovirals, in six drug categories, are available:

- *Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)*
- *Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*
- *Protease inhibitors (PIs)*
- *Fusion inhibitors (FIs)*
- *CCR5 receptor antagonists*
- *Integrase inhibitors (INIs)*

Currently, therapeutic combinations combining at least three highly active agents are recommended for treatment-naive patients, which are based on one of the following regimens:

- 2 NRTIs + 1 PI;
- 2 NRTIs + 1 NNRTI.

Fusion inhibitors, integrase inhibitors and CCR5 receptor antagonists are not the preferred choice of first-line treatments.

*The choice of the two NRTIs for triple therapy should preferably involve fixed combinations of tenofovir / emtricitabine (*TRUVADA*) or abacavir / lamivudine (*KIVEXA*).*
TRUVADA should be used in preference if the plasma viral load is ≥ 100,000 copies/ml, particularly in the case of a combination with atazanavir / ritonavir (REYATAZ) or efavirenz (SUSTIVA), owing to the greater risk of virological failure with KIVEXA in this sub-population (results of study ACTG A5202).
When the viral load is < 100,000 copies/ml, the choice between KIVEXA and TRUVADA can be made on a case-by-case basis, taking account of factors such as: HBV co-infection or renal impairment.
TRUVADA must be used with caution in patients with renal impairment or who are at risk of this occurring. KIVEXA must only be used in patients who are not carriers of allele HLA B*5701.

The 3rd agent should preferably be a PI / ritonavir or an NNRTI. There is no conclusive argument in favour of the use of either one of these two classes over the other. In preference, it is recommended:
- if a PI / ritonavir is chosen as the 3rd agent: atazanavir/r or darunavir/r
- if an NNRTI is chosen as the 3rd agent: efavirenz, rilpivirine (only if VL < 5 log copies/ml).

The therapeutic use of STRIBILD

The 2013 report on the clinical management of patients infected with HIV pre-dates the commercialisation of STRIBILD and is therefore not included in the therapeutic strategies.

STRIBILD is a fixed combination of two NRTIs (emtricitabine and tenofovir) and two new substances (1 integrase inhibitor [elvitegravir] plus 1 "potentiator" [cobicistat]).
This medicinal product is an alternative treatment method to ISENTRESS (raltegravir) plus TRUVADA (fixed combination of emtricitabine / tenofovir) triple therapy, when a treatment strategy with an integrase inhibitor is proposed for antiretroviral treatment-naive patients. No study has compared the efficacy of the two treatments, nevertheless the immune and virological response observed with STRIBILD appears to be of the same order as that described with raltegravir-based triple-therapy or first-line triple therapies (combination of 2 NRTIs + 1 PI or one NNRTI), in treatment-naive patients. However, available data suggest that the genetic barrier to resistance of elvitegravir (one of the components of STRIBILD) is relatively low, as is that of raltegravir (another integrase inhibitor). The safety of STRIBILD was satisfactory in the studies, but the known renal and musculoskeletal effects with tenofovir alone appear to be slightly increased with STRIBILD, probably due to the potential effect of cobicistat, and should be the subject of new evaluations within the context of the risk management plan (RMP). Strict monitoring of patients is necessary before and during treatment with STRIBILD (see Special warnings and precautions for use section of SPC). Furthermore, it should be noted that STRIBILD has a large potential for interaction with other medicines, which contraindicates its use with several medicinal products (see sections 4.4 and 4.5 of the SPC) and the full extent of interactions with other medicines is unknown.

In conclusion,
- For treatment-naive patients, due to the simplicity of use (1 tablet/day) and the demonstration of immuno-virological efficacy comparable to those of standard treatments, with good short- and medium-term safety, STRIBILD is a satisfactory alternative as long as renal function monitoring is carried out and the treatment regimen followed, due to the low genetic barrier. These last two points, combined with the possible cobicistat-related interactions, limit its use as a first-line treatment.

STRIBILD is proposed as a new treatment method as an alternative to ISENTRESS + TRUVADA triple-therapy, when a treatment strategy with an integrase inhibitor is suggested, but only for antiretroviral treatment-naive patients.

- For patients who have received prior treatment (Marketing Authorisation wording "*patients infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD*"), in the absence of clinical data, the Committee considers that STRIBILD is of no current therapeutic use.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

STRIBILD currently has Marketing Authorisation for the "treatment of infection with Human Immunodeficiency Virus Type 1 (HIV-1) in adults aged 18 years and above who are:
- antiretroviral treatment-naive,
- or infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD."

◗ HIV infection is a serious and life-threatening condition.
◗ This proprietary medicinal product aims to prevent and/or correct the immune deficiency caused by HIV infection in adult patients.
◗ The efficacy/adverse effects ratio for this medicinal product is high for antiretroviral treatment-naive patients, as long as renal function is monitored and the treatment regimen is followed, due to the low genetic barrier. For patients who have previously received treatment, including those "infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD," in the absence of clinical data, the efficacy/adverse effects ratio is not established.
◗ There are treatment alternatives to this proprietary medicinal product, both for treatment-naive patients and those who have received prior treatment.

◗ Public health benefit
The public health burden of HIV-1 infection is substantial. For treatment-naive patients starting first-line treatment, the burden is small on account of the limited number of such patients.
Reducing HIV-associated morbidity and mortality is a public health need that is an established priority.*
There is no available information that allows the impact of STRIBILD on morbidity and mortality or quality of life to be assessed directly. Moreover, on the basis of the available data (non-inferiority compared with the combination of tenofovir / emtricitabine / efavirenz or tenofovir / emtricitabine +atazanavir / ritonavir with a comparable safety profile), this proprietary medicinal product is not expected to have an impact on reducing morbidity and mortality in treatment-naive patients compared with other existing treatments.
Consequently, on the basis of the available data, it is not expected that STRIBILD will benefit public health in this indication.

*National programme against HIV-AIDS. DGS/DHOS 2005-2008 and Public Health Law 2004 (Law No. 2004-806 of 9 August 2004 relating to Public Health Policy)

Consequently, the Committee considers that the actual benefit of STRIBILD in the treatment of infection with Human Immunodeficiency Virus Type 1 (HIV-1) in adults aged 18 years and above is:
- **substantial for patients who are "*antiretroviral treatment-naive and infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD.*"**
- **inadequate for previously treated patients, including those "*infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD,"* given the absence of clinical data in this patient population.**

The Committee:

- **recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are antiretroviral treatment-naive" and at the dosages in the Marketing Authorisation.**
- **does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over, who have previously been treated, including those *infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD.*"**

◗ **Proposed reimbursement rate: 100%**

010.1 Improvement in actual benefit (IAB)

Despite the simplification of the dose regimen, given the absence of a demonstration of superiority in terms of immuno-virological efficacy compared with first-line triple-therapies, the low genetic barrier to resistance for elvitegravir and the need for increased renal monitoring and possible cobicistat-related interactions, which are all potential limitations, the Committee considers that STRIBILD does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of patients infected with HIV-1 who are antiretroviral treatment-naive.

010.2 Target population

The target population is the population of patients living with HIV-1, who are treatment-naive.

The target population was estimated based on the number of treatment-naive people infected with HIV able to start antiretroviral treatment. According to the 2013 report on the clinical management of patients infected with HIV, effective antiretroviral (ARV) treatment is proposed to all patients living with HIV, including early after contamination and/or when the number of CD4 cells remains > 500/mm^3, due to its benefits in terms of reducing morbidity and mortality and the risk of transmitting HIV.

The estimation of the target population was therefore based on the number of patients treated by the healthcare system.

It is estimated that 149,900 (95% CI: 134,700 - 164,900)[6] people were living with HIV in France in 2010. Of those patients, 81% were diagnosed and 74% were in the healthcare system (which is 99,000 to 122,000 people). On 31 December 2011,[7] the number of patients with a chronic HIV condition in the general scheme was 96,948. Extrapolating the data from the general scheme to the whole of the population in France, the number of people classed as having the chronic condition HIV infection can be estimated as approximately 113,600 people in 2011.

According to the FHDH[8] database,

- approximately 88% of people treated are receiving antiretroviral combinations, including 5.4% starting a first-line treatment (which is approximately 6,000 treatment-naive adult patients starting a first-line treatment).
- and 6.5% of patients are not receiving any form of treatment, 4.2% having previously been treated, but have discontinued and 1.3% are receiving treatment that is not a strong

[6] Prise en charge médicale des personnes vivant avec le VIH. Recommandation du groupe d'experts. Rapport 2013. Under the management of Professor Philippe Morlat and with the guidance of CNNS and ANRS. http://www.sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf
[7] CNAMTS [French National Salaried Workers' Health Insurance Fund] data.
[8] FHDH - ANRS CO4. Retour d'informations Clinico-Épidémiologiques June 2011. http://www.ccde.fr

antiretroviral combination such as a dual-therapy of two NRTIs. By applying the percentage of treatment-naive patients (6.5%) to the 113,600 people treated for HIV infection at the end of 2011, it can be estimated that approximately 7,000 patients did not receive any treatment at all and are able to start first-line treatment according to new guidelines for the management of HIV.

Thus, the target population of treatment-naive patients can be estimated as being approximately 13,000 patients in 2014. This population could increase in the years to come, depending on screening efforts, as this estimation does not take into account the higher proportion (20%) of those infected with HIV in France who ignore the fact that they have tested positive.

In practice, the number of patients likely to receive STRIBILD within the context of triple-therapy and who are treatment-naive will be less than 13,000 patients, as its use as a first-line treatment is be limited due to restrictions linked to its low genetic barrier, renal toxicity and the possible interactions associated with cobicistat, which favours other ARV combinations currently recommended as first-line therapies for treatment-naive patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescription conditions according to the indication, the dosage and the treatment duration.