HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

7 May 2014

TYBOST 150 mg, film-coated tablet

B/30 (CIP 34009 276 121 7 6)

Applicant: GILEAD SCIENCES

INN	cobicistat
ATC Code (2013)	V03AX03 (other therapeutic products)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Tybost is indicated as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults. "**

Actual Benefit	**The actual benefit of TYBOST is insufficient for reimbursement by National Health Insurance in the indication of the Marketing Authorisation.**
Improvement in Actual Benefit	**Not applicable**
Therapeutic use	**In view of:** **- the risks of drug interactions** **- unavailable clinical efficacy and safety data for the combination with darunavir,** **- the risk of misuse related to the use of cobicistat in combination with protease inhibitors other than darunavir and atazanavir.** **the role of TYBOST (cobicistat) used as a pharmacokinetic enhancer of darunavir or atazanavir in the therapeutic strategy for patients infected with HIV-1 is poorly established.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 19 September 2013
Prescribing and dispensing conditions/special status	List I Initial annual hospital prescription

ATC Classification	2013 V Various V03 All other therapeutic products V03A All other therapeutic products V03AX Other therapeutic products V03AX03 cobicistat

02 BACKGROUND

The company is requesting inclusion of TYBOST 150 mg, film-coated tablets, whose active ingredient is cobicistat [COBI], on the list of medicines refundable by National Health Insurance and approved for hospital use.

Cobicistat is a pharmacokinetic enhancer, irreversible inhibitor and substrate of CYP3A, structural analogue of ritonavir, devoid of antiviral activity.
Cobicistat [COBI] is one of the four compounds of the fixed combination STRIBILD assessed on 6 November 2013[1] by the Committee as part of an application for inclusion. This fixed combination is made up of 2 NRTI - nucleo(side)(tide) reverse transcriptase inhibitors (emtricitabine [FTC] and tenofovir disoproxil fumarate [TDF]), an integrase inhibitor (elvitegravir [EVG]) and cobicistat. As a pharmacokinetic enhancer, the role of cobicistat in this combination is to increase the elimination half-life of the integrase inhibitor, elvitegravir.

As a reminder, during this evaluation, the Transparency Committee delivered a favourable opinion (substantial AB, IAB V) for inclusion of STRIBILD 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 HIV-1 infection in adults aged 18 years and over who are antiretroviral treatment-naïve" Furthermore, the Committee found an insufficient AB in pretreated patients "infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in STRIBILD", given the lack of clinical data in this patient population.

Cobicistat (TYBOST) is the first alternative to ritonavir [RTV], the only enhancer sold to date, in the treatment of patients with HIV-1 whose treatment includes atazanavir or darunavir.

[1] Haute Autorité de Santé. Transparency Committee Opinion on STRIBILD. 6 November 2013

03 THERAPEUTIC INDICATION

"Tybost is indicated as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults. "

04 POSOLOGY

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

Dosage:

Tybost is used in combination with atazanavir or darunavir, therefore the atazanavir or darunavir Summary of Product Characteristics should be consulted.

TYBOST must be co-administered with atazanavir or darunavir, taken orally, once daily with food. The doses of TYBOST and the co-administered protease inhibitor, atazanavir or darunavir, are presented in Table 1.

Table 1: Dosing regimens

Dose of TYBOST	Dose of HIV-1 protease inhibitor
150 mg once daily	Atazanavir 300 mg once daily
	Darunavir 800 mg once daily

If the patient misses a dose of TYBOST and realises within 12 hours of the time it is usually taken, the patient should take Tybost with food as soon as possible and resume their normal dosing schedule in combination with atazanavir or darunavir. If a patient misses a dose of TYBOST and realises more than 12 hours later, the patient should not take the missed dose and simply resume the usual dosing schedule.

Special populations:
Elderly
No data are available on which to make a dose recommendation for patients over the age of 65 years (see section 5.2).

Renal impairment
No dose adjustment of TYBOST is required for patients with renal impairment, including those with severe renal impairment. Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for these patients.
Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. Cobicistat has not been studied in HIV-1 patients with creatinine clearance less than 70 ml/min at baseline. TYBOST should not be initiated in patients with creatinine clearance less than 70 ml/min if any co-administered agent (e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate, or adefovir) requires dose adjustment based on creatinine clearance. See sections 4.4, 4.8 and 5.2.
Hepatic impairment
No dose adjustment of TYBOST is required in patients with mild (Child Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Cobicistat has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, the use of TYBOST is not recommended in these patients (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of cobicistat in children aged less than 18 years have not been established (see section 5.1). No data are available.

Method of administration:
TYBOST should be taken orally, once daily with food (see section 5.2). The film-coated tablet should not be chewed or crushed."

05 THERAPEUTIC NEED[2]

HIV infection is a serious pathology that is life-threatening.

The aim of antiretroviral treatment, regardless of the situation (first-line, further lines, including after multiple failure), should be to achieve and maintain a plasma viral load < 50 HIV-1 RNA copies/ml and a CD4 lymphocyte count > 500/mm^3.

Six classes of anti-HIV drugs with different mechanisms of action are available for treatment of 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, treatment combinations of at least three highly-active agents are recommended. These treatment regimens increase survival, reduce opportunistic infections and complications related to HIV infection and improve quality of life.
The first-line tritherapy remains a combination of two NRTIs with a third agent (one PI or one NNRTI) Fusion inhibitors, integrase inhibitors and CCR5 receptor antagonists are not preferred first-line treatments.
Since HIV has a higher genetic barrier relative to PIs than NNRTIs, PIs rarely cause early resistance to all the medicines of the class when plasma concentrations are insufficient (particularly due to imperfect compliance).
Currently, the use of a PI is accompanied by pharmacokinetic enhancement (increase of bioavailability) by the addition of a low dose of ritonavir (100 to 200 mg/day).
To date, ritonavir (NORVIR) is the only proprietary medicinal product recommended in HIV treatment as a pharmacokinetic enhancer of PIs (protease inhibitor).

Cobicistat is a new pharmacokinetic enhancer of protease inhibitors (darunavir and atazanavir), a structural analogue of ritonavir.

[2] Morlat P. Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'experts. French documentation. 2013.

06 CLINICALLY RELEVANT COMPARATORS

Note that unlike ritonavir prescribed at therapeutic doses, cobicistat does not have any antiretroviral activity; however, in France, ritonavir (NORVIR) is only recommended in HIV treatment as a pharmacokinetic enhancer of other protease inhibitors and is no longer recommended for its protease inhibitor properties.
Moreover, ritonavir is indicted in combination with PIs (without restriction), unlike cobicistat, whose indication is restricted to the combination with darunavir or atazanavir only.

NAME (INN) *Company*	Same TC* Yes/No	Indication	Date of opinion	AB	IAB (Wording)	Reimbursement
NORVIR (ritonavir) 100 mg, film-coated tablet 80 mg/ml, oral solution *ABBOTT France*	No	"Ritonavir 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)."	23/03/2011 (Renewal of inclusion)	Substantial	-	Yes

*therapeutic category

◗ Conclusion

The only clinically relevant comparator for cobicistat (TYBOST) is ritonavir (NORVIR).

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Currently, TYBOST (cobicistat), is only authorised in Europe (FDA MA approval not granted in the USA as of April 2013, procedure in progress).

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

8.1.1 Introduction

Study with darunavir
No clinical efficacy and safety data are currently available to assess the combination of cobicistat with darunavir [DRV].
A phase III, open-label, non-comparative study (GS-US-216-0130) evaluating cobicistat/darunavir in combination with two NRTIs in naïve and pre-treated patients is in progress (see 8.4 Study Schedule).

The pharmacokinetic enhancement effect of cobicistat (TYBOST) on darunavir [DRV] was evaluated in a phase I pharmacokinetic study (study GS-US-216-0115). In this study, 31 healthy volunteers were enrolled to receive [DRV] 800 mg in combination with TYBOST 150 mg or with ritonavir [RTV] 100 mg, administered once daily for 10 days.

The pharmacokinetic parameters for [DRV] at equilibrium were comparable whether they were enhanced by cobicistat (TYBOST) or by ritonavir (see Table 2).

Study with atazanavir
The company has provided the results of two studies evaluating TYBOST as a pharmacokinetic enhancer for atazanavir in antiretroviral treatment-naïve HIV-1 patients (Table 1).

Table 1: Presentation of studies GS-US-216-0105 (phase II) and GS-US-216-0114 (phase III)

Study	Type of study	Numbers N	Treatment regimens	Primary endpoint
Study 105 **GS-US-216-0105**	Phase II, multicentre, randomised, double-blind study versus RTV combined with ATV and TVD, 60 weeks. Extension phase to 96 weeks during which all patients received COBI combined with ATV and TVD.	85	• ATV + COBI + TVD (n = 56) • ATV + RTV + TVD (n = 29)	Percentage of subjects with a viral load (VL) <50 copies of HIV-1 RNA/ml at 24 weeks
Study 114 **GS-US-216-0114**	Phase III, international, multicentre, randomised, double-blind study versus RTV combined with ATV and TVD, 96 weeks. Open-label extension phase	692	• ATV + COBI + TVD (n = 344) • ATV + RTV + TVD (n = 348)	Percentage of subjects with a VL <50 copies of HIV-1 RNA/ml at 48 weeks

COBI: Cobicistat; RTV: Ritonavir; ATV: Atazanavir; TVD: TRUVADA (FTC/TDF); VL: Viral Load; HIV-1: Type 1 human immunodeficiency virus; ARV: Antiretroviral; ATC + co: Atazanavir/cobicistat; ATV + r: Atazanavir+ ritonavir

The effect of cobicistat on the pharmacokinetics of atazanavir was demonstrated in a pharmacokinetics substudy (n = 48) of phase III study GS-US-216-0114. The pharmacokinetic parameters for atazanavir at equilibrium were comparable whether they were enhanced by cobicistat (TYBOST) or by ritonavir (see Table 2).
In this study, TYBOST was combined with TRUVADA; it is possible that this combination may interfere with the pharmacokinetics of other products.

There were no clinical data available for the use of TYBOST in patients infected with HIV-1 and pretreated.
Given the similarities between studies 105 (phase II) and 114 (phase III) and the small number of patients included in phase II study 105 (85 patients), in terms of efficacy, only the results of study 114 are given in detail.

Table 2: Pharmacokinetic parameters [mean ± standard deviation (% VL)] of 800 mg of darunavir [DRV] or 300 mg of atazanavir [ATV] administered in combination with 150 mg of cobicistat or 100 mg of ritonavir once daily

Study	Treatment groups	AUC_{tau} (µg.h/ml)	C_{max} (µg/ml)	C_{max} (µg/ml)
Phase I study GS-US-216-0115	DRV 800 mg + cobicistat (n = 31)	81.08 ± 25.15 (31.0%)	7.74 ± 1.69 (21.8%)	2.40 ± 1.22 (50.7%)
	DRV 800 mg + ritonavir (n = 31)	79.99 ± 27.20 (34.0%)	7.46 ± 1.52 (20.3%)	2.48 ± 0.85 (34.3%)
Pharmacokinetics substudy GS-US-216-0114	ATV 300 mg + cobicistat* (n = 22)	46.13 ± 26.18 (56.8%)	3.91 ± 1.94 (49.6%)	0.80 ± 0.72 (90.3%)
	ATV 300 mg + ritonavir* (n = 26)	47.59 ± 24.39 (51.2%)	4.76 ± 1.94 (40.8%)	0.85 ± 0.72 (84.7%)

*Combined with a background therapy consisting of a fixed-dose combination of 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate

8.1.2 Study 105 - Phase II

Multicentre, randomised, double-blind efficacy study which evaluated the efficacy and safety of TYBOST as an enhancer of the PI atazanavir [ATV], compared with ritonavir [RTV] combined with [ATV], both of these combined with TRUVADA ([TVD], emtricitabine, tenofovir disoproxil fumarate) for 60 weeks in 85 adult patients infected with HIV-1 and antiretroviral treatment-naïve.

The results of the ITT analysis on the percentage of patients with viral RNA count <50 copies/ml (primary endpoint) at week 24 and at week 48 did not show any difference between the two combinations (see Table 3).

Table 3: Study GS-US-216-0105: virological response results (percentage of patients with <50 copies/ml viral RNA) at weeks 24 and 48 (snapshot analysis, ITT population)

		ATV+ COBI + TVD (n = 50)	ATV+ RTV + TVD (n = 29)	ATV/cobicistat + TVD versus ATV/RTV + TVD
				Difference % (95% CI)
virological success (VL < 50 copies HIV-1 RNA/ml)	Week 24	84.0% (n = 42)	86.2% (n=25)	- 4.4% [- 22.5% - 13.6%]
	Week 28	82.0 % (n=41)	86.2 % (n=25)	- 5.4% [- 23.8% - 13.1%]

In this study, 70.9% of patients had a baseline viral load (VL) of ≤ 100,000 of viral RNA/ml (study stratified for VL).

8.1.3 Study 114 - Phase III

➢ Study design

The study design is described in Table 4.

Table 4: Design of study GS-US-216-0114

Type of study	Non-inferiority (delta 12% threshold), phase III, international, controlled, randomised, double-blind, active comparator study to evaluate the efficacy and safety of TYBOST as an ATV enhancer (ATV + co) in combination with TRUVADA (TVD, FTC/TDF) compared with ritonavir combined with ATV (ATV + r) and to TVD for 96 weeks in adult patients infected with HIV-1 and antiretroviral treatment-naïve.
Date and duration of the study	From 26 April 2010 to 01 December 2011 Open-label extension study in progress. Final report planned for the last quarter of 2015.
Study objective	Main objective: To evaluate the efficacy of the ATV + COBI + TVD combination compared with ATV + RTV + TVD, in terms of viral response (proportion of patients presenting a viral load <50 copies of HIV-1 RNA/ml) at 48 weeks. Secondary objectives: To evaluate the efficacy (sustained virological response and TLOVR analysis*), and safety of the two treatments at 96 weeks. * *Time to loss of virological response*
METHOD	
Population	692 antiretroviral treatment-naïve adult patients with HIV-1 infection.
Treatments	Two treatment arms: • COBI 150 mg + ATV 300 mg + TVD (FTC/TDF 200/300 mg) + placebo [RTV], once daily orally; • RTV 100 mg + ATV 300 mg + TVD (FTC/TDF 200/300 mg) + placebo [COBI], once daily orally.
Study design	• Randomised, double-blind phase: patients received treatment for 96 weeks and were followed-up at 2, 4, 8, 12, 16, 24, 32, 40 and 48 weeks after inclusion, and then every 12 weeks until 96 weeks; • Open-label extension phase: the blind was lifted after 96 weeks of treatment. All patients were able to participate in this extension phase until marketing or the end of product development. Patients who did not wish to participate in the open-label extension phase had to be monitored for 30 days after the end of their treatment during the randomised double-blind phase.
Patient screening	Inclusion criteria • Patients 18 years old or older, males and females who agreed to use appropriate birth control, antiretroviral treatment-naïve and with a life expectancy of less than one year; • Patients with a plasma VL ≥5000 copies of HIV-1 RNA/ml; • Patients with adequate renal function with a glomerular filtration rate estimated at ≥70 ml/min according to the Cockcroft-Gault formula; • Genotype screening revealing to sensitivity to FTC, TDF and ATV. Non-inclusion criteria: • Patients with active HIV-linked disease (AIDS) diagnosed within 30 days prior to randomisation; • Treatment for hepatitis C virus during the study; • Decompensated cirrhosis (ascites, encephalopathy); • Pregnant and breastfeeding women; • Patients with a history of malignant disease (including untreated carcinomas in situ) other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma or non-invasive resectable squamous cell carcinoma. Patients with cutaneous KS were eligible as long as they had not received systemic treatment in the 30 days prior to inclusion and were not likely to receive any during the study; • Patients with a severe active infection (other than the HIV-1 infection) requiring parenteral antibiotic or antifungal treatment in the 30 days prior to inclusion.

Endpoints	Primary endpoint: virological response, defined by the proportion of patients who attained a viral load (VL) <50 copies of HIV-1 RNA/ml at 48 weeks according to snapshot statistical analysis = (analysis consisting of considering the last VL value observed between weeks 44 and 54) *The non-inferiority of treatment with cobicistat relative to the comparator was established if the lower end of the 95% confidence interval of the difference in virological response (cobicistat-ritonavir) was greater than -12%.* Secondary endpoints, in particular: • virological response at 48 weeks TLOVR*) analysis; • Loss of virological response (TLOVR*) analysis; * *Time to loss of virological response*
Number of subjects necessary	It was planned to include 700 patients infected with HIV-1, randomised according to a 1: 1 ratio (350 in each treatment arm) to establish the non-inferiority of cobicistat relative to ritonavir in terms of percentage of responders at 48 weeks, with a power of at least 95% by estimating a percentage of response of 79.5% in both treatment arms, a non-inferiority limit of 12% and a one-sided significance level of 0.025.
Analysis population	Efficacy analysis ITT (intention-to-treat) population: all the randomised patients who received at least one treatment dose; PP (per protocol) population: all the randomised patients who received at least one treatment dose and who participated in the study without a major protocol violation (including no violation of the inclusion criteria); Safety analysis Safety analysis population: all the randomised patients who received at least one treatment dose;

➢ Results

Characteristics of the patients included:

A total of 692 patients were included: 344 in the ATV + COBI + TVD group versus 348 in the ATV + RTV + TVD group.
At baseline, the patient demographic and clinical characteristics (baseline VL, CD4 count) were similar in both treatment groups (Table 5). The median age of patients was 36 (predominantly male, 83%). The baseline plasma RNA HIV-1 viral load was 4.8 $\log_{10}$ copies/ml (including 60% with a low viral load ≤100,000 copies/ml) and the median baseline CD4+ count was 343 x 10^6 cells/l. The majority of patients (>80%) were at stage A (asymptomatic) of the infection.

Table 5: Biological and clinical characteristics of patients included in study 114.

	ATV + co + TVD (N = 344) n (%)	ATV + r + TVD (N=348) n (%)	Total (N = 692) n (%)	p-value*
Biological characteristics of the HIV infection				
Viral load (log_{10} copies HIV-1 RNA/ml)				
Median (Min-Max)	4.78 (3.22-6.43)	4.84 (3.21-6.44)	4.81 (3.21-6.44)	0.44
Viral load (number of copies/ml				
≤100,000	212 (61.6)	205 (58.9)	417 (60.3)	0.47
>100,000	132 (38.4)	143 (41.1)	275 (39.7)	
Absolute value of CD4+ T cells (cells/µl)				
Median (Min-Max)	348 (1-1075)	341 (10-1455)	343 (1-1455)	0.64
CD4+ T cell count				
Median (Min-Max)	20.2 (0.4-49.3)	20.4 (0.6-46.5)	20.4 (0.4-49.3)	0.54
Clinical stage of the HIV infection				
Asymptomatic	285 (82.8%)	292 (83.9%)	577 (83.4%)	0.60
Symptomatic	31 (9.0%)	32 (9.2%)	63 (9.1%)	
AIDS	28 (8.1%)	24 (6.9%)	52 (7.5%)	

*Estimate of p-values using the two-tailed Cochran-Mantel-Haenszel test (categorical data) and a Wilcoxon test (continuous data).

Among these patients, 89 (50 in the ATV + COBI + TVD arm and 39 in the ATV + RTV + TVD arm) prematurely discontinued the treatment and the study. The main causes for premature treatment withdrawal were generally comparable between the ATV + COBI + TVD and ATV + RTV + TVD arms. These were occurrence of an adverse event (respectively 7.3% and 7.2%) and patients lost to follow-up (3.2% versus 1.1%).

Efficacy:

- Primary endpoint:

The results of the PP analysis demonstrated the non-inferiority of the ATV + COBI + TVD combination relative to the active comparator ATV + RTV + TVD group, on the primary efficacy endpoint defined by virological response (viral load <50 copies of HIV-1 RNA copies/ml) at 48 weeks: 98.0% of responder patients at 48 weeks in each of the two arms (difference of -0.1%, 95% CI [-2.5%; 2.3%]).

These results were confirmed in the snapshot analysis on the ITT population (Table 6). The non-inferiority of the ATV + COBI + TVD combination relative to the active comparator ATV + RTV + TVD group was demonstrated on the primary efficacy endpoint defined by virological response (viral load <50 HIV-1 RNA copies/ml) at 48 weeks:

- ATV + COBI + TVD group: 85.2 %
- ATV + RTV + TVD group: 87.4%

Or a difference of -2.2%, 95% CI [-7.4%; 3.0%]; p = 0.40

Sensitivity analyses on the primary efficacy endpoint support the non inferiority of cobicistat relative to the comparator, with percentages of virological response in the ATV + COBI + TVD group comprised between 87.5% and 89.7% according to the analysis and the population studied.

Table 6: virological results at 48 weeks according to snapshot analysis (ITT population)

	ATV + co + TVD (N = 344) n (%)	ATV + r + TVD (N = 348) n (%)	ATV + co + TVD vs ATV + r + TVD	
			p-value*	% difference (95.2% CI)**
At 48 weeks				
Responders (VL <50 copies HIV-1 RNA /ml)	**293 (85.2 %)**	**304 (87.4 %)**	**0.40**	**-2.2 % [-7.4%; 3.0%]**
virological failure	**20 (5.8 %)**	**14 (4.0 %)**		
(VL ≥ 50 copies HIV-1 RNA /ml)	6 (1.7 %)	7 (2.0)		
Treatment discontinued due to lack of efficacy	1 (0.3%)	0 (0)		
Treatment discontinued due to other causes** and last available VL ≥50 HIV-1 RNA copies/ml	13 (3.8%)	7 (2.0)		
No virological data***	**31 (9.0%)**	**30 (8.6%)**		
Treatment discontinued due to AE/death	22 (6.4%)	23 (6.6%)		
Treatment discontinued for other causes** and last available VL <50 HIV-1 RNA copies/ml	9 (2.6%)	7 (2.0 %)		
Missing data	0 (0)	0 (0)		

**: The p value for the superiority test comparing the rate of responders is estimated using the adjusted two-tailed Cochran-Mantel-Haenszel test on the baseline viral load.*
***: The difference in the rate of responders and the 95.2% confidence interval was calculated according to the baseline viral load adjusted according to the Mantel-Haenszel proportions.*
****: Between D309 and D378.*

- Secondary endpoints

The rate of virological response at 48 weeks according to the TLOVR algorithm (Table 7) was comparable between the two treatment arms: 82.8% in the ATV + COBI + TVD arm versus 85.3 % in the ATV + RTV + TVD arm (ITT population), or a difference of -2.6% (95% CI [-8.1%; 2.8%]; p = 0.34), rates comparable to those obtained in the snapshot analysis of the primary endpoint.

Table 7: Virological results at 48 weeks according to TLOVR analysis (ITT population)

	ATV + co + TVD (N = 344) n (%)	ATV + r + TVD (N = 348) n (%)	ATV + co + TVD vs ATV + r + TVD	
			p-value*	% difference (95.2% CI)
At 48 weeks				
Responders (TLOVR analysis) (VL <50 copies HIV-1 RNA/ml)	**285 (82.8 %)**	**297 (85.3 %)**	**0.34**	**-2.6 % [-8.1%; 2.8%]**
Virological failure***	**12 (3.5 %)**	**14 (4.0%)**		
Rebound (VL ≥50 copies HIV-1 RNA/ml)	8 (2.3%)	5 (1.4%)		
Treatment discontinued because of lack of efficacy	4 (1.2%)	9 (2.6%)		
Treatment discontinued because of death	0	0		
Treatment discontinued because of AE	24 (7.0%)	23 (6.6%)		
Treatment discontinued because of other causes*****	23 (6.7 %)	14 (4.0 %)		

*: Between D309 and D378.
**: The p value for the superiority test comparing the rate of responders is estimated using the adjusted two-tailed Cochran-Mantel-Haenszel test on the baseline viral load.
The difference in the rate of responders and the 95% confidence interval was calculated according to the baseline viral load adjusted according to the Mantel-Haenszel proportions.
***Virological failures include confirmed virological rebounds and subjects who did not attain a VL <50 copies of HIV-1 RNA/ml at week 48.
****Treatment discontinuations for other causes were the following: decision of the investigator, withdrawal of consent, lost to follow-up, non-compliance, protocol violation and pregnancy.

08.2 Resistance data

Date from study GS-US-216-0105 (study 105) and study GS-US-216-0114 (study 114):

Among the 79 patients randomised and treated during study 105, the samples from two patients with virological failure (suboptimal virological response and/or virological rebound) were analysed; no sign of viral resistance to the antiretroviral used during the study was identified.

The samples of 692 patients included in study 114 were analysed to test for pre-existing resistance (non-inclusion criteria):

- No patient had a K65R or M184V/I mutation upon inclusion in the study.
- 2.6% of patients (18/692) had a primary mutation resistance to PIs, mainly L33F and L90M mutations, but were considered to be sensitive to ATV.
- 8.4% of patients (58/692) had resistance mutations to NRTIs, mainly a V118I mutation (5.2%).

In all, 24 patients (3.5%) considered to have virological failures were analysed to test for resistance. These were patients who presented with:

- A suboptimal virological response (defined at the 8th week by a VL ≥50 copies of HIV-1 RNA/ml and a reduction of VL <1 $\log_{10}$ relative to baseline and confirmed at the next visit);
- virological rebound (defined as VL ≥400 copies HIV-1 RNA/ml on two consecutive visits after having a VL <50 copies of HIV-1 RNA/ ml, or an increase in VL > 1 $\log_{10}$ at two consecutive visits).

A comparable proportion of patients in the ATV + COBI + TVD arm (3.5%; 12/344) and ATV + RTV + TVD group (3.4%; 12/348) presented with virological failure.

During an analysis of subjects who failed treatment up to week 48, evaluable genotype data from paired isolates obtained at baseline and during treatment failure were available for 11 of the 12 virological failures in the cobicistat group. Among these 11 patients, 2 (0.6%) developed the M184V mutation associated with emtricitabine resistance. No subject developed the K65R mutation associated with resistance to tenofovir, or any primary resistance mutation associated with protease inhibitors. Nine other patients did not have any resistance mutation and remained phenotypically sensitive to all the antiretrovirals used during the study.
In the ritonavir group, genotype data were available for all 12 virological failures and no subject had emerging resistance to the various treatment components (TDF, FTC and ATV).

No new cases of primary resistance mutation to NNRTIs were reported in either of the arms of the study. In all, 17.3% of patients had a resistance mutation to NNRTIs at baseline: 9.5% (n=66) in the ATV + COBI + TVD arm versus 7.8% (n=54) in the ATV + RTV + TVD arm.

08.3 Adverse effects

8.3.1 Safety data from clinical studies

➢ General safety (GS-US-216-0114 and GS-US-216-0105 studies)

The safety results are from phase III studies (study 114, 48 weeks of exposure) and phase II studies (study 105, 60 weeks of exposure during the blinded treatment phase, in which a total of all 771 patients received treatment:

- 394 patients treated with cobicistat (TYBOST) + ATV + TRUVADA (FTC/TDF); median treatment duration: 48.4 weeks
- 377 patients treated with ritonavir + ATV + TRUVADA (FTC/TDF)

In these two studies (grouped data analysis), the incidence of adverse events was comparable in both treatment groups:

- ATV + COBI +TVD group: 91.6% (361/394 patients)
- ATV + RTV +TVD group: 92% (347/377 patients)

During the grouped analysis of studies 105 and 114, among the most frequently reported adverse effects (≥ 10% in both treatment groups), four (jaundice, nausea, hyperbilirubinaemia and upper respiratory infections) were reported by a larger number of patients in the ATV + COBI + TVD group and four (diarrhoea, headache, rhinopharyngitis and ocular jaundice) were reported by a larger number of patients patients in the ATV + RTV + TVD group.
A frequency difference of more than 5% was observed for the following adverse events: diarrhoea (ATV + COBI 15.0% versus ATV + RTV 21.2%) and rhinopharyngitis (ATV+ COBI, 9.4% versus ATV + RTV, 14.9%).

The majority of adverse events reported were grade 1 or 2.
The most commonly reported adverse events (grade 2, 3 or 4) were:

- ATV + COBI + TVD group: hyperbilirubinaemia (8.9%), jaundice (6.1%), headache (3.6%) and nausea (3.6%)
- ATV + RTV + TVD group: hyperbilirubinaemia (7.2%), diarrhoea (4.8%), urinary tract infection (4.0 %)

The incidence of grade 3 or 4 adverse events was higher in the ATV + COBI group (17.8%, 70/394) compared with the ATV + RTV group (13.3%, 50/377). The majority of grade 3 or 4 adverse events reported were considered not to be treatment-related by the investigators (6.9% in the ATV + COBI group versus 4.5% in the ATV + RTV group were considered treatment related).

The incidence of adverse events considered to be potentially study treatment-related by the investigators was comparable between the treatment groups (56.9% in the ATV + COBI group and

57.3% in the ATV + RTV group). The most commonly observed events in both groups were: ocular icterus, nausea and jaundice.

In these two studies, serious adverse events were reported in 38/394 (9.6%) patients in the ATV + COBI group and by 25/377 (6.6%) patients in the ATV + RTV group. The only serious adverse event that was reported by more than 1% of subjects was acute renal failure (four patients, all in the ATV + RTV group). The most often reported serious adverse events were infections (14 patients per group).
In this grouped analysis, the incidence of serious adverse events considered potentially related to the study treatment was comparable between both groups:

- five patients (1.3%) in the ATV + COBI group: rhabdomyolysis, miscarriage, depression and kidney disease, including acquired Fanconi syndrome;
- six patients (1.6%) in the ATV + RTV treatment group: fever, increased gamma GT; acquired Fanconi syndrome, renal impairment, priapism and rash.

The most commonly reported adverse events during the updated data analysis at 96 weeks of the phase III study (study 114)[3] were:

- ATV + COBI + TVD group: jaundice (21.2%), ocular icterus (19.5) and nausea (17.76%)
- ATV + RTV + TVD group: diarrhoea (20.4%), ocular icterus (20.4%), jaundice (17.0%) and nausea (16.4%).

➢ Specific safety (study GS-US-216-0114):

The safety population results for study 114 show a comparable incidence of adverse events in both groups (318/344; 92.4% in the ATV + COBI + TVD group and 323/348; 92.8% in the ATV + RTV + TVD) group. The most frequently reported adverse events in this study are shown in Table 8.

Given the possible link between tenofovir, TDF, and bone and renal adverse events (AEs) and the link between atazanavir and hepatic adverse events, bone, renal or hepatic adverse events are specifically monitored.

In the phase III study (study 114), the incidence of these events was comparable in both treatment arms (ATV + COBI + TVD and ATV + RTV + TVD):

- Renal AEs: 0.3% (n=1) vs. 1.7% (n=6)
- Bone AEs 0.6 % (n=2) vs. 1.1% (n=4)
- Hepatic AEs: no case reported in either arm.

[3] EPAR, 25 July 2013, TYBOST, cobicistat ; No. EMEA /H/C/002572/0000.

Table 8: Common adverse events (incidence ≥10%) reported in study 114 (safety analysis population)

All AE grades combined by system organ classes, n (%)	ATV + co + TVD (N = 344)	ATV + r + TVD (N = 348)
Number of patients with an AE all grades combined	**318 (92.4)**	**323 (92.8)**
Ophthalmic disorders	**71 (20.6)**	**75 (21.6)**
Ocular icterus	61 (17.7)	64 (18.4)
Gastrointestinal disorders	**168 (48.8)**	**166 (47.7)**
Diarrhoea	53 (15.4)	71 (20.4)
Nausea	61 (17.7)	57 (16.4)
Hepatobiliary disorders	**94 (27.3)**	**76 (21.8)**
Jaundice	72 (20.9)	54 (15.5)
Hyperbilirubinaemia	39 (11.3)	34 (9.8)
Infections and infestations	**205 (59.6)**	**218 (62.6)**
Rhinopharyngitis	37 (10.8)	53 (15.2)
Upper respiratory infection	35 (10.2)	28 (8.0)
Nervous system disorders	**85 (24.7)**	**80 (23.0)**
Headaches	38 (11.0)	54 (15.5)

- *Renal adverse events:*

The most commonly reported renal AEs were acute renal failure (0 patient in the ATV + COBI + TVD arm and 4 in the ATV + RTV + TVD arm), of stage 3 (n = 2) or stage 4 (n = 2). All these patients had at least one concomitant AE related to an acute illness, such as infectious gastroenteritis.

The other renal AEs were one case of stage 3 renal failure reported in a patient of the ATV + RTV + TVD group and one grade 3 serious Fanconi syndrome, considered as treatment-related by the investigator and which led to premature treatment discontinuation in each of the two arms.

As for abnormal lab values, the observation of elevated serum creatinine was an expected adverse event given the inhibitor effect of cobicistat on tubular creatinine excretion.

In all, nine patients (two in the ATV + COBI + TVD arm and seven in the ATV + RTV + TVD arm) had increased serum creatinine. This was related to the reduced creatinine clearance, an increase of blood creatinine or a reduction of the GFR. Among these nine patients, eight were enrolled at the same centre. These cases were considered non-serious and did not lead to premature treatment discontinuation.

Moreover, tenofovir (a component of TRUVADA) may have renal toxicity.[4] Pharmacokinetic analyses performed during the development of the fixed combination STRIBILD (TVD + cobicistat + elvitegravir) showed that the levels of exposure to tenofovir increased by approximately 30% after administering STRIBILD relative to tenofovir alone.[1] Due to these known risks, warnings were included in the SPC for STRIBILD concerning administration in patients with renal failure or at risk for renal failure.
The use of TYBOST in patients with renal failure was identified as missing information in the phase III study (study 114).
A clinical study evaluating the use of cobicistat in combination with atazanavir and darunavir in renal failure patients (mild and moderate RF) is in progress (study GS-US-236-0118). However, according to data showing no significant difference in the pharmacokinetics of TYBOST in subjects not infected with HIV with severe renal failure and healthy subjects (GS-US-216-0124), no usage restriction in patients with renal failure is established at this time. On the other hand, TYBOST treatment should not be initiated in patients with creatinine clearance less than 70 ml/min if any co-administered agent (e.g. tenofovir disoproxil, adefovir, emtricitabine or lamivudine) requires dose adjustment based on creatinine clearance (see SPC).

[4] Cases of renal impairment, renal failure, elevated levels of creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported in connection with the use of tenofovir disoproxil fumarate in clinical practice (see VIREAD SPC).

- *Bone adverse events:*

Cases of bone fracture were reported in two patients (0.6%) in the ATV + COBI + TVD arm and four patients (1.1%) in the ATV + RTV + TVD arm.

- *Hepatic adverse events:*

Hepatic adverse events (increased transaminases) have been found more frequently in the ATV + COBI + TVD group:

- ALT elevation: 18.4% in the ATV + COBI + TVD group versus 12.5% in the ATV + RTV + TVD group.
- AST elevation: 21.2 % in the ATV + COBI + TVD group versus 14.1 % in the ATV + RTV + TVD group.

Gamma GT, AP and total bilirubin levels were comparable in both treatment groups.

No hepatic AEs of specific interest were reported during the study (acute liver failure, liver failure or liver damage).

- *Cutaneous adverse events:*

A comparable proportion of patients with rashes was reported in both treatment arms: 18.3% (n=63) in the ATV + COBI + TVD arm versus 20.1% (n=70) in the ATV + RTV + TVD arm (p<0.56). The most commonly observed AEs were:

- ATV + COBI + TVD group: rash (6.7%), pruritus (3.2%) and generalised rash (2.6 %);
- ATV + RTV+ TVD group: rash (6.0%), pruritus (5.2%) and papular eruptions (2.3%);

The majority of AEs were grade 1 or 2.
Two patients in the ATV + COBI + TVD arm and one in the ATV + RTV + TVD arm had a skin AE of grade 3. No grade 4 skin AE was reported during the study.

In all, a comparable proportion of patients who prematurely discontinued treatment for AEs was reported in both treatment arms: 7.3% (n = 25) in the ATV + COBI + TVD arm versus 7.2% (n = 25) in the ATV + RTV + TVD arm.

Premature treatment discontinuations for AEs reported during the study were consistent with the safety profile already known for the antiretrovirals used.

Except for cases of jaundice, ocular icterus and allergic dermatitis that were reported, respectively, in nine, eight and two patients, no AE leading to treatment discontinuation was observed in more than one patient in the ATV + COBI + TVD arm. Likewise, cases of jaundice, ocular icterus, hyperbilirubinaemia and rash were reported, respectively, in seven, four, two and two patients in the ATV + RTV + TVD arm.

8.3.2 SPC data

"Summary of the safety profile
Adverse reactions for cobicistat-boosted atazanavir were consistent with the safety profile of ritonavir-boosted atazanavir. The most frequently reported adverse reactions to cobicistat-boosted atazanavir were associated with elevated bilirubin levels (see Table 9).

Tabulated summary of adverse reactions
The safety of cobicistat has been evaluated in a phase 3 randomised, active-controlled clinical study (GS-US-216-0114), in which 692 treatment-naïve patients received at least one dose of cobicistat-boosted atazanavir (n = 344) or ritonavir-boosted atazanavir (n = 348) administered with emtricitabine and tenofovir disoproxil fumarate fixed dose combination. Of these 692 patients, 613 (300 atazanavir/cobicistat and 313 atazanavir/ritonavir) and 554 (271 atazanavir/cobicistat and 283 atazanavir/ritonavir) received at least 48 and 96 weeks of treatment, respectively.

Adverse reactions observed to cobicistat-boosted atazanavir during 96 weeks of clinical trial experience from study GS-US-216-0114 are listed in Table 3, below, by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 9: Tabulated summary of adverse reactions to cobicistat-boosted atazanavir based on experience for 96 weeks from phase 3 study GS-US-216-0114

Frequency	Adverse reaction
Metabolism and nutrition disorders	
Common:	hyperglycaemia, increased appetite
Psychiatric disorders	
Common:	insomnia, abnormal dreams
Uncommon	depression, sleep disorder
Nervous system disorders	
Common:	headache, dizziness, somnolence, dysgeusia
Eye disorders	
Very common:	ocular icterus
Gastrointestinal disorders	
Very common:	nausea
Common:	vomiting, diarrhoea, dyspepsia, abdominal pain, abdominal distension, flatulence, dry mouth
Hepatobiliary disorders	
Very common:	jaundice
Common:	hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Common:	rash
Uncommon	pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	myalgia
Renal and urinary disorders:	
Uncommon:	nephrolithiasis, haematuria, proteinuria
General disorders and administration site conditions	
Common:	fatigue
Uncommon:	pyrexia, asthenia

Description of selected adverse reactions

Renal impairment
Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. An increase from baseline in serum creatinine due to cobicistat's inhibitory effect generally does not exceed 0.4 mg/dl.
In study GS-US-216-0114, decreases in estimated creatinine clearance occurred early in treatment with cobicistat, after which they stabilised. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was -13.4 ± 15.2 ml/min in the cobicistat-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group and -8.7 ± 14.5 ml/min in the ritonavir-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group.

Effects on the liver
In study GS-US-216-0114, hyperbilirubinaemia (> 1 x ULN) was common: 97.7% in the cobicistat-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group, and 97.4% in the ritonavir-boosted atazanavir plus emtricitabine and tenofovir disoproxil fumarate fixed-dose combination group. However, a higher percentage of subjects in the cobicistat-boosted group had increases in total bilirubin > 2 x ULN than those in the ritonavir boosted group (85.7% versus 77.7%). The rates of study drug discontinuation due to increased bilirubin-related adverse events were low and similar in both groups (4.9% in the cobicistat-boosted group and 3.4% in the ritonavir-boosted group). An increase of > 3 x ULN in alanine aminotransferase or aspartate aminotransferase was recorded in 12.0% of subjects in the cobicistat boosted group and 8.7% in the ritonavir-boosted group.

Paediatric population
No data are available for children below 18 years of age. TYBOST is not recommended in this population (see section 4.2).

Other special population(s)
Elderly
Cobicistat has not been studied in patients over the age of 65."

08.4 Risk Management Plan

A summary of the various pharmacovigilance and risk minimisation activities provided for in the risk management plan is given in the table below.

	Pharmacovigilance		Risk minimisation	
	Routine PV	Supplemental studies	Statement in the SPC	Additional action
Identified risks				
None				
Potential risks				
Use of medicines contraindicated with COBI	X	X	X	
Off-label use of COBI as a booster of PIs other than ATV or DRV once daily.	X	X	X	
Missing Information				
Long-term safety data for ATV + co and DRV + co in adult patients infected with HIV-1	X	X		
Safety data in children	X	X	X	
Safety data in the elderly	X		X	
Safety data in pregnant women	X	X	X	
Safety data during breastfeeding	X		X	
Safety data in patients with severe liver failure	X		X	
Safety data in patients with renal failure	X	X	X	
Safety data in patients with heart disease	X			
Interaction with other medicinal products	X	X	X	

Potential risks outlined in the RMP are: off-label use of TYBOST as a pharmacokinetic enhancer of PIs other than ATV and DRV, concomitant administration of medicines whose use is contraindicated with cobicistat (drug interactions).
The RMP also recommends the provision of data on the following missing information: safety in children, elderly patients, pregnant women, patients with renal failure, and heart failure, severe liver disease, drug interactions, long-term safety in adults infected with HIV-1 of atazanavir + cobicistat and darunavir + cobicistat combinations.

08.5 Summary & discussion

➢ Efficacy

The efficacy of cobicistat as a pharmacokinetic enhancer of the protease inhibitor atazanavir was investigated in a phase III randomised, comparative, double-blind non-inferiority study (study 114), and in a phase II study (study 105), with a similar study design in a smaller population (n = 85).

The primary efficacy endpoint of these studies was the percentage of patients with a viral RNA count <50 copies/ml at week 48.
The non-inferiority of the ATV + COBI + TVD combination relative to the ATV + RTV + TVD combination was demonstrated (non-inferiority limit 12%, 95% CI, ITT analysis):

- ATV + cobicistat + TVD: responder rate = 85.2%
- ATV + ritonavir + TVD: responder rate = 87.4%,

Or a difference of -2.2%, 95% CI [-7.4%; 3.0%]; p = 0.40

The efficacy of TYBOST as an enhancer of the activity of ATV has only been demonstrated in combination with TRUVADA (emtricitabine, tenofovir) in antiretroviral-treatment-naïve patients. This combination of TVD + ATV is a currently-recommended first-line tritherapy.[2]

The evaluation of the efficacy of cobicistat as a pharmacokinetic enhancer for the protease inhibitor darunavir (DRV) mainly relies on data from a phase I study (study GS-US-216-0115). No clinical efficacy data on this combination is available; the use of this protease inhibitor enhanced by cobicistat relies solely on this phase I study and indirect comparisons of the results from various pharmacokinetic studies: [DRV] enhanced by [COBI] (study GS-US-216-0130) and [DRV] enhanced by [RTV] (ARTEMIS and ODIN studies). According to the Committee for Medicinal Products for Human Use (CHMP) these data confirm the comparable efficacy of the DRV + cobicistat combination and the DRV + ritonavir combination. The CHMP also reiterates the need to use darunavir in combination with cobicistat only in the sub population infected with HIV described in the SPC for darunavir, when used in a once-daily dose.

No clinical efficacy data are available in patients infected with HIV-1 and previously treated.

➢ Resistance

During these two studies, the rate of appearance of resistance was limited in both treatment arms and patients remained phenotypically sensitive to the antiretrovirals received in the study.

➢ Adverse effects

The use of ATV + COBI in combination with TVD for 48 weeks did not reveal any particular safety signal. The data at week 96 from phase II study (study 105) and the phase III study (study 114) do not show an increase in renal adverse events when [COBI] was coadministred with [TDF] relative to the [RTV] group. However, the data are insufficient to determine if co-administration of [TFV] and [COBI] is associated with an increased risk of renal adverse events compared with regimens using [RTV] as a pharmacokinetic enhancer.
The available safety data also indicate a slight increase in the number of cases of hyperbilirubinaemia and adverse events of higher grades in the ATV + co group versus ATV + RTV.
The effect on renal function of the combination of cobicistat with tenofovir remains uncertain. Consequently, although there is no objection to the use of cobicistat as a pharmacokinetic enhancer of atazanavir or darunavir and there is currently no reason not to use it in combination with tenofovir, it cannot be ruled out that new data will show an additional risk of renal dysfunction if ATV + cobicistat or DRV + cobicistat is administered in a treatment also combining tenofovir.

Moreover, co-administration of cobicistat with darunavir or atazanavir should not be combined with another antiretroviral agent that requires pharmacokinetic enhancement by a CYP3A4 inhibitor since data on drug interactions are still incomplete.

08.6 Planned studies

List of post-marketing studies requested by the European Medicines Agency (EMA) as part of the Marketing Authorisation for TYBOST:

Identified risk	Study description	Status of discussions with the EMA as of 04/07/2013
Use of medicines contraindicated with cobicistat	Post-marketing study to determine: - concomitant administration of medicines whose co-administration with cobicistat is contraindicated; - off-label use of cobicistat in combination with a PI other than DRV or ATV once daily.	Feasibility assessment report to be submitted on 31 December 2013
Off-label use of cobicistat as a booster of PIs other than ATV or DRV once daily.		
Long-term safety data for ATV + co and DRV + co in adult patients infected with HIV-1	Phase 3B randomised, double-blind, clinical study (GS-US-236-0128), evaluating the efficacy and safety of EVG/co/FTC/TDF (STRIBILD STR) vs. Atazanavir + ritonavir + TRUVADA in antiretroviral-treatment-naïve women infected with HIV-1	48-week report to be submitted in Q4 2016
	To evaluate the possible in vivo protease inhibitor activity of cobicistat by sequencing protease in subjects with virological failure in the various STRIBILD studies	Final analysis to be submitted 28 February 2017
	Phase 3 randomised and double-blind clinical study (GS-US-216-0114), to evaluate the efficacy and safety of ATV/co + TVD vs ATV/r + TVD at 96 weeks of treatment and beyond.	144-week report to be submitted in Q3 2014
	Phase 3B open-label and single-arm clinical study (GS-US-216-0130), to evaluate the safety of treatment with DRV + COBI + 2 NRTIs up to 48 weeks of treatment and beyond.	Final report to be submitted in Q3 2015
Safety data in children	Phase 2/3 multicentre, open-label, non-randomised, multiple cohort study (GS-US-183-0154), evaluating the pharmacokinetics, safety and antiviral efficacy of EVG co-administered with cobicistat and two NRTIs as a first-line in antiretroviral treatment-naïve patients above age 18 infected with HIV-1	Final report to be submitted in March 2022
	Open-label, multicentre, multiple cohort two-part study (GS-US-216 0128), to evaluate the pharmacokinetics, safety and efficacy of ATV/co and DRV/co in children and adolescents	48-week report to be submitted February 2018
Safety data in pregnant women	Registry of exposure to antiretrovirals during pregnancy to determine the risk of birth defects in patients exposed to cobicistat during pregnancy	Interim reports available every 6 months (June and December of each year)
Safety data in patients with renal failure	Phase 3 open-label study (GS-US-236-0118), evaluating the safety of an antiretroviral containing cobicistat in patients infected with HIV-1 with mild to moderate renal failure.	Final report to be submitted in Q3 2015
Interaction with other medicinal products	To evaluate the effect of TDF administered with or without cobicistat on renal function and renal tubular function markers in patients infected with HIV-1 and antiretroviral treatment-naïve.	Final report to be submitted in May 2015

Identified risk	Study description	Status of discussions with the EMA as of 04/07/2013
	Phase 1 study (GS-US-236-0135) evaluating the potential of drug interactions between telaprevir and STRIBILD (on the one hand) or ATV/r + EVG (on the other hand) in healthy subjects	Final report to be submitted in January 2014
	Phase 1 study (GS-US-236-0136) evaluating pharmacokinetic drug interactions between EVG/Co and rifabutine	Final report to be submitted in December 2014
	Phase 1 study (GS-US-236-0137) evaluating the potential of drug interactions between carbamazepine and EVG/Co in healthy subjects	Final report to be submitted in December 2014
	Physiology-based pharmacokinetic simulations to evaluate the potential effect of powerful CYP3A4 inhibitors on cobicistat exposure	Final report to be submitted in Q2 2014
	In-vitro studies to evaluate the effect of cobicistat and other components of STRIBILD on the cytotoxicity of tenofovir	Final report to be submitted in Q3 2013

09 THERAPEUTIC USE

The update to the French recommendations in 2013 is prior to the marketing of TYBOST. Consequently these recommendations do not include therapeutic strategies for cobicistat alone (TYBOST) as an "enhancer" or in the fixed combination STRIBILD.
In the 2013 report on the medical treatment of people living with HIV,[2] the treatment of this infection may combine many antiretrovirals (six medicinal classes):

- 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 of at least three highly active agents are recommended in naïve subjects, making use of the following regimens:
- 2 NRTI + 1 PI;
- 2 NRTI + 1 NNRTI.

Fusion inhibitors, integrase inhibitors and CCR5 receptor antagonists are not preferred first-line treatments.
The choice of the two NRTIs for tritherapy should preferably involve fixed combinations of tenofovir/emtricitabine (TRUVADA) or abacavir/lamivudine (KIVEXA).
TRUVADA should be preferred if the plasma viral load is ≥100,000 copies/ml, particularly in the case of combination with atazanavir/ritonavir (REYATAZ) or efavirenz (SUSTIVA), owing to the greater risk of virological failure with KIVEXA in this sub-population.
When the viral load is <100,000 copies/ml, the choice between KIVEXA and TRUVADA can be made on a case-by-case basis, and should take into account factors such as: HBV coinfection or renal failure.
TRUVADA must be used with caution in patients with renal failure or who are at risk of this occurring. KIVEXA must only be used in patients who are not carriers of HLA B*5701 allele.

The third agent should preferably be a PI/ritonavir or an NNRTI. There is no conclusive argument in favour of the use of one or these two classes over the other. Preferred usage recommendations are as follows:
- if a PI/ritonavir is chosen as the third agent: atazanavir/ritonavir or darunavir/ritonavir
- if an NNRTI is chosen as the third agent: efavirenz, raltegravir, rilpivirine (only if VL <5 log copies/ml).

Also, according to current recommendations on the treatment of patients infected with HIV 1,[2,5,6,7] when a protease inhibitor (PI) is used, the two recommended first-line PIs are darunavir 800 mg/day and 300 mg atazanavir/day (in combination with ritonavir as a pharmacokinetic enhancer).

Given its non-inferior efficacy to that of RTV, in combination with ATV and TVD, and its comparable safety profile, cobicistat (TYBOST) could be an alternative treatment with ritonavir (NORVIR) as a pharmacokinetic enhancer for this protease inhibitor in adult patients infected with HIV-1 at the doses of the Marketing Authorisation. Its efficacy as a pharmacokinetic enhancer for the protease inhibitor darunavir (DRV) was studied in a phase I pharmacokinetic study. Antiviral efficacy and safety data from randomised controlled studies are only available for atazanavir enhanced by cobicistat and not for darunavir enhanced by cobicistat.

The safety and efficacy of TYBOST have not been established in combination with atazanavir or darunavir when they are used at a different dosage (twice daily administration with darunavir, different dosage).
The use of TYBOST as a pharmacokinetic enhancer of another HIV-1 protease inhibitor or any other antiretroviral medicine requiring pharmacokinetic enhancement by the co-administration of a CYP3A4 inhibitor has not been assessed. TYBOST should therefore not be used in these situations (risk of loss of antiretroviral activity, development of resistance).
Moreover, the currently available data do not permit determining whether the coadministration of cobicistat with tenofovir disoproxil fumarate is associated with an increased risk of nephrotoxicity in comparison with treatments containing tenofovir disoproxil fumarate without cobicistat.

Since this is a pharmacokinetic enhancer and a powerful and irreversible CYP3A inhibitor, many drug interactions are foreseen. These remain poorly established at this time. The drug interactions expected with cobicistat rely on drug interaction studies (buprenorphine/naloxone, rifabutin) or, for the most part, on a prediction of interactions based on the expected magnitude of interaction and potential risk for serious events or loss of efficacy (see SPC section 4.5: Interaction with other medicinal products and other forms of interaction). Moreover, according to pharmacokinetic data,[1] cobicistat is not an inducer of CYP1A2, CYP2C9 or CYP2C19. It is a weak inhibitor of cytochromes CYP2D6, CYP2C8 and UGT1A1 and a modest inhibitor of CYP2B6. The clinical consequences of this pharmacokinetic profile that are more favourable than that of ritonavir in terms of drug interactions remain poorly documented.

The risk of misuse related to the use of cobicistat in combination with protease inhibitors other than darunavir and atazanavir and the many potential drug interactions related to the mechanism of action of cobicistat currently remain unresolved issues.

Unlike ritonavir, TYBOST must be taken with meals, which may be an obstacle to compliance for some patients. In fact, taking ritonavir with meals is preferable but not required; for patients preferring to take it without food, measuring the plasma concentration of antivirals will ensure their efficacy.

Given all of these elements (risk of misuse, risk of drug interactions, unavailable clinical efficacy and safety data for the combination with darunavir), the role of TYBOST (cobicistat) used as a pharmacokinetic enhancer for darunavir or atazanavir in the treatment strategy for patients with HIV-1 is poorly established.

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[5] Melanie A Thompson, Judit A Aberg, Jennifer F. Hoy et al. Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations of the International AIDS Society–USA Panel. JAMA. 2012; 308(4): 387-402

[6] Guidelines for the Use of Antiretroviral Agents in HIV 1-Infected Adults and Adolescents, DHHS, 2013 (http://aidsinfo.nih.gov/guidelines).

[7] European Aids Clinical Society, Recommandations Version 7.01, November 2013, (http://www.europeanaidsclinicalsociety.org)

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual Benefit

◗ HIV infection is a serious disease that entails a severe deterioration in quality of life and is also life-threatening.
◗ TYBOST, as a pharmacokinetic enhancer for darunavir or atazanavir seeks to prevent and/or correct the immune deficiency induced by HIV-1 infection in adult patients with HIV-1.
◗ The efficacy/adverse effects ratio for TYBOST is modest. Given the limited data on drug interactions and the absence of clinical safety and efficacy data in combination with darunavir, the use cobicistat (TYBOST) as a simple alternative to ritonavir as a pharmacokinetic enhancer for the protease inhibitors atazanavir or darunavir is not established.
◗ There is a therapeutic alternative, ritonavir, which has demonstrated its effectiveness as a pharmacokinetic enhancer of protease inhibitors and whose safety and drug interactions are documented.
◗ This proprietary medicinal product should only be used as a pharmacokinetic enhancer for atazanavir 300 mg (once daily) or darunavir 800 mg (once daily).

◗ Public health benefit:
The public health burden of HIV-1 infection is substantial.
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 the proprietary medicinal product TYBOST on morbidity and mortality or quality of life to be assessed directly. Moreover, given the available data (non-inferiority relative to the use of ritonavir as a pharmacokinetic enhancer for atazanavir with a comparable safety profile), it is not expected that this proprietary medicinal product, relative to other existing treatments, will have an impact on the reduction of morbidity and mortality in patients infected with HIV-1.
In conclusion, given the current state of knowledge, it is not expected that TYBOST will have an impact on public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of TYBOST is <u>insufficient</u> for reimbursement by National Health Insurance in the Marketing Authorisation indication.

The Committee 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 and at the dosages in the Marketing Authorisation.