Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tenofovir disoproxil fumarate/ Emtricitabine/Elvitegravir/Cobicistat

Proprietary Product Name: Stribild

Sponsor: Gilead Sciences Pty Ltd

August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission:	New fixed dose combination product
Decision:	Approved
Date of Decision:	7 February 2013
Active ingredients:	Tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat
Product Name:	Stribild
Sponsor's Name and Address:	Gilead Sciences Pty Ltd Level 6, 417 St Kilda Road Melbourne VIC 3004 Australia
Dose form:	Tablet, film coated
Strength:	300 mg (tenofovir disoproxil fumarate), 200 mg (emtricitabine), 150 mg (elvitegravir) and 150 mg (cobicistat)
Container:	Bottle, high density polyethylene (HDPE)
Pack size:	30
Approved Therapeutic use:	Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults. Stribild is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-type 1 (HIV-1) reverse transcriptase inhibitors.
Route of administration:	Oral
Dosage:	One tablet daily
ARTG Number:	194081

Product background

This AusPAR describes the application by Gilead Sciences Pty Ltd (the sponsor) to register a new fixed dose combination tablet containing 300 mg tenofovir disoproxil fumarate (TDF), 200 mg emtricitabine (FTC), 150 mg elvitegravir (EVG) and 150 mg cobicistat (COBI), under the product name Stribild, for the following indication:

> *as a complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of Stribild*

The product is referred to as 'Stribild' throughout this document; however, the names 'Quad' and 'Stribild' are considered interchangeable for the purpose of this AusPAR.

The proposed formulation is described as a single-tablet regimen (STR) and contains 2 new chemical entities, EVG and COBI, which were under evaluation for registration as individual therapeutic goods by the TGA at the time this application was considered. The other components, TDF and FTC, were registered in Australia since 2002 and 2005, respectively, and are currently available in Australia in a number of formulations/products, including fixed-dose combinations, for use in the treatment of human immunodeficiency virus (HIV).

Tenofovir disoproxil fumarate is a nucleotide (Nt) reverse transcriptase inhibitor (RTI; NtRTI); FTC is a nucleoside reverse transcriptase inhibitor (NRTI); and EVG is a HIV-1 integrase strand-transfer inhibitor (INSTI) and works by preventing integration of the HIV-1 deoxyribonucleic acid (DNA) into the host-cell genome. Cobicistat is a selective, mechanism-based inhibitor of the cytochrome P450 (CYP) 3A subfamily. Inhibition of CYP3A mediated metabolism by COBI enhances the systemic exposure of CYP3A substrates, one of which is EVG.

Elvitegravir is of the same drug class as the currently registered anti-HIV agent raltegravir (RTG). Cobicistat is a structural analogue of the registered protease inhibitor ritonavir (RTV) but it has no antiretroviral (ARV) activity. As with RTV, COBI acts as a pharmacokinetic (PK) enhancer/booster for CYP3A substrates including EVG. The currently approved INSTI RTG is not a CYP3A substrate. Ritonavir as a PK enhancer is routinely used with other protease inhibitors (such as atazanavir (ATV) and darunavir) in the treatment of HIV infection.

Stribild contains the current standard-of-care dual Nt/NRTI backbone, that is, TDF/FTC, in the same doses as currently approved in adults (300 mg TDF, 200 mg FTC). This is the first fixed-dose combination product for the treatment of HIV that contains 4 active ingredients. Currently 2 fixed-dose products containing 3 anti HIV agents are approved in Australia; both contain the TDF/FTC backbone in combination with, respectively, efavirenz (EFV) and rilpivirine (RPV). Efavirenz and RPV are non-nucleoside reverse transcriptase inhibitors (NNRTI).

Regulatory status

The product received registration on the Australian Register of Therapeutic Goods (ARTG) on 22 February 2013. At the time the TGA considered this application, a similar application was approved in the USA (on 27th August 2012) and was under consideration in the European Union (EU) and Canada.[1]

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

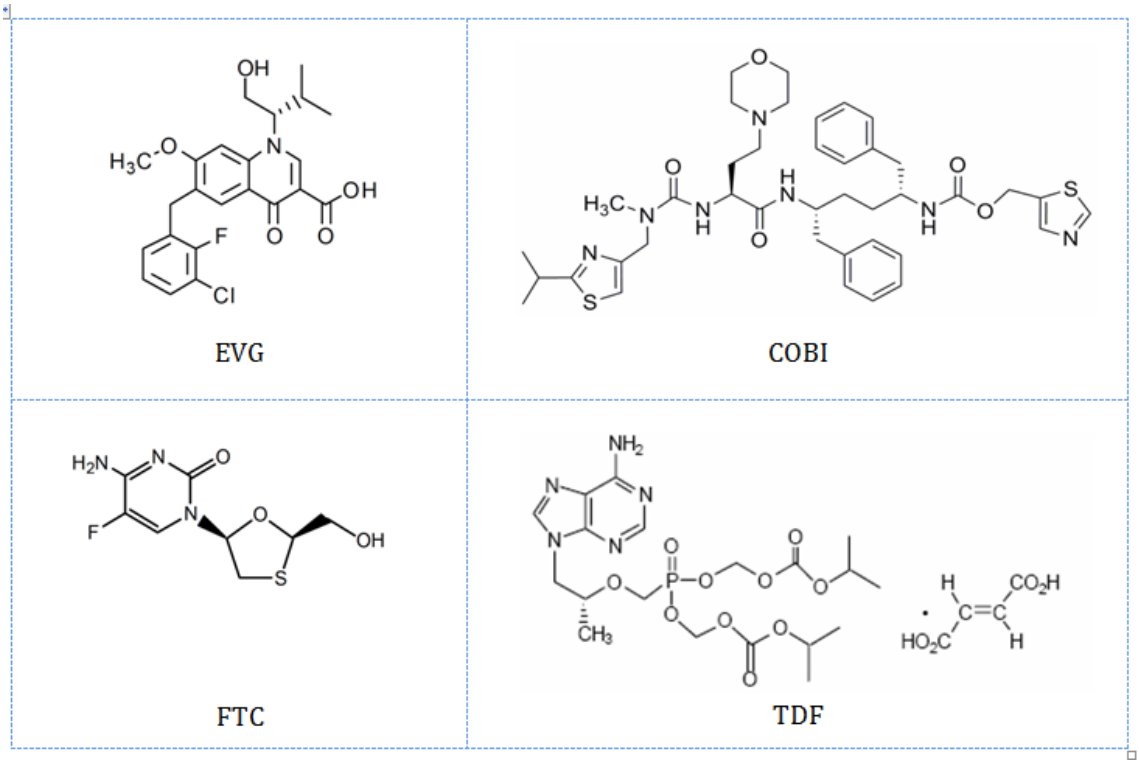
II. Quality findings

Tenofovir disoproxil fumarate and FTC are contained in a number of registered products, including Viread 300 mg TDF tablets, Emtriva 200 mg FTC capsules and Truvada tablets containing 300 mg TDF plus 200 mg FTC. The new chemical entities EVG and COBI are not

[1] The application was approved in Canada on 26th November 2012.

currently registered in Australia. The chemical structures of these agents are shown in Figure 1.

Figure 1. Chemical structures of tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat



Drug substance (active ingredient)

Tenofovir disoproxil fumarate and FTC drug substances are identical to the substances already registered.

Elvitegravir and COBI are new, synthetic substances. Cobicistat is not active against the HIV virus but is included in the tablets as a PK enhancer. It is a potent inhibitor of CYP3A4, resulting in significantly increased plasma concentrations of the 3 other active ingredients, particularly EVG.

There are a number of impurities in both EVG and COBI that are controlled at levels above the relevant International Conference on Harmonisation (ICH) guidelines on qualification threshold. The proposed levels are adequately qualified according to the TGA's Medicines Toxicology Evaluation Section (MTES).

Drug product

The drug product is an immediate release tablet containing EVG 150 mg, COBI 150 mg, FTC 200 mg, and TDF 300 mg (equivalent to 245 mg of tenofovir disoproxil). The tablets are green, capsule-shaped and film-coated. The tablets will be packaged in HDPE bottles containing silica gel desiccant.

Amendments to the dissolution method were made during drug development. However, the sponsor's justification for amending the dissolution test method and limits was not accepted by the evaluator, who recommended that a condition of registration should be that the original test method and limits are applied.

The stability data submitted support the proposed shelf life of 2 years below 25°C.

Limits for a number of degradants in the finished product were referred to the MTES for assessment. No objections to the limits were raised.

Biopharmaceutics

The tablet formulation proposed for registration ('Formulation 2') was used in Phase III clinical studies. However, an earlier formulation ('Formulation 1') had been used in a Phase II study. A steady state bioequivalence study (Study GS-US-236-0110) was conducted to compare the 2 formulations. The study also involved comparison with the registered FTC 200 mg capsule and the registered TDF 300 mg tablet given concomitantly. The study demonstrated bioequivalence between Formulations 1 and 2 with regard to EVG and COBI. Emtricitabine area under the concentration-time curve (AUC) and maximum concentration (Cmax) were increased by 21% and 16%, respectively, in Formulation 2 compared to the single agent product. Tenofovir AUC and Cmax were increased by 26% and 50%, respectively, in Formulation 2 compared to the single agent product. The company claims that these increases are not clinically relevant as they are similar to the exposures observed when these agents are given with other CYP3A4 inhibitors, for example, RTV (the so-called 'boosted' protease inhibitor regimen).

Study GS-US-236-0105 assessed the effects of a high fat meal and a light meal on tablet bioavailability compared to administration in the fasted state. The results (AUC extrapolated to infinity (AUC_∞) and Cmax) are summarised Table 1 below (means and 90% confidence intervals (CIs)). Emtricitabine bioavailability is not affected. Tenofovir bioavailability is increased slightly in the presence of food, while COBI bioavailability is decreased slightly in the presence of a high fat meal. Elvitegravir bioavailability is increased substantially with food, particularly with a high fat meal. The company considers the differences between a light meal and a high fat meal in respect of EVG bioavailability to be not clinically significant. The PI recommends that the tablets be taken with a meal.

Table 1. Effect of food on the bioavailability of tenofovir disoproxil fumarate, emtricitabine, elvitegravir and cobicistat.

	Elvitegravir		Cobicistat		Emtricitabine		Tenofovir	
	AUC_∞	Cmax	AUC_∞	Cmax	AUC_∞	Cmax	AUC_∞	Cmax
High fat meal/ fasting	187% (166-210%)	156% (138-176%)	83% (73-95%)	76% (68-84%)	96% (92-100%)	96% (87-106%)	123% (117-129%)	103% (89-120%)
Light meal/ fasting	134% (119-151%)	122% (108-138%)	103% (90-117%)	104% (94-114%)	95% (91-100%)	95% (86-105%)	124% (118-130%)	120% (104-139%)

Advisory committee considerations

This submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 145th meeting in May 2012. The subcommittee did not raise any additional chemistry, manufacturing and controls (CMC) questions beyond those that had been raised by the TGA. However, the subcommittee considered that insufficient information had been provided concerning the population pharmacokinetics (PK) modelling. This was brought to the attention of the Delegate.

Quality summary and conclusions

All of the CMC questions raised by the TGA following the initial review of this submission were satisfactorily addressed by the company. There are no objections in respect of CMC to registration of Stribild tablets provided the PI is amended to include the correct pKa values of COBI. Furthermore, it should be a condition of registration that the dissolution test and limits for the product be as originally submitted.[2]

III. Nonclinical findings

Introduction

Overall quality of the submission. The nonclinical dossier was adequate, with appropriate studies generally being compliant with principles of Good Laboratory Practices (GLP), although there were some issues as indicated below. Submitted studies related only to the 2 new chemical entities, EVG and COBI. References to FTC and TDF in the nonclinical information below are from previous TGA evaluation reports of these agents and the Emtriva and Viread PI documents.

Pharmacology

Primary pharmacodynamics. The integrase inhibitor EVG is a new chemical entity which showed potent anti-HIV-1 activity *in vitro*. Studies were included in the clinical part of the submission along with clinical anti-viral studies, but there were sufficient details in the virology summary to demonstrate its efficacy, with typical concentration that results in 50% inhibition (IC_{50}) values of approximately 0.1-1.3 nM. The main human metabolites M1 and M4 were also active, although less potent than the parent drug (approximately 7 to 10 times in one study, in terms of IC_{50}). However, they probably made a minor contribution to anti-HIV-1 activity as their plasma concentrations were low compared with EVG (see *Pharmacokinetics and relative drug exposures*, below). The other anti-HIV components of the proposed combination tablet, which are both RTIs, were less potent, with corresponding values of 1.3-640 nM for FTC and 0.07-8.5 μM for tenofovir. As may be expected, development of resistance to EVG was demonstrated *in vitro*, and was associated with single and multiple integrase gene mutations, including initially T66I with concentration-escalation, and E92Q and Q148R during breakthrough resistance to high concentrations. Respective plasma EVG Cmax and minimum concentration (Cmin) values in humans of 1.73 and 0.45 μg/mL are equivalent to approximately 3.9 and 1 μM, that is, considerably higher than the anti-HIV-1 IC_{50} value.

Cobicistat, also a new chemical entity, is structurally related to RTV but did not show any anti-HIV activity. *In vitro*, it demonstrated its desired activity of inhibiting human CYP3A activity (testosterone β-hydroxylase and midazolam 1'-hydroxylase), with an IC_{50} value of 0.15 nM which was similar to that for RTV. This activity should increase exposure to EVG which is metabolised by this CYP isoform, but this was not demonstrated in the experimental species (see *Pharmacokinetics and relative drug exposures*, below). Hepatic microsomal CYP3A from rats and dogs as well as cynomolgus monkeys was, however, shown to be susceptible to COBI (respective IC_{50} values of 0.17, 0.12 and 0.12 μM), although in contrast to human samples this inhibition was generally not mechanism-based. The specificity of COBI CYP inhibition was shown *in vitro*, with the only other human CYP isoforms investigated for which COBI IC_{50} values were <25 μM were CYP2B6

[2] Acceptable finished product release and expiry specifications that incorporated appropriate tests and limits were provided prior to the TGA issuing its decision on the registration of this product.

and CYP2D6 (respectively 2.8 and 9.2 μM). The demonstrated weak inhibition of the enzyme uridine diphosphate glucuronosyltransferase (UGT1A1) *in vitro* (IC_{50} of 16.3 μM) is unlikely to affect drug interactions as the expected human COBI Cmax is approximately 1.5 μM (1.14 μg/mL).

Safety and secondary pharmacology. Safety pharmacology investigations of EVG were adequate. It elicited a small but significant inhibition of the *human Ether-à-go-go Related Gene* (hERG) current in stably transfected HEK293 (kidney) cells *in vitro* at the highest concentration tested of 10 μM (29.5% versus 6.9% for the vehicle), but it had no adverse effect on action potentials in isolated guinea pig papillary muscles, although the maximum concentration tested was only 3 μM due to limited solubility. This finding is probably of little toxicological significance, especially as the assay was conducted in protein-free medium and binding to plasma proteins is very high (99.3% for human plasma *in vitro*). In an *in vivo* study, oral (PO) doses up to 100 mg/kg did not elicit any cardiovascular effects, including QT interval prolongation.[3] Although quantitative electrocardiogram (ECG) values were unaffected in the dog repeat-dose toxicity studies, measurements were conducted prior to dosing (that is, 24 h post-dosing). Other *in vivo* assessments failed to show any central nervous system (CNS), renal or gastrointestinal (GI)-tract transport effects in rats, or respiratory effects in dogs, with PO doses of up to 2000 mg/kg (rats) or 100 mg/kg (dogs).

In contrast to EVG, COBI elicited significant, concentration-dependent inhibition of hERG current in stably transfected HEK293 cells *in vitro*, by 37-89% at 1-10 μM with a non-significant inhibition of 3.2% at 0.1 μM and an IC_{50} value of 1.8 μM. Consistent results (IC_{50} value of 1.85 μM) were obtained in a subsequent, non-GLP study by the same laboratory (study TX-216-2015), in which the corresponding value for RTV was 8.75 μM. Inhibition of the hCav 1.2 (calcium subtype) channel and, at very high concentrations, the hNav 1.5 (sodium subtype) channel was also shown in this study, with respective IC_{50} values of approximately 6 and 86 μM. Together, these results suggest a potential for untoward cardiovascular effects, although (to a lesser extent than EVG) COBI was highly plasma protein bound (93.7% at 1 μM in human plasma *in vitro*). The *in vitro* effect of COBI on electrophysiology/electrocardiography was investigated in 2 non-GLP studies (PC-216-2007 and PC-216-2009) by different laboratories, each in both paced and unpaced Langendorff isolated rabbit hearts. Consistent findings in both studies were a prolongation of the PR (electrical wave) interval and a negative inotropic effect (reductions in left ventricular diastolic pressure (LVDP) and ventricular performance measures), but despite the clear inhibition of hERG current observed above, QT interval prolongation was not observed. In fact, a reduction in QT interval was observed in paced hearts in study PC-216-2007.

In an *in vivo* study in dogs, however, significant increases in QT interval were observed, mainly at a dose of 45 mg/kg PO which resulted in a plasma 1 h drug concentration of approximately 6 μg/mL, although changes were minor (10% for QT, <4% for corrected QT (QTc)) and were largest towards the end of the 24 h measurement period. Small increases were also seen for PR intervals, which were also apparent in a 4 week dog toxicity study using the same doses (measurements were at 1-2 h post-dosing), but only in females on one of 2 measurement days (day 3), while increased RR (electrical wave) intervals were seen in males only on day 22. QT and QTc were unaffected by treatment in this study. There were no ECG findings in a one week toxicity study in which very high lethal doses were examined (50, 125, 250 mg/kg/day), although surviving animal numbers were small,

[3] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. QT_c: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval (QTc) is often calculated.

or in the 39 week study in which treatment achieved COBI exposure ratios of >5. Despite the findings relating to hERG currents, it appears that the potential for untoward cardiovascular effects with the proposed dose is low. A modest increase in PR interval was seen in a clinical study requested by the FDA to investigate pro-arrhythmic potential (GS-US-216-0107) but this was not considered clinically significant, and apparently neither EVG or COBI elicited significant ECG changes (according to the sponsor's clinical overview).

Other safety pharmacology studies, at doses up to 500 mg/kg in rats, showed no effect on respiratory values, but did show reductions in body temperature and reduced locomotor activity, with a no-effect dose of 50 mg/kg. Studies of each of the 3 areas examined (CNS, cardiovascular, respiratory) were also conducted with GS-8374, an investigational HIV-1 protease inhibitor, together with a fixed COBI dose, but only the cardiovascular study included a COBI alone group (15 mg/kg). There were, however, no studies with COBI plus EVG and some combination investigations would be warranted as both agents inhibited hERG currents, *albeit* with different potencies. Unlike EVG, effects of COBI on renal function were not examined, although urinary volume was increased in the rat toxicity studies, a finding of unknown cause and relevance (see *General toxicity*, below).

Emtricitabine and TDF apparently did not elicit cardiovascular changes in dogs, although the study with the former was not GLP-compliant and did not include full data. Emtricitabine also was without effect on renal function in rats, but TDF elicited reductions in urinary volume and excretion of electrolytes (but not urea or creatinine). As discussed below (see *General toxicity*), it was also associated with renal histological changes.

Notable findings in the secondary pharmacology studies of EVG were the lack of inhibition of topoisomerases, effect on mitochondrial DNA *in vitro* or convulsogenic interaction with non steroidal anti inflammatory drugs (NSAIDs) in mice. Cobicistat and its E1, E3 and E5 metabolites were shown not to inhibit HIV-1 *in vitro*, while the parent drug had little or no effect on lipid accumulation and glucose uptake by adipocytes.

Pharmacokinetics

Pharmacokinetics and relative drug exposures. Elvitegravir was rapidly cleared from plasma following single intravenous (IV) administration to male rats or dogs (0.5-1.0 L/h/kg), with associated short half life (t½β) values of 1.5-1.6 h, which were only slightly shorter than for radioactivity (carbon 14; ^{14}C) following administration of ^{14}C labelled drug. There were apparently no IV data in humans for comparison, although a t½ value of 3.1 h was quoted in one study following single PO administration (GS-US-183-0102, in the sponsor's summary of clinical pharmacology studies). Plasma clearance of COBI was even faster in male rats and dogs (respectively 3.6 and 2.2 L/h/kg), and also in male cynomolgus monkeys (1.4 L/h/kg) which were not a species used for toxicity testing. Drug exposures achieved in the main toxicity studies are tabulated below (Table 2).

Table 2. Drug exposure in animal toxicology studies

Species	Duration (weeks)	Dose (mg/kg/ day PO)	$AUC_{0\text{-}t}$ (µg.h/mL)†, sample day/week	Cmax (µg/mL)^	AUC exposure ratio (ER)&
Elvitegravir: General toxicity and carcinogenicity					
Mouse	13	100, 500, 2000	4.4, 23.1, 86.2 m 7.3, 36.8, 125.3 f days 1 and 91	3.1, 13.1, 24.9 2.7, 13.3, 35.8	0.2, 1.0, 3.7 0.3, 1.6, 5.4
Mouse	104*	200, 600, 2000, 2000R#	7.5, 21.4, 42.7, 268 m 13.3, 36.3, 64.8, 249 f day 4 and wk 26$	4.1, 12.6, 20.2, 72.9 7.6, 24.8, 29.9, 55.9	0.3, 1.0, 1.9, 11.6 0.6, 1.6, 2.8, 10.8

Species	Duration (weeks)	Dose (mg/kg/ day PO)	AUC_{0-t} (µg.h/mL)†, sample day/week	Cmax (µg/mL)^	AUC exposure ratio (ER)&
Rat	13	100, 300, 1000, 2000	45.5, 142, 183, 240 m 83.6, 172, 233, 306 f days 1 and 90	16.6, 23.7, 24.6, 28.4 32.8, 48.4, 46.4, 50.7	2.0, 6.2, 8.0, 10.4 3.6, 7.5, 10.1, 13.3
Rat	26	100, 300, 2000	65.5, 161, 468 m 152, 321, 821 f days 1 and 181	17.0, 28.6, 35.8 44.6, 56.1, 72.3	2.8, 7.0, 20.3 6.6, 13.9, 35.7
Rat	88-90*	100, 300, 2000	51.2, 62.0, 254 m 107, 211, 502 f days 4, 178 and 360	15.2, 20.8, 33.5 29.7, 46.3, 62.7	2.2, 2.7, 11.0 4.6, 9.2, 21.8
Dog	39	10, 30, 100	7.5, 24.9, 51.3 m 8.7, 23.1, 61.6 f days 58 and 273	1.1, 4.1, 8.5 1.3, 3.0, 8.2	0.3, 1.1, 2.2 0.4, 1.0, 2.7
Elvitegravir: Reproductive toxicity					
Rat	GD 7-17	300, 1000, 2000	155, 379, 612 GD 7 and 17	28.4, 46.5, 58.1	6.7, 16.5, 26.6
Rat	GD 6-17	100R, 1000R, 1000	59.2, 169, 183 GD 6 and 17	11.3, 29.2, 27.9	2.6, 7.3, 8.0
Rat	GD 7-PPD 20	300, 1000, 2000	67.2, 200, 408 PPD 14	17.5, 34.7, 36.0	2.9, 8.7, 17.7
Rat juvenile Δ	PPD 22-49	300, 1000, 2000	45.0, 89.2, 136 m 54.6, 126, 164f PPD 22 and 49	11.8, 19.1, 25.3 16.8, 25.0, 25.2	2.0, 3.9, 5.9 2.4, 5.5, 7.1
Rabbit	GD 7-19	50, 150, 450	1.1, 2.4, 4.3 GD 7 and 19	0.08, 0.12, 0.29	<0.1, 0.1, 0.2
Cobicistat: General toxicity and carcinogenicity					
Mouse	13	5, 15, 50	0.70, 11.9, 39.3 m 1.1, 10.2, 53.2 f weeks 1 and 13	0.31, 3.5, 8.7 0.35, 3.6, 11.4	<0.1, 1.4, 4.7 0.1, 1.2, 6.4
Mouse	87-100*	5, 15, 50 10, 30, 100	2.3, 13.3, 113 m 9.1, 54, 136 f day 1 and wk 29	1.2, 3.9, 9.7 4.9, 10.2, 19.2	0.3, 1.6, 13.6 1.1, 6.5, 16.4
Rat	267	10, 30, 100	1.0, 7.9, 36.6 m 2.5, 12.5, 55.3 f day 1, wks 13 and 26	0.66, 1.6, 3.9 1.0, 2.9, 6.1	0.1, 0.9, 4.4 0.3, 1.5, 6.7
Rat	97-102*	10, 25, 50 5, 15, 30	0.69, 5.8, 21.7 m 0.42, 5.1, 15.9 f day 1 and wk 26	0.23, 1.1, 2.7 0.37, 1.4, 2.7	<0.1, 0.7, 2.6 <0.1, 0.6, 1.9
Dog	39	5, 10, 20	3.8, 15.7, 45.8 m 4.1, 11.3, 68.8 f day 1, wks 13 and 39	0.80, 2.4, 5.0 0.83, 1.7, 6.2	0.5, 1.9, 5.5 0.5, 1.4, 8.3
Cobicistat: Reproductive toxicity					
Rat	GD 6-17	25, 50, 125	8.5, 20.9, 59.6 GD 6 and 17	1.2, 2.2, 4.6	1.0, 2.5, 7.2
Rat	GD 6-PPD 20	10, 30, 75	1.9, 6.4, 9.9 PPD 10	0.38, 1.1, 1.8	0.2, 0.8, 1.2
Juvenile rat Δ	PPD 22-49	10, 30, 75	0.31, 7.0, 26.3 m 1.1, 7.5, 19.8 f PPD 22 and 49	0.09, 1.4, 3.4 0.26, 1.8, 3.1	<0.1, 0.8, 3.2 0.1, 0.9, 2.4
Rabbit	GD 7-20	25, 50, 100	0.86, 9.7x, 23.4 GD 7 and 20	0.37, 2.4, 2.9	0.1, 1.2, 2.8
Elvitegravir/ COBI combination: General toxicity					
Rat	13	100/30, 1000/30, 1000/0 0/30, 100/30, 1000/30	Elvitegravir: 92.9, 302, 123 m 102, 295, 238 f Cobicistat: 9.3, 7.2, 4.2 m 14.6, 13.7, 9.4 f days 1 and 90	 26.9, 52.8, 35.3 23.5, 60.9, 58.1 2.2, 1.8, 1.2 2.9, 2.6, 3.0	 4.0, 13.1, 5.3 4.4, 12.8, 10.3 1.1, 0.9, 0.5 1.8, 1.6, 1.1

† concentrations were generally given as ng in reports and these have been standardised (and rounded) as µg; ^ highest measured mean concentration rather than true Cmax because of relatively sparse sampling times; * carcinogenicity studies, # R = EVG together with 10 or 25 mg/kg/day RTV;
& $AUC_{0\text{-}t}$ relative to human steady state values of 23.0 (EVG) and 8.3 (COBI) µg.h/mL after treatment with the 4-drug combination in HIV-1 infected subjects ; $AUC_{0\text{-}t}$ values are to times of last measurable concentration up to 24 h with daily dosing; $ only week 26 for the low dose and mid dose (not determined in week 1); Δ part of the pre-/post-natal studies; offspring also dosed *in utero* and *via* milk; x mean of 0.31 and 19.2 µg.h/mL; GD = gestation day, PPD = post-partum day, wks = weeks

Elvitegravir exposure ratios were high in the rat studies, with noticeably higher values in females than males, but relatively low in dogs and mice, although these were boosted considerably by co-administration of RTV in the latter species. Particularly low values were achieved in the rabbit embryofetal development study, which is discussed further under *Reproductive toxicity*, below. Cobicistat exposure ratios were relatively low in all studies, but were acceptable except for those achieved in the rat pre-/post-natal study in which the high dose exposure was comparable to those expected in humans. There were no toxicokinetic data for the fertility and early embryonic development studies conducted in rats, but they could be estimated from the 13 week (EVG) or 26 week (COBI) general toxicity study values. Exposures were less than optimal in the rat COBI carcinogenicity study, with only the high-dose values being above that expected in humans.

In vitro plasma protein binding assessments showed almost complete binding for EVG (0.1-10 µg/mL) in human, dog and rat samples, with only minimally higher values in rats (99.9% versus 99.3% in humans), and no adjustment in exposure ratios is required. *In vitro* data were obtained for mouse plasma following *in vivo* exposure, with a similarly high binding of added ^{14}C-EVG (0.5 µg/mL) being measured (99.7%). Cobicistat showed lower binding, that is, 93.7% at 0.78 µg/mL (which approximates the mean Cmax of 1.1 µg/mL) in human plasma, and there was a noticeable inverse dose-relationship in rats. However, the overall pattern of binding values did not suggest any adjustment of exposure ratios was needed. Adequate tissue distribution studies were conducted in male rats receiving PO ^{14}C-COBI or ^{14}C-EVG, with no unexpected findings, but it was notable that radioactivity was low in the CNS after treatment with both compounds. Little solid tissue radioactivity was measurable in dogs at the only sample time of 168 h after PO or IV administration of ^{14}C-EVG in what was primarily a plasma PK study.

Metabolism. Plasma radioactivity was associated primarily with unchanged drug following PO ^{14}C-EVG administration in humans (94%), with minor metabolites including the glucuronide M4 (GS-9200). This metabolite, which also showed some anti-HIV-1 activity, was present in mouse and rat plasma after PO administration, but only sporadically in dog plasma although it was present in more substantial amounts in this species after IV administration. Plasma AUC over time zero to 24 h ($AUC_{0\text{-}24\ h}$) measurements in the mouse 13 week toxicity study showed that high-dose exposure to GS-9200 was 27-30% that for the parent drug on day 91. Following administration of PO ^{14}C-COBI to humans, plasma radioactivity was overwhelmingly associated with parent drug (98.6% over 24 h). This was in contrast to the male rat and dog in which systemic exposure to metabolites, including the human faecal metabolites M21 (cleavage product) and M31 (hydroxylated derivative), was higher. M31 (also known as E3 or GS-9612) was measured in the mouse 13 week, rat 26 week and dog 39 week PO toxicity studies, with high-dose $AUC_{0\text{-}t}$ values at the end of dosing being approximately 2-3% those for parent drug.

As in humans, excretion of both EVG- and COBI-related material was primarily *via* the faeces in the experimental species (there were no data for EVG in the mouse), and biliary excretion was shown in the dog and/or rat. Additionally, human faecal components after PO EVG (parent drug and M1 hydroxylated derivative) and COBI (parent drug, M21 and M31) were prominent in the faeces of the experimental species used, and overall these species were appropriate for toxicity testing with respect to their metabolism. By contrast, FTC and tenofovir showed largely urinary excretion with, respectively, limited or no metabolism in the experimental species, as in humans. Additionally both agents did not

substantially inhibit major CYP450 isoforms *in vitro*. Plasma clearance values for both compounds in male rats were 1.7-1.8 L/h/kg with a 10 mg/kg dose, with a lower value of 0.23 L/h/kg for tenofovir in male dogs (there were no data for FTC in dogs).

Elvitegravir was shown to be metabolised *in vitro* by recombinant CYP3A with the formation mainly of the hydroxylated compound M1 (GS-9202) which was also the main metabolite formed by human hepatic microsomal fractions. Ritonavir and COBI are potent and relatively specific inhibitors of CYP3A *in vitro*, and co-administration should elevate EVG exposure. Cobicistat (unlike RTV) has the advantage of not showing anti-HIV activity. However, in the only toxicity study involving EVG and COBI alone and co-administered (13 week rat study, TX-236-2001), 30 mg/kg/day COBI had little effect on 1000 mg/kg/day EVG $AUC_{0\text{-}24\ h}$ values on day 90 (1.7 times the value with EVG alone in males, 0.8 times in females), although they were higher on day 1 (respectively 3 and 1.6 times). The achieved COBI $AUC_{0\text{-}24\ h}$ values with this combination were relatively low (5.2-7.5 µg.h/mL versus 8.3 µg.h/mL in humans), but were sufficient to result in modest increases in hepatic microsomal fraction CYP3A activity (approximately 2-2.8 times vehicle values for testosterone 6β-hydroxylase). Consequently, terminal EVG exposures would be expected to be influenced in rats both by inhibition and induction of CYP3A, but combination PK were not investigated in another species.

The same COBI 30 mg/kg/day dose substantially elevated exposure to lower doses of ATV (20 and 50 mg/kg/day), an HIV-1 protease inhibitor also metabolised by CYP3A4, in another 13 week rat toxicity study (TX-216-2024). Day 90 $AUC_{0\text{-}24\ h}$ values were, respectively, 3.9 and 2.9 (males) or 2.6 and 1.45 (females) times those in the absence of COBI. This was despite significantly higher terminal CYP3A activities in females receiving combination treatment with COBI (2.6-3.5 times vehicle values). A 4 week PO rat toxicity study was conducted with COBI in combination with the same doses of EVG (30 and 50 mg/kg/day) to compare regular and degraded mixtures (TX-236-2002), but this did not include groups receiving each drug alone.

Co-administration of RTV and EVG was also assessed, with variable results. A dose of 10 mg/kg/day had no (rat embryofetal development study TX-183-2008) or slight (rat 13 week toxicity study TX-183-2007) effects on EVG exposure, while 25 mg/kg/day elicited a 6.3 (males) or 3.8 (females) fold higher value in the mouse carcinogenicity study. In a clinical study 100 mg twice daily (bid) RTV plus 100 mg bid EVG apparently enhanced EVG exposure ($AUC_{0\text{-}24\ h}$) approximately 20 fold after 10 days, and there was evidence for autoinduction of EVG metabolism when this was given alone. By comparison, although induction of CYP3A by EVG was shown in human hepatocytes *in vitro*, multiple dosing in the toxicity studies did not result in consistent decreases in EVG exposure in mice, rats or dogs. Clinical studies also apparently demonstrated COBI inhibition of CYP3A, as judged by midazolam substrate PK, and it (as part of the proposed combination tablet) resulted in a similar EVG exposure as that measured with the same EVG dose co-administered with RTV.

By comparison, COBI was shown to elevate CYP3A4 and CYP1A2 messenger ribonucleic acid (mRNA) levels in hepatocytes *in vitro*, and to consistently increase hepatic CYP3A activity (testosterone 6β-hydroxylase) in the mouse and rat toxicity studies, sometimes together with CYP2B and CYP1A. It is noteworthy in this context that COBI was also shown to activate rat pregnane X-receptor *in vitro*. The response was different in dogs, however, with reduced CYP3A being measured in the 1 and 4 week toxicity studies, but this was not examined in the long term 39 week study. It was suggested in the reports that these reductions may have reflected inhibition by high concentrations of COBI remaining in the liver. Rodent hepatic enzyme induction was associated with increased liver weight and hepatocytic hypertrophy, and effects on the thyroid in rats (see *General toxicity*, below).

Toxicology

General toxicity

Elvitegravir and COBI are new chemical entities and their toxicity was investigated in a range of single and repeat-dose studies, although there was only one (13 week rat) study with these agents alone and in combination. Emtricitabine and TDF are established drugs, with information on their toxicity being available from previous evaluation reports. They are both present in the proposed combination tablet at the same level as in individual tablets (respectively 200 mg and 300 mg) and the Truvada and Atripla combination tablets containing these 2 drugs.

Elvitegravir. This showed little toxicity in the repeated-dose studies, although drug exposures (AUC) ranged from high in rats to relatively low in mice and dogs. The high-dose was boosted in the mouse carcinogenicity study by co-administration of RTV, but the high-dose in the 39 week dog study (100 mg/kg/day) could probably have been increased. There was a substantially reduced body weight gain with this high-dose relative to the vehicle (by 39%), but not compared with an additional water control group. The only changes seen with the high-dose, which achieved a drug exposure ratio of approximately 2.5, were reduced urinary volume and electrolyte excretion (females only) and the presence of very slight lipid droplets in the duodenum and jejunum lamina propria.

The significance of the urinalysis changes seen only in one sex is not clear, but there were no comparable findings in the other species tested. By contrast, lipid droplets in the duodenum/jejunum were consistent findings in the rat studies, and a series of mechanistic studies was conducted to investigate this. These suggested that lipid was of dietary origin and that droplet formation was related to the local drug concentration rather than systemic exposure, but are probably of little toxicological significance especially at a low unit dose of 3 mg/kg for a 50 kg patient. Another notable finding in rats, increased caecal weights without histological correlates, was probably related to anti-bacterial activity as seen in the bacterial reverse mutation assay. Anti-bacterial activity was not specifically investigated but may be expected given that EVG is a quinolone carboxylic acid derivative. Rats in the longest duration (26 week) study also showed stomach erosion, fibrosis and oedema, mainly in males with the high-dose of 2000 mg/kg/day, which probably reflected local irritation after prolonged treatment, although this was not noted with the same dose in the carcinogenicity study. Incidences of liver basophilic foci were also increased in the 26 week but not the carcinogenicity study in which they were relatively common in the controls (7/60 males, 16/60 females).

The corn oil vehicle used in the PO dog studies was shown in single dose toxicity/toxicokinetic studies (JTK303-TX-013, JTK303-TX-014) to give higher EVG exposures than 0.5% methylcellulose, the vehicle used in the rodent studies. Surprisingly, vomiting which was apparent at doses as low as 10 mg/kg/day was not a major finding in the repeat-dose studies, being only sporadic and also involving vehicle control dogs (4 week study) or virtually absent (39 week study). Vomiting may explain the apparently low high-dose AUC0-24 h value in single dose study 03133, while a single-dose IV study indicated that vomiting was related to local rather than systemic drug levels.

Cobicistat. Treatment elicited increased liver weights and hepatocytic hypertrophy in mice, rats and dogs, and was associated with thyroid changes in rats. Thyroid follicular cell hyperplasia/hypertrophy was apparent with doses of 50 and 100 mg/kg/day for 4 weeks and 100 mg/kg/day for 27 weeks, and thyroid stimulating hormone (TSH) was shown to be elevated in the latter study. Although these thyroid changes are almost certainly rat specific, TSH, triiodothyronine (T3) and thyroxine (T4) were measured in one clinical study (according to the sponsor's summary of clinical safety) with apparently no effect of combination treatment being seen. Other findings included elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities in mice, which

were probably related to hepatocyte hypertrophy which in this species was associated with vacuolation, and clinical pathology changes. These included slightly decreased erythroid values and increased platelets (rat), increased cholesterol (mouse, rat), increased serum protein (rat) and increased urinary volume (rat). Increased urinary volumes in rats were often substantial, for example, 4.4 times the vehicle control value in high-dose females in the 4 week study, and were associated with significantly higher sodium excretion in the 27 week study. This diuretic-like effect was, however, not associated with changes in antidiuretic hormone or aldosterone which were monitored in the longer duration study. A substantially increased urinary volume was also noted in a 4 week rat toxicity study using a regular and impurity-spiked COBI batch (TX-216-2045).

There was some indication of possible renal effects in the dog 39 week study, although results were difficult to interpret, with tendencies for reduced electrolyte excretion in high-dose females but not males. Although the mechanism for these urinary changes was not investigated, there were no associated elevations in serum urea or creatinine and no renal histological findings, in rats or dogs. Additionally, urinary volume and sodium excretion values in rats had normalised after the recovery periods. In a response to a request for information from the TGA, the sponsor considered that although the mechanism of such changes was not fully understood, the weak diuretic effect was probably related to calcium channel inhibition, which has been demonstrated for hCav 1.2 (see *Safety and secondary pharmacology*, above). Cobicistat apparently elicited small increases in serum creatinine in the clinical trials, with results being consistent with inhibition of renal creatinine secretion and a similar effect being apparent with RTV (according to the sponsor's clinical overview). This probably reflects inhibition of organic cation transporter-1 (OCT1) or multidrug and toxin extrusion transporter-1 (MATE1) by COBI, for which respective IC_{50} values of 8.24 and 1.87 μM were obtained *in vitro*.

Higher doses were used in an initial 1 week dog study (50, 125 and 250 mg/kg/day), which elicited marked toxicity, including deaths, weight loss and lymphoid depletion in the thymus, spleen and lymph node. Body weight loss in males or excessive reductions in body weight gains in both sexes were seen with the mid- and high-doses in the 4 week dog study (respectively, 15 and 45 mg/kg/day). Further, significantly lower male body weight gains were seen with the mid- and high-doses used 39 week study (respectively, 10 and 20 mg/kg/day), and thymic involution and adrenal cortical hypertrophy were seen in high-dose males and indicative of toxicity. It would not have been appropriate to have increased doses, although these achieved drug exposure ratios that while acceptable were relatively low (to 5.5 in males and 8.3 in females). Drug exposure ratios in the mouse and rat studies were also acceptable but relatively low, and the high-dose of 50 mg/kg/day in the mouse 13 week study probably could have been higher. The high-dose of 100 mg/kg/day in the rat 27 week study resulted in impaired male body weight gain (by 22%) associated with slightly reduced food consumption.

A special 4 week immunotoxicity study (JTK303-TX-011) in rats revealed some effects of treatment, notably increased incidences of lymphoid depletion in spleen germinal centres and reduced antibody response to keyhole limpet haemocyanin. There was little effect on immunoglobulin M (IgM) levels, but significant decreases in IgG were seen in mid- and high-dose (50 and 150 mg/kg/day) females with tendencies for reduced high-dose levels in high-dose males. Toxicokinetic data gave drug exposure ratios of <1 (low-dose, 20 mg/kg/day), approximately 2.2 (mid-dose) and 5.7-9.5 (high-dose). The significance of the impaired antibody response is not clear, but there were no other indications of specific immunotoxicity in other studies which included peripheral blood immunophenotyping in the longest duration rat and dog studies. Spleen weights were elevated in rats (4 and 27 week studies), but there were no histological correlates. Small decreases in IgG and IgM were apparently seen in a clinical study with combination treatment of HIV-1 patients (according to the sponsor's summary of clinical safety).

Cobicistat was also tested in rats in combination with EVG in a 13 week study, but the COBI dose of 30 mg/kg achieved exposures with little or no safety margin for this drug. Although there were no unexpected findings for the combination compared with the drugs alone, the full potential for interactions may not have been fully assessed in this study. The EVG/COBI ratio used was quite different to that proposed in Stribild (1000/30 mg/kg/day versus equal doses), and although equal doses were used in a 4 week female rat impurity study (TX-236-2002), they were relatively low (30 and 50 mg/kg/day of each component). Nevertheless, the high-dose non-degraded combination achieved a COBI exposure ratio of 4.1 (mean of days 1 and 28 $AUC_{0\text{-}t}$), and it was notable that the corresponding ratio for EVG decreased from 6.9 on day 1 to 1.9 on day 28. Combinations were well tolerated, suggesting that a higher COBI dose could have been used in the main 13 week combination study. Additional 13 week rat combination studies tested COBI plus ATV and EVG plus RTV, and were of limited relevance to the current application.

Ritonavir is closely related to COBI and its use has been associated with untoward effects including pancreatitis, hyperglycaemia/diabetes and elevated triglycerides (Norvir PI). Serum glucose and cholesterol were not consistently affected in the COBI toxicity studies. Elevated glucose levels were seen with 250 and 500 mg/kg in a rat single-dose study, doses that were generally above those in the repeat-dose studies. It was also elevated in a 4 week female rat impurity study (TX-216-2045) at 100 mg/kg/day, but not by the same dose in the 4 and 27 week general toxicity studies. Cholesterol was elevated in mice, the 4 week rat study and the 13 week rat EVG/COBI combination study (together with triglycerides), but not in dogs and only in females in the 27 week rat study. Increases were also apparent in the impurity study noted above, and in the 4 week rat study using degraded and non-degraded EVG/COBI mixture (TX-236-2002) although COBI alone was not tested in the latter. Serum lipase and amylase were not measured but there were no histological indications of pancreatic toxicity. As noted above (under *Secondary pharmacology*), COBI showed little effect on lipid accumulation and glucose uptake *in vitro*.

Emtricitabine. The toxicity of this NRTI (closely related to lamivudine in structure) has been assessed in mice, rats and cynomolgus monkeys, with respective durations of 6 months (2 studies), 3 months and 12 months for the pivotal studies. The high doses that were used achieved high drug systemic exposures, which gave exposure ratios of approximately 84 and 185 (mouse), 151 (rat) and 26 (cynomolgus monkey based on a human $AUC_{0\text{-}24\,h}$ value of 9.65 µg.h/mL rather than 12.7 µg.h/mL for the proposed combination tablet. Emtricitabine was generally well tolerated and there was an absence of significant drug-related toxicity in these studies, although the evaluation report assessment noted that there was often large inter-animal variability which precluded meaningful interpretation of clinical pathology values.

Tenofovir disoproxil fumarate. This is the prodrug of tenofovir which, following intracellular phosphorylation, is a nucleotide analogue inhibitor of reverse transcriptase. By contrast with FTC, TDF showed significant toxicity notably osteopenia in the main experimental species used (rat, dog) and nephrotoxicity in dogs and rhesus monkeys and to a lesser extent mice and rats. The pivotal 13-42 week toxicity studies used high-doses that achieved drug exposure ratios of approximately 15 (rat) and 9 (dog), based on a human $AUC_{0\text{-}24\,h}$ value of 3.2 µg.h/mL compared with 4.4 µg.h/mL for the proposed combination. Untoward effects were observed at relatively low drug exposures, and there were safety margins of only 2-2.3 for bone mineral loss in rats and dogs, which appeared to be due to impaired phosphorus absorption and altered homeostasis. However, the proposed PI for Stribild notes that clinically relevant bone abnormalities have not been seen in long-term clinical studies. TDF-elicited nephrotoxicity was apparent in dogs at 10 mg/kg/day (tubular dilation, tubular degeneration/regeneration, glucosuria) and there was no safety margin at the no observed effect level (NOEL) of 3 mg/kg/day. Renal findings in rhesus monkeys after 8 weeks treatment, including tubular single cell necrosis and tubular dilation, were apparent at a dose giving an ER of approximately 5 (1.2 at the

NOEL). The proposed PI for Stribild and that for Viread note that a range of renal and urinary disorders have been observed during post-marketing surveillance. High PO TDF doses also elicited GI-tract toxicity in rats, including gastritis, stomach mucosal erosion and duodenal and jejunal epithelial hyperplasia, probably related to local irritation effects.

Overall, there were no findings of concern in the adequate toxicity studies conducted with EVG and COBI alone. However, while the fixed combination of TDF plus FTC is a registered (Truvada) product, and the new chemical entity combination EVG/COBI was tested over 13 weeks in one species, *albeit* with some deficiency (see above), other potential interactions have not been investigated. On the other hand, TDF shows the highest toxicity profile of the 4 components in Stribild, but there was little indication of overlapping toxicities for the individual drugs other than GI-tract irritation, and it is considered that unexpected interactions between all 4 drugs, in terms of enhanced or additional toxicity is unlikely, although this cannot be completely excluded. Although TDF may affect the kidneys in experimental animals and in humans, the urinary changes seen with COBI were not associated with plasma changes or renal histological findings. A TDF/COBI combination toxicity study would, however, have helped to provide reassurance of a lack of renal interaction between these drugs. The 13 week EVG/COBI study was designed to be in accordance with the FDA guideline *Guidance for Industry. Nonclinical Safety Evaluation of Drug or Biologic Combinations*[4] regarding nonclinical safety evaluation of drug combinations, specifically for 2 new chemical entities. It would have been desirable to have tested all 4 drugs together, although the use of doses that would have achieved substantial exposure ratios in terms of AUC for each component may not be practical. In this context, the complexity of performing and interpreting a combination toxicity study with more than 2 drugs was noted in a recent (2012) European Medicines Agency (EMA) question and answer document[5]. Given the above, the acceptability of this 4 drug combination will depend on the extent to which it is clinically justified.

Genotoxicity and carcinogenicity

Elvitegravir showed an equivocal positive response in an *in vitro* test for clastogenicity in Chinese hamster lung cells, with an increased frequency of cells with chomosomal aberrations being seen at 55-75 µg/mL with 6 h exposure in the absence of microsomal enzyme activation. Although, no response was seen in the 24 h exposure, concentrations tested were lower (25-45 µg/mL). However, EVG gave negative results in an *in vivo* rat micronucleus test using high PO doses (500-2000 mg/kg) and together with negative results for bacterial reverse mutation (*albeit* at concentrations limited by growth inhibition), it was not considered to be genotoxic. It should be noted that concentrations for which metaphases were scored (as opposed to concentrations tested) did not achieve cytotoxicity of >50%. However, there were no oncogenic responses to EVG in mice and rats using high-doses (2000 mg/kg/day) that achieved drug exposure ratios of >10, although in the case of mice this was achieved only by co-administration of RTV.

Cobicistat did not show any genotoxicity in adequate assays, resembling RTV in this respect (Novir PI), and the only oncogenic response in long-term rodent carcinogenicity studies involved thyroid follicular cell tumours in rats. These were almost certainly related to hepatocytic hypertrophy and changes in thyroid hormones as seen in the rat toxicity studies (see *General toxicity* above). Adrenal medullary phaeochromocytoma incidences tended to be higher in mid- and high-dose male rats but these appeared to be incidental, based on lack of a significant trend, incidences within the historical control range, no associated histological changes and occurrence only in one sex. Drug exposures in the rat study were relatively low, and while the high-dose achieved exposure ratios of

[4] U.S. FDA Center for Drug Evaluation and Research (CDER), March 2006. Available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/05d-0004-gdl0002.pdf>
[5] International Conference on Harmonisation (ICH) guideline M3 (R2) – questions and answers. EMA/CHMP/ICH/507008/2011. Feb. 2012.

approximately 2 or slightly above, low- and mid-dose values exposures were below that expected in humans. Based on the pattern of mortality and body weight changes, and lack of significant additional toxicities, the high-doses (50 (males) or 30 (females) mg/kg/day) could probably have been increased, although 100 mg/kg/day in the male 27 week toxicity study resulted in a pronounced decrease in body weight gain (by 22%). By contrast, drug exposures in the mouse study were much higher, especially in females in which doses of 10-100 mg/kg/day were used.

Emtricitabine was not genotoxic and also showed no oncogenic responses in rodent PO carcinogenicity studies using high-doses of 750 (mouse) or 600 (rat) mg/kg/day, which achieved AUC exposure ratios of >25 (mean of weeks 2 and 26). By contrast and as noted in the Viread PI, TDF showed positive responses in the mouse lymphoma L5178Y (tk locus) assay and an ex vivo assay for unscheduled DNA synthesis in rat hepatocytes, but not for bacterial reverse mutation or in the *in vivo* micronucleus test. The tenofovir base did not show genotoxic activity in the bacterial reverse mutation assay but was equivocally positive in the L5178Y lymphoma assay. Long-term rodent carcinogenicity studies with TDF failed to show any oncogenic response other than a low incidence of upper duodenal tumours with associated epithelial hyperplasia in mice, which probably reflected local irritation by formaldehyde released during hydrolysis of the disoproxil diester. Apparently increased incidences of some other tumours (hepatocellular adenomas in female mice, Harderian gland adenomas in male mice, subcutaneous lipomas in male rats and uterine endometrial stromal polyps in rats) were previously considered by TGA evaluators to be incidental or of little relevance to human risk assessment. PO high-doses used in these studies (600 mg/kg/day in mice, 300 mg/kg/day in rats) achieved respective tenofovir exposure ratios of 15 (mice) or 5 (rats).

Combination genotoxicity or carcinogenicity studies have not been conducted and are not considered necessary.

Reproductive toxicity

Reproductive toxicity was assessed in a full range of PO studies with both EVG and COBI separately, often with initial pilot studies, although both agents in combination were not used. An additional rat embryofetal development study was conducted with EVG co-administered with RTV but this was of limited relevance to the current submission. Milk secretion was observed for EVG and to a greater extent COBI but placental transfer was not investigated for either compound.

Elvitegravir. Fertility and early embryonic development were unaffected by doses up to 2000 mg/kg/day in male or female rats, which would be expected to have achieved high drug exposures based on data from the 13- and 26-week general toxicity studies. Elvitegravir was similarly without effect in the rat embryofetal development study, but as noted above (under *Pharmacokinetics and relative drug exposures*), the doses used achieved particularly low EVG exposures (AUC) in the corresponding rabbit study. Comparison with the rat study shows that drug exposures in the rat were very much higher than in the rabbit (for example, 155 µg.h/mL at 300 mg/kg day versus 4.3 µg.h/mL with 450 mg/kg/day). The reason for this large difference is not clear, and there were no other PK data for rabbits. Although the vehicle used was 0.5% methylcellulose in rats and corn oil in rabbits, the latter was shown to give higher exposures after single administration to male dogs (see *General toxicity*). Additionally, there was little or no effect of treatment in the main rabbit study, which was preceded by a pilot study using doses of up to 600 mg/kg/day. These resulted in somewhat higher exposures but still with a high-dose exposure ratio of only approximately 0.5. The pilot study was confounded by anorexia in some does, which was not drug-related and of no obvious cause, but there was little effect of EVG on embryofetal development. The high-dose for the main study (450 mg/kg/day) was a cautious selection and it would have been prudent to have repeated the pilot study to include doses higher than 600 mg/kg/day, and to have

explored the reason for the apparently low bioavailability. Overall, it is considered that the developmental toxicity of EVG has not been adequately investigated in the rabbit.

There was no clear evidence of maternal or reproductive toxicity in the rat pre-post-natal study, with doses that achieved adequate drug exposure. Although EVG is proposed for use only in adults, this study included a juvenile toxicity study in which offspring were dosed for 4 weeks from post-partum day 22, following exposure *in utero* and *via* milk. Doses were the same as their respective dams (to 2000 mg/kg/day), with little or no effect of treatment beings seen, although drug exposures were not as high as in dams (exposure ratios of up to 5.9 in males and 7.1 in females versus up to 17.7 in dams).

Cobicistat. PO doses and drug exposure ratios were lower than in the corresponding EVG studies, with the exception of the rabbit embryofetal development study, but food consumption and body weight gain in rats were adversely affected at doses of ≥ approximately 100 mg/kg/day, resulting in marked mortality at 200 mg/kg/day. Maximum doses used decreased with duration of the studies in rats (that is, 125, 100 and 75 mg/kg/day for the embryofetal development, fertility and pre/postnatal studies, respectively) and were considered appropriate. Significant decreases in maternal body weight gain were seen with the high-dose in all these studies, but there were no specific effects on reproductive parameters.

A non-significant increase in post-implantation loss, and a reduction in fetal weight (only significant after covariate analysis) was seen with the high-dose in the rat embryofetal development study, but this resulted in markedly lower body weight gain over the dosing period (by >50%) associated with reduced food consumption. Increased incidences of incomplete ossification of a number of fetal bones in this study probably reflected lower fetal weights. Based on toxicokinetic data from the 26-week rat study, exposure ratios with the high-dose in the fertility and early embryonic development study were 4.4 (males) or 6.7 (females). However, there was no safety margin with the high-dose in the rat pre-/post-natal development study for which the drug exposure ratio was 1.2, but it is not clear why AUC values were several fold lower than those in other studies, including the pilot embryofetal development study. As with EVG, the pre-post-natal study included a similar juvenile toxicity study, in which there were a number of findings. These notably included hepatocytic hypertrophy, elevated thyroid stimulating hormone and thyroid follicular cell hypertrophy, as in adults (see *General toxicity* above). Other observations such as small increases in platelets and serum protein were also apparent in adults, although urinary volumes were unaffected, and overall there were no unexpected toxicities.

The high-dose used in the main rabbit embryofetal development study (100 mg/kg/day) was appropriate based on the results of the pilot study, although this predicted more severe body weight changes than were actually observed in the main study. Although this resulted in a drug exposure ratio of only 2.8, it elicited a 25% decrement in maternal body weight gain over the dosing period, associated with reduced food consumption.

Emtricitabine. Drug exposures were high in the reproductive toxicity studies (exposure ratios of >50), with no specific effects being observed (Emtricitabine is in Pregnancy category B1[6]).

Tenofovir disoproxil fumarate. High-dose drug exposures were much lower than for FTC in the standard rat reproductive toxicity studies (4-6, but 66 in rabbits) with no specific effects being observed. There were, however, several untoward effects at maternotoxic (mid 2- and high-) doses of 450 and 600 mg/kg/day, including decreased live pups and

[6] The Australian categorisation system for prescribing medicines in pregnancy defines Category B1 as: *'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.'*

their weight at birth and weaning, increased offspring mortality over days 1-4 and post-weaning, and slightly delayed sexual maturation. Additionally, and as noted above (*General toxicity*), tenofovir may exhibit bone toxicity associated with alterations in phosphorus haemostasis. In a published study, subcutaneous treatment of pregnant rhesus monkeys with 30 mg/kg/day tenofovir during the last half of pregnancy elicited reduced offspring serum phosphorus at birth, and continued neonatal treatment resulted in severe bone toxicity. The TDF pregnancy category is B3[7]. Stribild is also proposed to be included in pregnancy category B3.

The 2 new chemical entities have not been tested in combination, although based on findings with each drug alone unexpected or enhanced toxicities are considered unlikely, which is consistent with the relevant EMA guideline.[8] A combination rat embryofetal development study was conducted with EVG plus RTV, a close structural analogue of COBI with a similar CYP3A inhibitory action, with no clear effects of the combination compared with each drug alone. However, as noted above (*Pharmacokinetics and relative drug exposures*), EVG exposure was unaffected by RTV and it is not certain that the dose used was pharmacologically active.

Impurities

Elvitegravir and COBI specifications included proposed limits for several specified impurities and (for COBI only) degradation products. Studies and information to justify the proposed limits were provided. For FTC or TDF, their proposed impurity profile is presumably the same as for Truvada.

Overall, there are no objections on toxicological grounds to the proposed limits for the COBI and EVG-related impurities/degradants.

Nonclinical summary and conclusions

- The proposed combination contains 2 new chemical entities, an HIV-1 integrase inhibitor (EVG) and an inhibitor of CYP3A (COBI) that is structurally related to RTV and which is included to enhance EVG plasma levels. The other components are the HIV-1 reverse transcriptase inhibitors TDF and FTC, which are registered as single agents and as a combination. It is proposed that respective doses of these 4 agents are 150, 150, 300 and 200 mg/day. The nonclinical dossier included only studies with the new chemical entities. Nonclinical virology studies were only included in the clinical part of the submission.
- In *in vitro* experiments, EVG inhibited the HIV-1 integrase strand transfer reaction and integration of viral DNA into host cell chromosomal DNA, but it had no effect on reverse transcriptase. It was a potent inhibitor of HIV-1, with typical IC_{50} values of 0.1-1.3 nM which were increased in the presence of 50% human serum (7.5 times in one experiment). The 2 main human metabolites were also active, *albeit* less potent. The EVG/tenofovir/FTC combination, with and without COBI, showed synergistic interaction. Variants of varying resistance could be generated in EVG ascending concentration or high dose breakthrough cultures. These were associated with viral integrase gene mutations resulting in amino acid substitutions including T66I, E92Q

[7] Category B3 is defined as: *'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.'
[8] Guideline on the non-clinical development of fixed combinations of medicinal products. CHMP/SWP/258498/2005

and Q148R. It showed no activity against topoisomerases and did not affect mitochondrial DNA.

- Cobicistat exhibited a largely mechanism-based (cofactor-dependent) inhibition of human microsomal fraction CYP3A activity *in vitro*, with a similar potency to RTV (IC_{50} of 0.15 nM). It had little or no activity against other CYP isoforms tested, except for weak inhibition of CYP2B6 and CYP2D6 (respective IC_{50} values of 2.8 and 9.2 μM), and it also weakly inhibited UGT1A1 (IC_{50} of 16.3 μM). Unlike RTV, COBI had no activity against HIV-1. It also had no effect on the anti-HIV-1 activities of EVG, FTC or tenofovir.
- Safety pharmacology studies conducted with EVG were adequate. Weak inhibition of hERG currents were seen *in vitro* (by approximately 29% at 10 μM versus 7% for the vehicle), but it had little effect on papillary muscle action potentials at the highest concentration tested (3 μM). There were no CNS, renal or GI-tract transport effects of PO treatment in rats or cardiovascular or respiratory effects in dogs. Elvitegravir did not show phototoxicity in a single-dose study in mice.
- Cobicistat significantly inhibited hERG currents and at higher concentrations the hCav 1.2 calcium channel (respective IC_{50} values of approximately 1.8 μM and 6 μM). Inhibition of the hNav 1.5 sodium channel occurred at much higher concentrations (IC_{50} of 86 μM). Although COBI treatment elicited some changes in isolated rabbit hearts, including prolonged PR interval and a negative inotropic effect, QT interval prolongation was not seen. *In vivo*, QT intervals were slightly prolonged (single dose) or unaffected (4 week toxicity study) by PO treatment of dogs with up to 45 mg/kg. No respiratory effects were seen in rats treated with up to 500 mg/kg PO, but a CNS study showed decreased body temperatures and reduced motor activity with a NOEL of 50 mg/kg. Renal effects of COBI were not investigated.
- Elvitegravir plasma clearance values in the rat and dog after single IV administration were 0.5-1.0 L/h/kg for males. Respective PO bioavailabilities in non-fasted rats and dogs were approximately 33-35% or 26-30% with 0.5% methylcellulose vehicle, compared with 41% absorption of radioactivity in both species after dosing with ^{14}C labelled drug. *In vitro* plasma protein binding was very high in rat, dog and human samples at 0.1-10 μM concentrations (≥99.2%). In rat tissue distribution studies using ^{14}C-EVG, high radioactivity concentrations were seen in the liver and adrenals, with particularly low values for the brain, eye, fat and testes. Radioactivity was not measurable or was very low by 96 h, and multiple PO dosing for 7 days resulted in accumulation of radioactivity in some organs (such as liver, kidney, skin, lymph node). Elvitegravir was a p-glycoprotein substrate in an *in vitro* assay with LLC-PK1 porcine kidney epithelial cells.
- Prominent *in vitro* EVG metabolites were the hydroxy derivative M1, generated largely by CYP3A, and the acyl glucuronide conjugate M4, generated largely by UGT1A3, but with several other derivatives also being seen. Elvitegravir was a weak inhibitor of CYP3A4 (IC_{50} value of approximately 30 μg/mL) and some other CYP isoforms. M1 and M4 were also prominent *in vivo* metabolites in the rat and dog, together with an oxidation and glucuronidation product (M6) in the latter. Low levels of M4 were reported for human plasma, while M1 was a major faecal metabolite. Excretion of radioactivity after PO or IV administration to rats and dogs was overwhelmingly *via* the faeces, as in humans, and biliary excretion was demonstrated in the rat. CYP3A induction was shown in human hepatocytes *in vitro*.
- Cobicistat plasma clearance values were relatively high in the rat and dog after single IV administration (2.2-3.6 L/h/kg). PO bioavailabilities using ethanol/propylene glycol/water vehicles (pH 3 adjusted for the rat) were 34% (rat) and 12% (dog). *In vitro* plasma protein binding was extensive in mouse, rat, dog and human samples (91.1-97.7% at 1-10 μM). Rat tissue distribution studies showed high radioactivity

concentrations in the liver, adrenals and pituitary and low values in the brain/spinal cord and testes. There was no specific association of radioactivity with skin melanin in pigmented rats although the uveal tract concentration was higher than that in another study with albino rats. Cobicistat was a p-glycoprotein substrate in transfected canine kidney MDCKII cells, but no significant efflux was seen across human epithelial colorectal adenocarcinoma (Caco-2) cell monolayers.

- Prominent COBI metabolites *in vitro* were a carbamate cleavage product (M21), a dealkylated methylurea derivative (M26) and a hydroxylated product (M31), seen in mouse, rat, dog and human samples. Metabolism by human recombinant CYP2D6 and to a lesser extent CYP3A were shown. M21 and M31 were also prominent in mice, rats and dogs *in vivo* after PO administration, and were human faecal metabolites. Excretion of radioactivity after PO ^{14}C-COBI administration was overwhelmingly *via* the faeces in the mouse, rat and dog, as in humans, and biliary excretion was shown in the rat and dog. Weak induction of CYP3A4 and CYP1A2 mRNA levels was shown in human hepatocytes *in vitro*.
- Elvitegravir was shown to inhibit organic anion transporter peptide (OATP1B3) *in vitro* with an IC_{50} value of 0.44 µM. Cobicistat was screened against of a range of cellular transporters, with notable inhibition of OATP1B3, MATE1, OCTN1 (organic cation transporter) and OATP1B1 (respective IC_{50} values of 1.9, 1.9, 2.5 and 3.5 µM) being measured. Cobicistat activated rat and, to a lesser extent, human pregnane X receptors, with activation of the human form being less pronounced than with RTV.
- Repeat-dose toxicity studies with EVG were conducted in rats and dogs, with respective durations of up to 26 and 39 weeks, and a mouse 13 week study was also carried out. PO doses achieved systemic drug exposure ratios (AUC relative to the expected human value) in the pivotal studies that were high in rats (up to 36) and relatively low in mice and dogs (respectively up to 5.4 and 2.7). Cobicistat studies were also conducted in these 3 species for these durations, with achieved drug exposure ratios of up to 6.4 (mouse), 6.7 (rat) and 8.3 (dog).
- Elvitegravir was well tolerated. Notable findings in rats were lipid droplets in the duodenum/jejunum, increased caecal weights with no histological correlates and with the high-dose (2000 mg/kg/day) for 26 weeks, stomach erosion/fibrosis/oedema. Mechanistic studies suggested that lipid in the droplets was of dietary origin and droplets were related to local rather than systemic drug concentrations. Reduced urinary volume and electrolyte excretion of uncertain cause and significance was seen in dogs, but in females only, together with very slight duodenal lipid droplets.
- A salient finding with COBI was hepatocytic hypertrophy, which was associated with thyroid follicular cell hypertrophy/hyperplasia and elevated thyroid stimulating hormone in rats, and which represented an adaptive response. Other findings (mainly in rats) included slightly decreased erythroid values and increased platelets, and elevated cholesterol, serum protein and urinary volumes. The latter were often substantial and were associated with increased sodium excretion in the rat 27 week study. There were some indications of functional renal effects in the longest duration dog study but findings were difficult to interpret. Cobicistat elicited an impaired IgG response in a special 4 week immunotoxicity study, and increased incidence of lymphoid depletion in spleen germinal centres. There were no indications of immunotoxicity in the general toxicity studies.
- A 13 week combination study using EVG with and without COBI was conducted in rats, with no unexpected findings for the combination relative to each drug alone, although the fixed COBI dose used (30 mg/kg/day) was insufficient to achieve high enough drug exposures. Elvitegravir exposure was not substantially affected by COBI except in males after the first dose (3 times higher AUC). Other combination studies conducted

(ATV with and without COBI, EVG with and without RTV) were of limited relevance. The combination of all 4 components of Stribild has not been tested.

- Elvitegravir was not considered to be genotoxic, although an equivocal positive response was obtained in an *in vitro* test for clastogenicity. No oncogenic response was seen in long-term carcinogenicity studies in mice and rats using doses that resulted in drug exposure ratios of up to >10, although in the case of mice this was achieved by co-administration with RTV.
- Cobicistat was not genotoxic in adequate assays. There were no oncogenic responses in a long-term carcinogenicity study in mice, in which doses achieved adequate drug exposures. Thyroid follicular cell tumours were seen in the corresponding rat study, associated with hepatocytic hypertrophy and considered to be specific to this species. Achieved drug exposure ratios in rats were less than 1.0 (low and mid-doses) or approximately 2 or slightly above (high-dose).
- Reproductive toxicity was examined in full range of studies with EVG and COBI alone, and an additional rat embryofetal development study was conducted with EVG with and without RTV. Elvitegravir was present in rat milk at low concentrations at the only measurement time (0.5 h after dosing), but 2 h milk concentrations of COBI were higher than maximal maternal plasma values. The pre- and post-natal studies included assessment of juvenile rat toxicity in which selected offspring from treated dams were dosed for 4 weeks.
- Elvitegravir elicited little or no effect in these studies, but exposures in the rabbit embryofetal development study were inadequate and below that expected in humans. Cobicistat doses that could be used were limited by maternal toxicity, but no specific effects on reproductive parameters were observed. However, no safety margin was measurable with the high-dose (75 mg/kg/day) in the pre- and post-natal study.
- The nonclinical profile of FTC (from a previous TGA evaluation report) included an absence of significant drug-related toxicity, genotoxicity or oncogenic responses in long-term rodent carcinogenicity studies. It also did not exhibit reproductive toxicity in adequate studies.
- By contrast, TDF elicited osteopenia (probably secondary to impaired dietary phosphorus absorption), nephrotoxicity and GI-tract lesions. Positive results were obtained in some genotoxicity assays, notably the mouse L5178Y lymphoma test, but there were no oncogenic responses in long-term rodent carcinogenicity studies except for a low incidence of duodenal tumours in high-dose mice. These were most likely related to local hydrolysis of the disoproxil ester. Specific reproductive toxicity was not apparent in standard rat and rabbit studies, but SC treatment of pregnant rhesus monkeys with 30 mg/kg/day of tenofovir resulted in reduced offspring serum phosphorus concentrations.

Conclusions and recommendations

The intended pharmacological activities of the 2 new chemical entities, anti-HIV-1 activity and CYP3A inhibition, were adequately demonstrated *in vitro*, but COBI-induced enhancement of EVG exposures in experimental species was not specifically investigated.

There were no findings in the adequate toxicity studies with EVG and COBI conducted alone that would preclude registration, however no safety margin (based on AUC) for COBI was demonstrated in the only combination study with these 2 drugs. While there were no untoward effects in this 13 week rat study, and FTC and TDF are components of Truvada and Atripla, all 4 proposed drugs in combination have not been investigated in nonclinical studies. Such a combination toxicity study may not be practicable, however, in terms of achieving adequate exposures to each drug. The acceptability of the proposed combination will therefore depend on the extent to which it is clinically justified.

Cobicistat elicited an increased incidence of thyroid follicular cell tumours in rats, but these were associated with an adaptive hepatocytic response and altered thyroid hormones, and are considered to be to be specific to this species.

Cobicistat showed significant inhibition of hERG and hCav 1.2 channels *in vitro*, and although it elicited only minor ECG changes in dogs *in vivo*, any potential for cardiovascular effects should be addressed in the clinical studies. Functional renal changes were observed with COBI, mainly a reversible diuretic-like effect in the rat toxicity studies, but these were not associated with any serum chemistry or histological indications of renal toxicity. The significance of these findings, if any, is not clear, but given the known potential of TDF for nephrotoxicity, renal effects of treatment should receive attention in the clinical studies.

It should be noted that the full potential for reproductive toxicity of EVG may not have been revealed because of low and inadequate drug exposures in the rabbit embryofetal development study. No objections were raised to the proposal to include Stribild in pregnancy category B3.[9]

The nonclinical evaluator recommended amendments to nonclinical statements in the proposed Stribild PI; details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

This is a submission to register a fixed-dose combination tablet comprising 300 mg of TDF, 200 mg of FTC, 150 mg of EVG and 150 mg of COBI. Tenofovir disoproxil fumarate 300 mg and FTC 200 mg have been previously approved as single active ingredient medicines by TGA (under the brand names of Viread and Emtriva, respectively) for the treatment of HIV infection. A fixed-dose combination tablet combining 300 mg of TDF and 200 mg of FTC (Truvada) has also been previously approved by TGA. Elvitegravir and COBI are new chemical entities.

The proposed indication (as stated in the draft PI document) is for the use of [Stribild] as a complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of [Stribild].

Clinical rationale

In the clinical dossier for this submission, the sponsor has stated that current treatment guidelines recommend that initial treatment for ARV treatment-naïve HIV-1 infected patients should involve 2 N(t)RTIs (such as FTC and TDF) and either a NNRTI (such as EFV), a boosted protease inhibitor, or an INSTI. Currently in Australia, RTG is the only INSTI approved for use in adults and it requires a twice daily dosing regimen.

As adherence to ARV drug regimen is important in preventing viral rebound and to reduce risk of drug resistance development, fixed-dose combination STRs have been developed to

[9] Category B3: *'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.*
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.'

improve compliance. Currently in Australia, there are 2 NNRTI/N(t)RTI based STRs approved for once daily administration in the treatment of HIV-1 infection: Atripla (FTC/TDF/EFV) (approved in July 2009) and Eviplera (FTC/TDF/RPV) (approved in January 2012). No STRs exist that combine an INSTI with an N(t)RTI backbone.

The sponsor has stated that the clinical rationale for formulating Stribild is that there remains a need for alternative STRs with potent and sustained efficacy and with a favourable tolerability and safety profile across subgroups of the HIV-1 infected patient population.

Scope of the clinical dossier

The submission contained the following clinical information:

- two pivotal Phase III efficacy/safety studies (GS-US-236-0102 and GS-US-236-0103)
- one Phase II efficacy/safety study (GS-US-236-0104)
- The sponsor's *Clinical overview*, *Summary of clinical efficacy* and *Summary of clinical safety*, and literature references.

Paediatric data

This submission did not include paediatric data. In addition, as the sponsor is not proposing to include an indication for use in children (aged <18 years), information on a Paediatric Development Program was not included in this application.

Good clinical practice

The 3 clinical studies reviewed in this evaluation were in compliance with the EMA's Committee for Medicinal Products for Human Use (CPMP) *Note for Guidance on Good Clinical Practice* (CHMP/ICH/135/95).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each PK topic.

Table 3. Submitted pharmacokinetic studies.

PK topic	Subtopic		Study ID	Primary Drug
PK in healthy adults	General PK	Single dose	GS-US-216-0101	COBI
			GS-US-216-0113	COBI
		Multi-dose	GS-US-216-0101	COBI
			GS-US-216-0113	COBI
	Bioequivalence†	Single dose	GS-US-236-0105 GS-US-183-0140	EVG* EVG*
		Multi-dose	GS-US-236-0105 GS-US-183-0140	EVG* EVG* QUAD*
	Food effect		GS-US-236-0105	EVG
	Mass Balance Study		GS-US-183-0126 GS-US-216-0111	EVG COBI

PK topic	Subtopic	Study ID	Primary Drug
PK in special populations	Target population § Single dose		
	Multi-dose	GS-US-183-0101 GS-US-183-0105	EVG EVG
	Hepatic impairment	GS-US-183-0133	EVG/COBI
	Renal impairment	GS-US-216-0124	EVG/COBI
PK interactions	ritonavir	GS-US-183-0102	EVG/COBI
	ritonavir	GS-US-183-0113	EVG/COBI
	atazanavir	GS-US-183-0106	EVG/COBI
	ritonavir	GS-US-183-0106	EVG/COBI
	atazanavir	GS-US-183-0108	EVG/COBI
	lopinavir	GS-US-183-0116	EVG/COBI
	omeprazole	GS-US-183-0119	EVG/COBI
	ketoconazole	GS-US-183-0146	EVG/COBI
	darunavir	GS-US-201-0104	EVG/COBI
	dmeprazole	GS-US-216-0120	EVG/COBI
	famotidine	GS-US-216-0120	EVG/COBI
	famotidine	GS-US-216-0122	EVG/COBI
	atazanavir	GS-US-216-0123	EVG/COBI
	rosuvastatin	GS-US-216-0123	EVG/COBI
	rifabutin	GS-US-216-0123	EVG/COBI
	Oral Contraceptive	GS-US-236-0106	EVG/COBI
Population PK analyses	Healthy subjects		EVG
	Target population		EVG§

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies unless otherwise stated.

Elvitegravir is a potent HIV-1 integrase strand-transfer inhibitor. Emtricitabine and tenofovir are potent and selective inhibitors of HIV-1 reverse transcriptase. Cobicistat (COBI) is a pharmaco-enhancer that is a potent mechanism-based inhibitor of CYP3A enzymes that reduces systemic clearance and increases exposure of EVG. Both EVG and COBI undergo hepatic metabolism and are minimally excreted in the urine. EVG is primarily metabolized *via* CYP-mediated aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation. There are 2 main metabolites M1 (GS-9202) and M4 (GS-9200) both of which are present at lower concentrations than EVG in plasma. Both metabolites are much less potent than EVG and do not contribute to the clinical effects of the drug. Similarly COBI was the predominant species in plasma; observed metabolites were at undetectable to very low concentrations relative to systemic exposure of COBI. Metabolites M21, M26, and M31 are weaker inhibitors of CYP3A compared with COBI, and due to their low systemic concentrations, should not contribute to the primary pharmacodynamic (PD) effect of CYP3A inhibition.

EVG is rapidly absorbed with peak plasma concentrations occurring 3-4 h after the dose. Taken with a high fat meal the absorption is increased. EVG is highly bound (>95%) to plasma proteins with a large volume of distribution (exceeding total body water) indicating extensive distribution to the tissues. EVG demonstrates non-linear PK with less than dose proportional increases in systemic exposure with increasing doses of EVG alone. In the presence of a CYP3A inhibitor (as in the proposed combination product) systemic

exposures were greater than dose proportional. Elimination half life was also prolonged (from approximately 3 h to 9 h) in the presence of RTV (a CYP3A inhibitor).

No clinically relevant changes in EVG or COBI exposures are observed in the setting of renal or moderate hepatic impairment. The PK profiles of FTC, EVG, COBI and TDF, and of Stribild have been established in HIV-1 infected subjects and some special populations. No clinically relevant differences in the PK of the Stribild STR were observed with respect to demographic variables.

Cobicistat has been shown to decrease estimated creatinine clearance (CLcr), due to inhibition of tubular secretion of creatinine, without affecting renal glomerular function. Dose adjustment of EVG or COBI would not be warranted in subjects with renal impairment. However, dose-interval adjustment is required for FTC and TDF in patients with CLcr <50 mL/min which cannot be achieved with the fixed-dose combination tablet. Consequently, Stribild would need to be discontinued in such patients (CLcr <50 mL/min).

Dose adjustment of Stribild STR in patients with mild or moderate hepatic impairment would appear to be unnecessary as the PK of its components is unaffected in moderate hepatic impairment. No data are available regarding the use of EVG or COBI in subjects with severe hepatic impairment. Stribild STR is not recommended for use in these patients.

Based on the drug-drug interaction profile of EVG and COBI the Stribild STR may have clinically significant interactions with drugs metabolised by or which inhibit CYP3A. Thus potent CYP3A inducers could decrease COBI and EVG plasma concentrations, potentially reducing therapeutic efficacy. Similarly Stribild STR may inhibit the metabolism of drugs dependent on CYP3A for clearance and potentiate adverse or life threatening events. Antacids co-administered with EVG reduced the absorption due to a chelating effect. Staggered dosing, by at least 2 h, has been shown to avoid this issue.

Evaluator's overall conclusions on pharmacokinetics

The main drug in the STR, for which the sponsor seeks approval, is EVG boosted with the CYP3A inhibitor COBI. The other 2 components of Stribild are compounds which already have approval for use, namely FTC and TDF. The PK (and PD) studies have therefore mostly focused on EVG and COBI either alone or in combination with some studies conducted with the Stribild (formerly called the Quad) formulation. The sponsor has provided an extensive range of PK studies evaluating single and multiple doses of EVG, COBI or the combination usage in special populations as well as in patients with HIV. In general these studies have been performed to a high standard and for each of the studies *a priori* power analysis has been undertaken to justify sample sizes. The studies where power may have been an issue is in those of renal and hepatic impairment, where the numbers in each group were probably less than that needed to examine strict bioequivalence (n=10-12 per group). A *post-hoc* calculation of power based on the observed differences may be more convincing for these 2 studies.

The drug-drug interaction studies have primarily focused on the other ARV agents and their potential for interaction with EVG. Based on the metabolism of EVG by CYP3A4, and the known propensity of ARV agents to inhibit this cytochrome, this would seem to be appropriate. Similarly the ability of other known CYP3A4 inhibitors (such as ketoconazole) to affect EVG/COBI PK has also been investigated.

Given the occurrence of psychiatric disorders in patients with HIV (mania/hypomania and depression) it was surprising that no formal *in vivo* studies were performed to examine potential PK interactions. While the *in vitro* profile of EVG/COBI suggests some interaction with psychotropic medications there is no mention of a potential interaction with lithium, which is known to affect renal function.

The proposed PI reflects adequately the PK studies that have been performed and provides suitable warnings about the potential for drug-drug interactions based on the studies that have been performed as well as theoretical possibilities given the known metabolic pathways for EVG and COBI.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 4 shows the studies relating to each PD topic.

Table 4. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary drug
Primary Pharmacology	Antiviral activity	GS-US-183-0101	EVG
	Antiviral activity	GS-US-183-0105	EVG
Secondary Pharmacology	ECG (QTc F) ECG (QTcF)	GS-US-183-0128 GS-US-216-0107	EVG COBI
	Renal function (CrCL)	GS-US-216-0121	COBI
PD Interactions	P-glycoprotein, CYP2B6, CYP 2D6	GS-US-216-0112	COBI
	midazolam	GS-US-216-0116	COBI

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ And adolescents if applicable.

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacodynamics

A small number of PD studies, which were generally well conducted and adequately powered, were presented by the sponsor. The primary endpoint of antiviral activity in HIV infected patients was assessed in a PK-PD analysis of data obtained from a short term (10 day) study and a comparative 48 week trial. Taken alone EVG was able to reduce viral load. When combined with RTV, EVG demonstrated non-inferiority to a comparative protease inhibitor (CPI) combined with RTV (CPI/r[10]). In both studies the PK-PD data fitted simple models of maximum PD effect (Emax models). EVG trough concentrations with the dosing regimens used exceeded the concentration that results in 95% inhibition (IC_{95}) for the entire dosing interval.

The cardiovascular safety of both EVG and COBI were assessed in healthy volunteers. Assay sensitivity was established in both studies by using moxafloxacin as a control condition. At doses which would exceed that recommended in clinical practise there was no significant effect on QTcF. The effect of COBI on left ventricular function assessed with echocardiograms showed no clinically significant change from baseline. Taken together the data would suggest that EVG or COBI do not produce significant effects on cardiovascular function, at least at the doses investigated.

COBI tended to decrease the estimated glomerular filtration rate (GFR, using the Cockcroft-Gault equation). However measurement of actual GFR *via* assessment with iohexol clearance showed no effect on renal clearance.

[10] The abbreviation '/r' indicates treatment boosted with ritonavir.

Some studies appear to be out of place in the PD section: the studies on interactions were reported as PD studies by the sponsor but were clearly PK studies as there were no PD endpoints. Nevertheless, these studies addressed some issues of potential drug-drug interactions of COBI and supported the notion that it was a CYP3A4 inhibitor, which might be successfully used to increase systemic exposure to EVG, if administered together.

Efficacy

Dosage selection for the pivotal study

The Stribild (formerly called Quad) STR formulation used in the pivotal Phase III studies was a fixed-dose combination tablet comprising of 300 mg of TDF, 200 mg of FTC, 150 mg of EVG and 150 mg of COBI. The doses of FTC and TDF in the proposed Stribild STR were the respective therapeutic doses approved for use in Australia.

EVG and COBI are both new chemical entities. In describing the justification for choice of dose of EVG, the sponsor has stated that in study GS-US-183-0105, which was a dose-finding study that assessed the non-inferiority of RTV-boosted EVG relative to an RTV-boosted comparative protease inhibitor, the highest EVG dose tested was 125 mg. Study GS-US-183-0140, which evaluated the multiple-dose relative bioavailability of RTV-boosted EVG 125 mg and RTV-boosted EVG 150 mg, showed that the 125 mg dose and the 150 mg dose of EVG provided bioequivalent EVG exposures. No rationale was given by the sponsor for the eventual choice of 150 mg instead of 125 mg of EVG in the proposed Stribild STR.

In describing the justification of choice of dose of COBI, the sponsor has stated that study GS-US-236-0101 showed that although administration of EVG as an STR with COBI at a dose of 100 mg resulted in bioequivalent EVG exposure relative to RTV-boosted EVG (as assessed by AUC over the dosing interval (AUC_{tau}) and Cmax), it was 37% lower relative to RTV-boosted EVG when assessed using observed drug concentration at the end of the dosing interval (Ctau). With the STR containing COBI 150 mg, EVG exposure was modestly higher for Cmax and met the definition of bioequivalence, and the upper limit of the 90% CI of AUC_{tau} exceeded the criteria by 1%. The sponsor has stated that it was also taken into consideration that there could be a potential difference in exposure of COBI and EVG in HIV-1 infected patients compared with healthy subjects, as boosted agents frequently have lower exposures in the HIV-1 infected patient population compared to in healthy subjects, and this led to the selection of 150 mg dose of COBI to be used in the proposed STR formulation.

Studies providing efficacy data

The principal clinical efficacy and safety data in support of this application submission were derived from 2 Phase III registration studies, Study GS-US-236-0102 and Study GS-US-236-0103. This was supplemented by data from a Phase II study, Study GS-US-236-0104, which had been conducted for the purpose of providing an estimation of the response rate of Stribild, to allow for the planning of the Phase III studies. The 2 Phase III studies contained data up to Week 48 of the respective studies. The sample size of the Phase II study was small (n=71), but provided data beyond Week 48 through Week 96, and hence provided some preliminary efficacy and safety data on the long-term use of Stribild beyond 48 weeks.

Study GS-US-236-0102 was a Phase III, double-blind, double-dummy, multi-centre, randomised, active-control study to assess the safety and efficacy of the Stribild STR versus Atripla (ATR) STR in HIV-1 infected, ARV treatment-naïve adult subjects. Subjects were randomised in a 1:1 ratio to Stribild or ATR once daily.

The primary objective of this study was to evaluate the efficacy of Stribild STR (containing 200 mg FTC/300 mg TDF/150 mg EVG/150 mg COBI) versus ATR STR (containing 200 mg FTC/300 mg TDF/600 mg EFV) in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the achievement of HIV-1 RNA <50 copies/mL at Week 48. The secondary study objective was to evaluate the efficacy, safety, and tolerability of the 2 STRs through 96 weeks of treatment.

Study GS-US-236-0103 is a Phase III, double-blind, double dummy, multi-centre, randomised, active-control study to assess the safety and efficacy of the Stribild STR versus RTV-boosted ATV (ATV/r) plus Truvada (TVD; comprising of 200 mg FTC and 300 mg TDF) in HIV-1 infected, ARV treatment-naïve adult subjects. Subjects were randomised in a 1:1 ratio to 1 of 2 treatment groups: Stribild STR and placebo for RTV, ATV, and TVD each once daily, or ATV 300 mg, RTV 100 mg, and TVD (FTC 200 mg/TDF 300 mg) and placebo for Stribild STR each once daily.

The primary objective of this study was to evaluate the efficacy of Stribild STR versus a regimen containing ATV/r and TVD (ATVr+TVD) in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48. The secondary study objective was to evaluate the efficacy, safety, and tolerability of the 2 treatment regimens through 96 weeks of treatment.

Study GS-US-236-0104 was a Phase II, double-dummy, randomised, double-blind, multicentre, active-control study evaluating the safety and efficacy of the Stribild STR versus ATR in 71 HIV-1 infected, ARV treatment-naïve adult subjects (≥18 years of age). This study was conducted to provide an estimation of the response rate of HIV-1 RNA <50 copies/mL of Stribild, in order to allow for the planning of the Phase III studies. This is a multicentre study where subjects were enrolled in a total of 30 study sites in the United States. The study start date (first subject screened) was 30th March 2009. The study was ongoing in an open-label extension phase at the time of this submission, and data through Week 96 were presented in the clinical study report (CSR) submitted. The date of last subject observation for this CSR was 17th May 2011.

The primary objective of this study was to evaluate the efficacy of Stribild STR (EVG/COBI/FTC/ TDF) versus ATR STR (EFV/FTC/TDF) in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the achievement of HIV-1 RNA <50 copies/mL at Week 24. The secondary study objectives were to evaluate the efficacy of Stribild STR versus ATR STR in HIV-1 infected, ARV treatment-naïve adult subjects at Week 48, and to evaluate the safety and tolerability of the 2 STRs through 48 weeks of treatment.

Evaluator's conclusions on clinical efficacy of Stribild as a complete regimen for the treatment of HIV infection in adults

Overall, in the 2 Phase III registration trials, the conclusion from the primary efficacy analyses was that there was non-inferiority in the virologic efficacy of Stribild STR compared with co-formulated EFV /FTC/TDF (Atripla; ATR) or ATV/r +TVD. This conclusion was appropriate. The study designs of both Phase III registration trials are sound. Inclusion and exclusion criteria are in line with recommendations on the study population in the TGA-adopted EMA guideline on the clinical development of medicinal products for the treatment of HIV infection, and study primary endpoints are in agreement with current HIV research guidelines and recommendations.[11]

[11] See the EMA *Guideline on the clinical development of medicinal products for the treatment of HIV infection*. EMEA/CPMP/EWP/633/02 (20 Nov 2008).
The current HIV treatment guidelines in Australia can be accessed online at <http://arv.ashm.org.au/pdf/ARV_Guidelines_AustCommentary_March28.pdf>

The choices of active control ARV drug regimen of ATR in Study GS-US-236-0102 and of ATV/r+TVD in Study GS-US-236-0103 are appropriate as both ARV drug regimens are recommended first-line treatment regimen for ARV treatment-naïve HIV-1 infected patients, in accordance with current treatment guidelines.

In each of the 2 Phase III studies, demographic and baseline disease characteristics were similar between treatment groups. The majority of subjects in each study had CD4 (a subtype of T lymphocyte helper cells) counts ≤ 500 cells/μL, and median CD4 counts were 380 and 367 cells/μL in studies GS-US-236-0102 and GS-US-236-0103, respectively, suggesting clinical relevance of the study population, as current treatment guidelines for treatment of HIV infection recommend initiation of ARV treatment when CD4 cell counts are <500 cells/μL.

Primary efficacy outcomes demonstrated non-inferiority of Stribild versus ATR or ATV/r+TVD. Secondary and tertiary endpoints analyses showed that the conclusion of non-inferiority of Stribild versus ATR or ATV/r+TVD obtained in the respective primary efficacy outcomes was supported by other analyses, including analysis in the per protocol (PP) dataset, analysis using the time to loss of virologic response (TLVOR) algorithm, and analysis using different imputation methods. Virologic response measured in terms of decrease in HIV-1 RNA levels from baseline, and drug effect measured in terms of immunological response were both consistent with the primary efficacy outcome: virologic response measured in terms of decrease in HIV-1 RNA levels from baseline at Week 48 was similar between treatment groups in both studies, while drug effect measured in terms of immunological response was statistically significant in favour of Stribild over ATR, and did not show any statistically significant difference between Stribild and ATV/r+TVD.

Subgroup analyses in the 2 Phase III studies generally supported the respective primary efficacy results. In both studies, homogeneity tests performed for the primary endpoint did not show a significant difference in treatment effects between subgroups. In both studies, the lower limits of the 95% CI of the difference in response rate in the subgroup analyses were all greater than the prespecified −12% non-inferiority margin in all the subgroups, except for the subgroup of patients who were females (-15.5% and -20.6% in studies GS-US-236-0102 and GS-US-236-0103, respectively). However, the 95% CI of the difference in response rate in this subgroup was very wide in both studies (-15.5% to 20.1% in study GS-US-236-0102 and -20.6% to 18.3% in study GS-US-236-0103) reflecting the small sample size in this subgroup (n=41 and n=24 in studies GS-US-236-0102 and GS-US-236-0103, respectively), which makes interpretation of the results difficult.

In the small Phase II study, Study GS-US-236-0104, although the results in the primary and secondary endpoint analyses in the randomised phase mostly failed to demonstrate non-inferiority of Stribild versus ATR, the analysis at Week 48 using the FDA snapshot analysis algorithm (a secondary endpoint in this study) yielded results suggesting non-inferiority of Stribild versus ATR. *These results need to be taken in the context that this study was not powered to evaluate non-inferiority of QUAD [Stribild] versus ATR, but to obtain an estimation of the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for [Stribild] STR.*

The virologic response rate in the Stribild group at Week 48 using snapshot analysis was comparable to those obtained in Study GS-US-236-0102 and Study GS-US-236-0103, as was the mean change from baseline at Week 48 of HIV-1 RNA levels and CD4 counts in the Stribild group, providing some evidence of consistency in the virological and immunological response rates of Stribild.

Results in the open-label phase of Study GS-US-236-0104 suggested that in patients who were on Stribild in the randomised phase and who continued on Stribild in the open-label phase (that is, >60 weeks of Stribild), there was further and sustained suppression of HIV-1 RNA levels and increase in CD4 cell count, suggesting that both virological and

immunological responses were sustained beyond 48 weeks of Stribild dosing. The sample size was small and inadequate for definitive evaluation of long-term efficacy, but gave a preliminary indication of potential long-term efficacy.

Pooled efficacy analysis is appropriate as the study designs of the 3 studies were similar and baseline demographic and disease characteristics of the study populations were similar. Pooled efficacy analysis results were consistent with the individual study results, showing non-inferiority of pooled Stribild group versus pooled ATR group, of pooled Stribild group versus pooled ATV/r+TVD group, and of pooled Stribild versus pooled active control group.

The main issues with regards to the efficacy results were the emergent study drug resistance results, and the rationale for the doses of the EVG of Stribild. With regards to emergent study drug resistance, in Study GS-US-236-0102, although the proportions of patients who developed emergent reverse transcriptase resistance (RT-R) mutations were similar between the Stribild and ATR groups, seven out of the 8 subjects in the Stribild group who were tested for study drug resistance developed INSTI-resistance (INSTI-R) mutations, compared with none in the ATR group. In Study GS-US-236-0103, out of 12 subjects tested in the Stribild group, 4 subjects developed RT-R mutations, and 4 subjects developed INSTI-R mutations, while in the ATV/r+TVD group, out of the 8 subjects tested, none developed emergent resistance to a study drug. Although the number of patients analysed for emergent study drug resistance were too small for meaningful statistical analysis, the above results suggest that development of INSTI-R mutations may be an issue with the use of Stribild, compared to the active controls. This is, however, within expectations, as neither ATR nor ATV/r+TVD contain an INSTI, whereas the EVG component of Stribild is an INSTI. This also needs to be taken in the context that the calculated percentage of patients in the Stribild group with emergent INSTI-R mutations was low: 2.0% in Study GS-US-236-0102, and 1.1% in Study GS-US-236-0103 (assuming that subjects who did not show virologic failure, and hence were not tested for study drug resistance, did not have the resistance mutations).

With regards to the rationale for the doses of the EVG of Stribild, in describing the justification for choice of dose of EVG, the sponsor has stated that in study GS-US-183-0105, RTV-boosted EVG of 125 mg dose formulation was used, and that study GS-US-183-0140 showed that the 125 mg dose and the 150 mg dose provided bioequivalent EVG exposures. No rationale was given for the choice of 150 mg instead of 125 mg of EVG.

Safety

Studies providing safety data

The principal clinical safety data in this submission were derived from the 2 Phase III studies (GS-US-236-0102 and GS-US-236-0103) and supported by the Phase II study, Study GS-US-236-0104.

The sponsor has provided a pooled safety analysis (using pooled safety data up to Week 48 plus the available data up to the respective cut-off dates for Studies GS-US-236-0102 and GS-US-236-0103, and up to Week 60 [that is, randomised phase] for Study GS-US-236-0104) in the clinical summary of safety data, in addition to individual safety data of the 3 studies in the respective CSRs.

It is considered by the evaluator that a pooled analysis is appropriate as the study designs of the 3 studies were similar apart from the active control used. In this evaluation, the pooled safety analysis as well as the safety data in the open-label phase of Study GS-US-236-0104 will be presented.

Patient exposure

Exposure in the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 is summarised in Table 5 below**.** Overall, 749 subjects received Stribild (formerly known as Quad) in these studies, 375 subjects received ATR, and 355 subjects received ATV/r+TVD. The median duration of exposure to study drug was 48.4 weeks in the Stribild group, 58.9 weeks in the ATR group, and 48.1 weeks in the ATV/r+TVD group.

Table 5. GS-US-236-0102, 0103, 0104: Duration of Exposure to Study Drug (Safety Analysis Set)

	QUAD 236-0102, 0103, 0104 (N=749)	ATR 236-0102, 0104 (N=375)	ATV/r + TVD 236-0103 (N=355)
Total Exposure to Study Drug (Weeks)[a, b]			
N	749	375	355
Mean (SD)	50.3 (12.12)	50.1 (15.77)	46.8 (13.21)
Median	48.4	58.9	48.1
Q1, Q3	47.9, 60.0	48.1, 60.1	46.1, 51.0
Min, Max	0.1, 64.6	0.1, 69.0	0.6, 62.6
Total Exposure to Study Drug			
> 4 Weeks (28 days)	737 (98.4%)	359 (95.7%)	342 (96.3%)
> 8 Weeks (56 days)	731 (97.6%)	357 (95.2%)	339 (95.5%)
> 12 Weeks (84 days)	727 (97.1%)	347 (92.5%)	334 (94.1%)
> 16 Weeks (112 days)	715 (95.5%)	342 (91.2%)	332 (93.5%)
> 24 Weeks (168 days)	707 (94.4%)	336 (89.6%)	328 (92.4%)
> 32 Weeks (224 days)	697 (93.1%)	334 (89.1%)	323 (91.0%)
> 40 Weeks (280 days)	688 (91.9%)	331 (88.3%)	316 (89.0%)
> 48 Weeks (336 days)	509 (68.0%)	283 (75.5%)	185 (52.1%)
> 60 Weeks (420 days)	164 (21.9%)	111 (29.6%)	52 (14.6%)

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

b If the last dose date was completely missing (eg, lost to follow-up) or a subject was still on study drug, the maximum of study drug start and end dates, clinic and laboratory visit dates excluding the 30-day follow-up visit date was used to impute the last dose date.

Note: The name Quad was subsequently changed to Stribild. Quad and Stribild are considered interchangeable for the purpose of this AusPAR.

The safety analysis set in the open-label phase of Study GS-US-236-0104 (called the "All Stribild" group) consisted of 62 subjects (48 subjects in the Stribild/Stribild group and 14 subjects in the ATR/Stribild group). The median exposure was 96.1 weeks in the Stribild/Stribild group and 37.2 weeks in the ATR/Stribild group.

The evaluator considered that, overall, the amount of exposure to Stribild is adequate to evaluate the safety profile of the drug. In the 2 Phase III trials, 509 HIV1-infected patients were exposed to Stribild for at least 48 weeks. Longer-term safety data was derived from the open-label phase of the Phase II study, where subjects were exposed to Stribild beyond 48 weeks, but the sample size was small.

Evaluator's overall conclusions on clinical safety

Overall, there were no significant concerns of note in the incidences of adverse events (AEs) with administration of Stribild. The most frequently reported study drug-related AEs in the Stribild group were nausea, diarrhoea and abnormal dreams. Results in the All Stribild group showed that in patients who continued on, or were switched to Stribild, the incidences and types of AEs remained stable.

There were no particular concerns raised with regards to the AE of special interest of bone fractures. Although the incidence of renal AEs of interest as well as the percentage of patients who discontinued study drug due to renal AEs, were higher in the pooled Stribild group than in the ATR or ATV/r+TVD group, the renal AEs and the abnormal renal parameters appeared to be reversible after drug discontinuation, and none of the 4 subjects with renal failure in the Stribild group required dialysis or other forms of renal

replacement therapy during the study. It is also noted that the reporting of the AE of renal failure was based on renal laboratory abnormalities (raised serum creatinine and reduced estimated GFR), and analysis of renal laboratory parameters showed that although there were greater increases in median values for serum creatinine and a greater decrease in median estimated GFR calculated using the Cockroft-Gault equation ($eGFR_{CG}$) in the pooled Stribild group compared to the ATR and ATV/r+TVD groups, there were no corresponding decreases from baseline of estimated GFR calculated using the Cystatin-C method (cysGFR), suggesting that the raised serum creatinine levels and reduced $eGFR_{CG}$ could be due to the inhibition of tubular secretion of creatinine by COBI, and not reflecting an actual nephrotoxic effect of Stribild.

The main concern pertaining to the laboratory safety results is with regards to hypophosphatemia and urine fractional excretion of phosphate. The percentage of subjects with hypophosphatemia was higher in the Stribild group than in the ATR group in Study GS-US-236-0102. However, it was lower in the Stribild group than in the ATV/r+TVD group in Study GS-US-236-0103, and most of the hypophosphatemia were of Grades 1 or 2 in severity. The median increases from baseline of urine fractional excretion of phosphate at Week 48 was greater in the Stribild group compared to those in the ATR group in Study GS-US-236-0102, and those in the ATV/r+TVD group in Study GS-US-236-0103. However, the increases from baseline were small, of up to 2.7% through to Week 48, and the maximum median urine fractional excretion of phosphate were comparable between the Stribild groups and the respective active controls. The maximum median urine fractional excretion of phosphate in the Stribild groups was 12.4% and 12.6% in Study GS-US-236-0102 and Study GS-US-236-0103, respectively, falling within the normal range of 5% and 20%. Urine fractional excretion of phosphate was not measured in Study GS-US-236-0104, thus no results for beyond Week 48 was available.

List of questions

Pharmacokinetics

Question 1a. Although EVG has the potential for stereoisomeric forms there were no studies on the possible inter-conversion of isomers *in vivo*. Was this issue addressed in nonclinical studies and inter-conversion ruled out?

Question 1b. In assessing the drug interaction potential of the Stribild reliance has been placed on *in vitro* assessments and some *in vivo* studies with 'model' substrates. There have been few *in vivo* studies with medications used to treat possible co-morbid, non-virus related conditions. Given the effect of COBI on renal function and the potential use of lithium in HIV patients, and its known effect on renal function, has a study been conducted to examine this interaction? A study using the Stribild rather than any of the components would seem to be potentially more useful in deciding the clinical significance of any such interaction effects found.

Pharmacodynamics

Question 2. Has the potential PD interaction with the Stribild and alcohol been considered? Perhaps an *in vivo* study assessing the effects on cognitive and psychomotor performance would be useful.

Efficacy

Question 3. Please justify the dose for EVG in the formulation of Stribild. In describing the justification for choice of dose of EVG, the sponsor has stated that in study GS-US-183-0105, RTV-boosted EVG of 125 mg dose formulation was used, and that study GS-US-183-0140 showed that the 125 mg dose and the 150 mg dose of EVG provided bioequivalent EVG exposures. No rationale was given for the choice of 150 mg instead of 125 mg of EVG.

First round clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The benefit of Stribild in the proposed usage is as an alternative STR, combining an INSTI with an N(t)RTI backbone, for the treatment of ARV treatment-naïve HIV-1 infected adult patients. Current treatment guidelines recommend that initial treatment for ARV treatment-naïve HIV-1 infected patients should involve 2 N(t)RTIs (for example, FTC and TDF) and either an NNRTI (for example EFV or RPV), a boosted protease inhibitor, or an INSTI. Currently in Australia, RTG is the only INSTI approved for use in adults. It requires twice daily dosing regimen, and is not formulated as an STR with an N(t)RTI combination. Currently in Australia, there are 2 STRs approved for once daily administration in the treatment of HIV-1 infection, and both combine an NNRTI with an N(t)RTI backbone of FTC and TDF: Atripla (FTC/TDF/EFV) and Eviplera (FTC/TDF/RPV). No approved STRs exist that combine an INSTI with an N(t)RTI backbone. The Stribild STR has a role as an alternative treatment for patients who cannot tolerate NNRTIs or boosted PIs, while allowing for a simplified drug regimen which can improve compliance and reduce the risk of development of drug resistance.

Efficacy results showed that the use of Stribild STR in the treatment of ARV treatment-naïve HIV-1 infected adult patients with baseline HIV-1 RNA ≥5000 copies/mL, led to approximately 89% of patients achieving virologic levels of <50 HIV-1 copies/mL at Week 48, as defined by the FDA snapshot analysis algorithm. When benchmarked against treatment guidelines-recommended first-line ARV drug of ATR STR or ARV drug regimen of ATV/r+TVD, this proportion of virologic response of Stribild was found to be non-inferior to those of ATR STR or ATV/r+TVD.

In addition, efficacy results in patients who were on Stribild for more than 48 weeks showed that there was further and sustained suppression of HIV-1 RNA levels and increase in CD4 cell count, suggesting that both virological and immunological responses were sustained beyond 48 weeks of Stribild dosing.

First round assessment of risks

The risks of Stribild in the proposed usage are:

- the potential adverse effect on the renal system

In the 2 pivotal Phase III registration studies, safety results showed that the incidence of renal AE of interest as well as the percentage of patients who discontinued study drug due to renal AEs, were higher in the pooled Stribild group than in the ATR or ATV/r+TVD group. In addition, the majority of the renal AEs of interest in the Stribild group were that of renal failure.

However, the renal AEs and the abnormal renal parameters appeared to be reversible after drug discontinuation, and none of the subjects with renal failure in the Stribild group required dialysis or other forms of renal replacement therapy during the study. This also needs to be considered in the context that the renal AEs and abnormal laboratory parameters can be monitored and detected by routine laboratory tests. It is also noted that the reporting of the AE of renal failure was based on renal laboratory abnormalities (raised serum creatinine and reduced eGFR), and analysis of renal laboratory parameters showed that although there were greater increases in median values for serum creatinine and a greater decrease in median $eGFR_{CG}$ in the pooled Stribild group compared to the ATR and ATV/r+TVD groups, there were no corresponding decreases from baseline of cysGFR, suggesting that the raised serum creatinine levels and reduced $eGFR_{CG}$ could be due to the inhibition of tubular secretion of creatinine by COBI, and not reflecting an actual nephrotoxic effect of Stribild.

In the 2 pivotal Phase III registration studies, the median increase from baseline of urine fractional excretion of phosphate, used as a measure of proximal renal tubular injury, was greater at Week 48 in the Stribild group compared to those in the ATR or ATV/r+TVD group. However, the increases from baseline were small (up to 2.7% through to Week 48) and the maximum median urine fractional excretion of phosphate were comparable between the Stribild groups and the respective active controls. In addition, the maximum median urine fractional excretion of phosphate in the Stribild groups of 12.4% and 12.6% in Study GS-US-236-0102 and Study GS-US-236-0103, respectively, fell within the normal range of 5% and 20%. This was also not associated with significant concerns regarding the incidence of hypophosphatemia, with safety results showing that the percentage of subjects with hypophosphatemia in the Stribild group, although higher than that in the ATR group, was lower than that in the ATV/r+TVD group, and that most of the hypophosphatemia were of Grades 1 or 2 in severity.

- the emergence of resistance to INSTI

Study results suggested that development of INSTI-R mutations may be an issue with the use of Stribild, compared to the active controls of ATR and ATV/r+TVD. This, however, is within expectations as neither ATR nor ATV/r+TVD contain an INSTI, whereas the EVG component of Stribild is an INSTI. The calculated percentage of patients in the Stribild group with emergent INSTI-R mutations was low: 2.0% in Study GS-US-236-0102, and 1.1% in Study GS-US-236-0103 (assuming that subjects who did not show virologic failure, and hence were not tested for study drug resistance, did not develop the resistance mutations). The proportions of patients who developed emergent RT-R mutations were similar between the Stribild and ATR groups, but higher in the Stribild group compared to the ATV/r+TVD group, although the number of patients analysed for emergent study drug resistance was too small for meaningful statistical analysis

First round assessment of benefit-risk balance

The benefit-risk balance of Stribild, given the proposed usage, is favourable.

- Efficacy results showed that the use of Stribild STR in the treatment of ARV treatment-naïve HIV-1 infected adult patients with baseline HIV-1 RNA ≥5000 copies/mL, led to approximately 89% of patients achieving virologic levels of <50 HIV-1 copies/mL at Week 48, as defined by the FDA snapshot analysis algorithm. When benchmarked against treatment guidelines-recommended first-line ARV drug of ATR STR or ARV drug regimen of ATV/r+TVD, this proportion of virologic response of Stribild was found to be non-inferior to those of ATR STR or ATV/r+TVD.
- Preliminary efficacy results in patients who were on Stribild for more than 48 weeks suggested that there was further and sustained suppression of HIV-1 RNA levels and increase in CD4 cell count, suggesting that both virological and immunological responses were sustained beyond 48 weeks of Stribild dosing.

The main risks involve the potential adverse effect on the renal system and the emergence of resistance to INSTI with the use of Stribild.

- potential adverse effect on the renal system

  Although safety results showed that there was a higher incidence of renal AE of interest in the Stribild group than in the ATR or ATV/r+TVD group, and that the majority of these renal AEs of interest in the Stribild group were renal failure, the reporting of these AEs of renal failure was based on renal laboratory abnormalities (raised serum creatinine and reduced eGFR). Analysis of renal laboratory parameters showed that although there were greater increases in median values for serum creatinine and a greater decrease in median $eGFR_{CG}$ in the Stribild group compared to the ATR or ATV/r+TVD groups, there were no corresponding decreases from baseline of cysGFR. This raised the possibility that the increased serum creatinine levels and

reduced $eGFR_{CG}$ could be due to the inhibition of tubular secretion of creatinine by COBI, and not reflecting an actual nephrotoxic effect of Stribild, and that the renal AEs were triggered when the raised serum creatinine and reduced eGFR were noted. In addition, the renal AEs and the abnormal renal parameters appeared to be reversible after drug discontinuation. It is also taken into consideration that the renal AEs and abnormal laboratory parameters can be monitored and detected by routine laboratory tests.

Overall, the potential risk of adverse effect on the renal system with the use of Stribild is not considered to be high, given that safety results suggested that the renal AEs and abnormal renal laboratory parameters detected in the studies may be reflecting the effect of COBI on tubular secretion of creatinine rather than an actual nephrotoxic effect of Stribild, and given that it is monitorable and reversible. It is also noted that appropriate precautions are stated in the proposed PI.

- emergence of resistance to INSTI with the use of Stribild

With regards to the emergence of resistance to ARVs, there are no significant concerns that the rate of emergence of RT-T mutations was higher with the use of Stribild compared to ATR or ATV/r+TVD. However, results suggested that INSTI-R mutations may be an issue with the use of Stribild, compared to the active controls of ATR and ATV/r+TVD. This, however, is within expectations, as neither ATR nor ATV/r+TVD contains an INSTI, whereas the EVG component of Stribild is an INSTI with the use of Stribild. The degree to which the INSTI resistance mutations which was found to emerge with the use of Stribild will lead to resistance to other INSTIs is not known. Additional data needs to be collected with regards to cross-resistance in this relatively new class of ARV medications. However, it is noted that the percentage of patients in the Stribild group in the Phase III studies with emergent INSTI-R mutations was low, at between 1 to 2%.

First round conclusions

Overall, the benefit-risk balance of Stribild is positive, and meets the EMA guideline on the clinical development of medicinal products for the treatment of HIV infection, which recommended that a *"convincingly demonstrated non-inferior benefit-risk at 48 weeks versus a well recognised reference product may serve as a basis for approval".*[12] With study results showing that efficacy is comparable with that of ATR and of ATV/r+TVD, both recognised reference ARV drug or drug regimens for the treatment of ARV treatment-naïve HIV-1 infected adult patients, and with a safety profile that does not raise significant concerns, Stribild has a role as an alternative treatment option for HIV-1 infected treatment-naïve adult patients who cannot tolerate NNRTIs or boosted PIs.

[12] EMA. Guideline on the clinical development of medicinal products for the treatment of HIV infection. 20 Nov 2008 (EMEA/CPMP/EWP/633/02).

First round recommendation regarding authorisation

It is recommended that the application for registration of Stribild, for the proposed indication of treatment of HIV-1 infection in ARV treatment-naïve adult patients be approved, subject to a satisfactory response to the recommended changes to the PI.[13]

It is recommended that the indications of [Stribild] be further clarified, from the original proposed text of

"[Stribild] is indicated as a complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of [Stribild]"

to

"[Stribild] is indicated as a complete regimen for the treatment of HIV-1 infection in ARV treatment-naive adults aged 18 years and over, who have no known mutations associated with resistance to the individual components of [Stribild]."

It is noted that at the time of submission of this clinical dossier, the 2 pivotal Phase III studies and the Phase II study were both ongoing. It is recommended that the sponsor submit the results of these studies as soon as they are completed.

Second round clinical evaluation

Evaluation of data submitted in response to questions

Sponsor's response to TGA question 1a:

The *in vivo* interconversion of EVG to the (R)-enantiomer (JTP-65381) was evaluated in a study in rats and dogs. JTP-65381 was not detected in rat and dog plasma after oral administration of EVG. Additionally, the chiral center in the EVG molecule (that is, the (S)-enantiomer) is not inter-convertible because of the relatively high pKa value of the proton on the chiral center contained in the valinol moiety and the strong connective bonds between the stereogenic center and the appending groups. Thus, the chiral center is not labile and formation of the (R)-enantiomer starting from EVG is highly unlikely. Stability study results support this assessment as the (R)-enantiomer of EVG has not been detected under long term and accelerated conditions. Thus, based on the results from the nonclinical study in rats and dogs, and the chemical knowledge and understanding of the pathways necessary for epimerization of chiral centers to occur, the chemical activity of the chiral center in the EVG molecule, and the chemical stability data for EVG, the potential inter-conversion of isomers *in vivo* is highly unlikely therefore, clinical studies evaluating the inter-conversion are not considered necessary.

TGA evaluator's comment

The response is considered acceptable.

Sponsor's response to TGA Question 1b.

The assessment of drug interaction potential between Stribild and concomitant medications that may be used to treat co-morbidities in HIV-1 infected patients is based on a thorough evaluation of the relevant absorption, distribution, metabolism and excretion (ADME) properties of each of the components, including the investigational agents EVG and COBI, and the marketed agents TDF and FTC. These overall recommendations are consistent with the approach taken for other ARV agents which are used as part of an ARV regimen (along with concomitant medications if necessary).

[13] Details of revisions regarding the PI are beyond the scope of this AusPAR.

This approach is also consistent with the European Guidelines: *Guideline on the investigation of Drug Interactions (EMA/CHMP/EWP/125211/2010)* and the US Guideline for Industry *Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing and Labelling Recommendations* (February 2012) for evaluation of drug interactions.

Following oral administration, lithium is excreted almost entirely by the kidney, *via* glomerular filtration. Study GS-US-216-0121 demonstrated that COBI affects the eGFR, which is calculated based on serum creatinine (an endogenous agent that is both filtered and secreted) and not the actual GFR, as assessed by clearance of iohexol, a exogenous marker that is eliminated almost exclusively by filtration. The mechanism of change in eGFR has been elucidated to be a transporter mediated interaction between COBI and creatinine (that is, inhibition of primarily the MATE-1 transporter-mediated secretion of creatinine by COBI). Therefore it is unlikely for COBI to undergo clinically relevant interactions with lithium.

Elvitegravir, the other investigational component of Stribild, is minimally eliminated in urine (and not as unchanged parent), and is not associated with changes in GFR. The PK properties of the marketed NRTI components of Stribild, TDF and FTC, have been well established, and the exposures of TDF and FTC with Stribild are comparable to those historically observed upon their administration as individual agents with other ARVs. Mechanistically, these agents are not expected to affect lithium PK. From a drug interaction perspective, the clinical experience with Stribild and lithium is expected to be consistent with that when lithium is coadministered with other ARV regimens, including RTV-boosted protease inhibitors used in combination with TDF and/or FTC.

In summary, the totality of data indicates that it is unlikely for COBI or any other component of Stribild to undergo clinically relevant interactions with lithium.

TGA evaluator's comment

The response is considered acceptable.

Sponsor's response to Question 2.

There are no relevant interactions expected between the components of Stribild and alcohol that may affect alcohol PK. The metabolism of alcohol is mediated by alcohol dehydrogenase and also by CYP2E1. These enzymes are not considered to be affected by the components of Stribild, including COBI. In particular, the substrate and inhibitor specificities of these enzymes are restrictive, such that COBI (based on molecular weight) is not expected to interact with these enzymes. Further data with a structurally related molecule RTV indicate the lack of inhibition of CYP2E1. Report JTK303-AD-027 demonstrates that EVG, when tested as an inhibitor of CYP2E1 *in vitro* had no effect (IC_{50} >30 μg/mL). In the absence of a PK-driven interaction between Stribild and alcohol, a PD interaction is considered unlikely.

TGA evaluator's comment

The response is considered acceptable

Sponsor's response to TGA Question 3:

The dose of EVG (150 mg) was selected based on results from GS-US-183-0101, as well as a Phase II study in heavily treatment-experienced HIV-1 infected subjects (GS-US-183-0105), and a Phase I biopharmaceutics/formulation study (GS-US-183-0140). The reports for these studies were provided to TGA in the clinical part of the submission.

During the development program of EVG, a Phase I study to evaluate the relative bioavailability of the various formulations of RTV-boosted EVG was performed in Study GS-US-183-0121. Study GS-US-183-0121 was ongoing at the time of the submission for Stribild, however it is provided in response to the above question. Among the formulations tested, this study demonstrated that EVG 125 mg Test Formulation 2 provided

approximately 10% lower EVG exposures compared to the Reference Formulation used in the Phase II Study GS-US-183-0105. Accordingly, a higher dose of EVG 150 mg using Test Formulation 2 was evaluated further in Study GS-US-183-0140 as a potential Phase III and proposed commercial formulation.

Study GS-US-183-0140 then demonstrated that the newer EVG formulation 150 mg in boosted condition provides bioequivalent EVG exposures relative to the Phase II tablet of boosted-EVG 125 mg, including EVG trough concentrations, resulting in the selection of 150 mg of the newer EVG formulation as the dose and formulation for the Phase III study and commercial use of the stand-alone tablet for boosted-EVG 150 mg, and for the formulation of Stribild.

TGA evaluator's comment

The sponsor's response is considered acceptable.

Second round benefit-risk assessment

The risk-benefit assessment provided by the Round 1 evaluators (see above) is considered final with respect to this clinical evaluation report.

Second round recommendation regarding authorisation

The recommendation with respect to market authorisation made by the Round 1 evaluator (see above) is considered final with respect to this evaluation report.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (Version: 0.1, dated 24 November 2011) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the OSE and the clinical aspects of the SS by the OMA, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Tables 6 and 7):

Table 6. Ongoing Safety Concerns for Stribild as a whole

Important Potential Risks	Overdose (occurring through accidental concurrent use of QUAD with any of its marketed active components)
Important Missing Information	Long-term safety information
	Safety in patients with renal impairment

Table 7. Ongoing Safety Concerns for the components of Stribild

Important Identified Risks	TDF: Renal toxicity
	FTC, TDF: Post-treatment hepatic flares in HIV/HBV coinfected patients
	TDF: Interaction with didanosine
	TDF: Pancreatitis
	FTC, TDF: Lactic acidosis and severe hepatomegaly with steatosis
	FTC, TDF: Lipodystrophy
Important Potential Risks	EVG, COBI: Concurrent use of drugs whose coadministration with EVG and/or COBI is contraindicated
Important Missing Information	EVG, COBI: Long-term safety information
	EVG, COBI, TDF: Safety in children (including long-term safety for TDF)
	EVG, COBI, FTC, TDF: Safety in elderly patients
	EVG, COBI, FTC, TDF: Safety in pregnancy
	EVG, COBI, FTC, TDF: Safety in lactation
	TDF: Safety in patients with renal impairment
	EVG, COBI: Safety in patient with severe hepatic impairment (CPT score C)

OPR reviewer comment:

The above ongoing safety concerns are generally consistent with those previously accepted for Eviplera and its components: tenofovir and FTC. Pursuant to the evaluation of the nonclinical and clinical aspects of the SS, the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance (PV) activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)* including targeted follow-up questionnaires where applicable, are proposed to monitor all the specified ongoing safety concerns. However copies of these targeted follow-up questionnaires were not provided. Subsequently the sponsor advised that only the important missing information: 'Safety in patients with renal impairment', yet inclusive of the important identified risk: 'Renal toxicity', currently had an associated targeted follow-up questionnaire. A copy of this document was provided to the TGA.

In addition to routine activities, ongoing clinical studies are proposed to further monitor the following missing important information:

- 'Long-term safety information' relating to Stribild as a whole and the COBI component
- 'Safety in patients with renal impairment' relating to Stribild as a whole and the TDF component
- 'Safety in pregnancy' relating to the EVG, FTC and TDF components
- 'Safety in children' relating to the COBI component and the TDF component

Studies are also proposed to further monitor the important identified risk: 'Renal toxicity' relating to the TDF component.

The OPR reviewer's recommendations in relation to the above are shown below under *Summary of recommendations*.

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities for all the specified ongoing safety concerns are sufficient, except for the important identified risk: 'Renal toxicity' for which additional risk minimisation activities are also proposed; and the important missing information: 'Long-term safety information' for which no routine risk minimisation is proposed.

OPR reviewer comment:

The above conclusion was previously accepted for Eviplera. In addition the specified ongoing safety concerns related to the EVG and COBI components would not appear to warrant additional risk minimisation activities.

Routine risk minimisation activities will comprise product labelling, including contraindications, PK data, special warning and precaution statements, instructions for use, drug interactions and/or notification of undesirable effects for all the specified ongoing safety concerns, except for the important missing information: 'Long-term safety information' for which no routine risk minimisation is proposed.

The sponsor states that the important identified risk: 'Renal toxicity' associated with the TDF component of Stribild is being addressed by the HIV renal educational program for healthcare providers.

Further details of the medical education activities for HIV treating physicians have been provided, including an assurance that all educational materials will be in line with TGA and Medicines Australia requirements and the educational programs will be continued post launch.

The sponsor's proposed application of routine and additional risk minimisation activities would appear to be reasonable, except for some aspects of the PI.

Summary of recommendations

The OPR provides these recommendations[14] in the context that the submitted RMP is supportive to the application; and the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration:

- The sponsor should include the information provided in its correspondence to TGA listing the ongoing safety concerns which are the focus of a targeted follow-up questionnaire in the Australian (AU)-RMP when this document is next updated. In addition a copy of this targeted follow-up questionnaire should be provided as an annex to the AU-RMP.
- The sponsor should include the information provided in its correspondence to the TGA relating to an update to the estimated timelines for interim and/or final results, including the completion of some activities, in the *'Overview of Study Protocols for the Pharmacovigilance Plan'* of the AU-RMP when this document is next updated. Revisions should be made to update milestones for planned data availability for proposed additional PV activities as appropriate and this information should be included in the AU-RMP when this document is next updated.
- An update on the progress/results/analysis of ongoing studies will be expected in future PSURs.
- Draft protocols for studies that have not yet been provided should be provided to the TGA when they become available.

[14] Issues relating to the RMP were satisfactorily addressed prior to the Delegate issuing a decision for this application.

- The sponsor's proposed application of routine and additional risk minimisation activities would appear to be reasonable, provided certain modifications are made to the PI. Details of recommended PI revisions are beyond the scope of this AusPAR.
- It remains unclear as to how the effectiveness of the educational programs as a measure to reduce the important identified risk: 'Renal toxicity' will be reported to the TGA. The sponsor should state and justify a specific timeframe for the reporting of these results to the TGA and include such information in the AU-RMP when this document is next updated.

In addition, the OPR reviewer recommended several revisions be made to the text of tables in the RMP and to information in the PI and Consumer Medicine Information (CMI). Details of these recommendations are beyond the scope of this AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

This submission seeks registration of a new fixed-dose combination of TDF, FTC, EVG and COBI. The TDF/FTC/EVG/COBI (300/200/150/150 mg) formulation, which is described as a STR, contains 2 new chemical entities that is, EVG and COBI. Both EVG and COBI are currently unregistered in Australia. Applications for registration of both individual drugs as mono-agents have been received and are currently under early stages of evaluation.

Stribild contains the current standard-of-care dual Nt/NRTI backbone, that is, TDF/FTC in the same doses as currently approved in adults (300 mg TDF, 200 mg FTC). TDF and FTC are currently available in Australia in a number of formulations/products, including fixed-dose combinations.

This is the first fixed-dose combination product for the treatment of HIV that contains 4 active ingredients. Currently 2 fixed-dose products containing 3 anti HIV agents are approved in Australia; both contain the TDF/FTC backbone in combination with, respectively, EFV and RPV.

The indication for Stribild proposed by the sponsor is: *as a complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of Stribild.* The pivotal clinical data for Stribild were obtained in 'antiretroviral treatment-naïve' adult HIV-1 patients although the proposed indication does not make this explicit.

The current *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* [Incorporating Australian commentary of 18 May 2012] can be accessed online at <http://arv.ashm.org.au/pdf/ARV_Guidelines_AustCommentary_March28.pdf>.

Quality

Elvitegravir and COBI are both new agents. Tenofovir disoproxil fumarate and FTC are identical to the drug substances already registered.

EVG and COBI both are synthetic agents. The Pharmaceutical Chemistry Section (PCS) of the TGA pointed out the presence of a number of impurities with EVG and COBI. These are currently controlled at levels above the relevant ICH threshold. The MTES of TGA has not

raised any objection in this regard. The submission has been considered by the PSC of the ACPM at its 145th meeting.

The PCS of the TGA recommends approval of the product. The PCS also recommends that it should be a condition of registration that the dissolution test and limits for the product are as originally submitted.[15]

Nonclinical

The toxicology findings and the toxicology conclusions were as described under *Nonclinical summary and conclusions*, above. There were no objections on nonclinical grounds to the registration of the product.

Clinical

Pharmacokinetics, bioequivalence, dose selection

Absolute bioavailability of neither EVG nor COBI was studied. Mass balance studies were Study 183-0126 (EVG) and Study 216-0111 (COBI).

Elvitegravir: 95% radioactivity was recovered in faeces after oral administration. The combined faecal and urinary recovery accounted for 100% of the drug and indicated hepatobiliary excretion. The EVG biotransformation is primarily *via* aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation. In plasma, nearly 94% activity is from the intact drug with the remaining radioactivity made up of low levels of metabolites from hydroxylation and/or glucuronidation including GS-9200 (M4) and GS 9202 (M1). In faeces, the radioactivity was accounted for mainly by intact EVG and GS-9202 (M1) In urine, the radioactivity was mainly accounted for by GS-9200 (M4) or other glucuronides of EVG hydroxylation (M7, M19, M20). Intact EVG radioactivity was not recovered from any urine sample.

Cobicistat: 94% radioactivity is recovered from faeces (86%) and urine (<10%). Intact drug is the predominant species in plasma (99%) with no quantifiable metabolites in plasma. In faeces, 27% radioactivity was accounted for by the intact molecule and remaining by metabolites (mainly E3 and E1).

Both EVG and COBI are highly protein bound.

Single and multiple dose PK were examined in Study 183-0102 in healthy volunteers (EVG 100 mg bid with and without RTV 100 mg). The AUC for EVG following multiple doses was about 20% lower compared to the AUC after single dose. The t½ was 3 to 3.5 h. Addition of RTV 100 mg to a single dose of EVG increased exposure to EVG by nearly 7 fold. After multiple dosing the exposure was higher by >20 times. The continuous accumulation over a 10 day treatment period (t½ 18 h after single dose, 9.5 h at 10 days) indicated non-linear clearance. The exposure difference with EVG compared to EVG/r in this study is the claimed basis for including a PK booster with EVG. RTV also behaved non-linearly in this setting (single dose AUC of 4979.4 ng.h/mL versus multiple dose AUC of 9402.5 ng.h/mL).

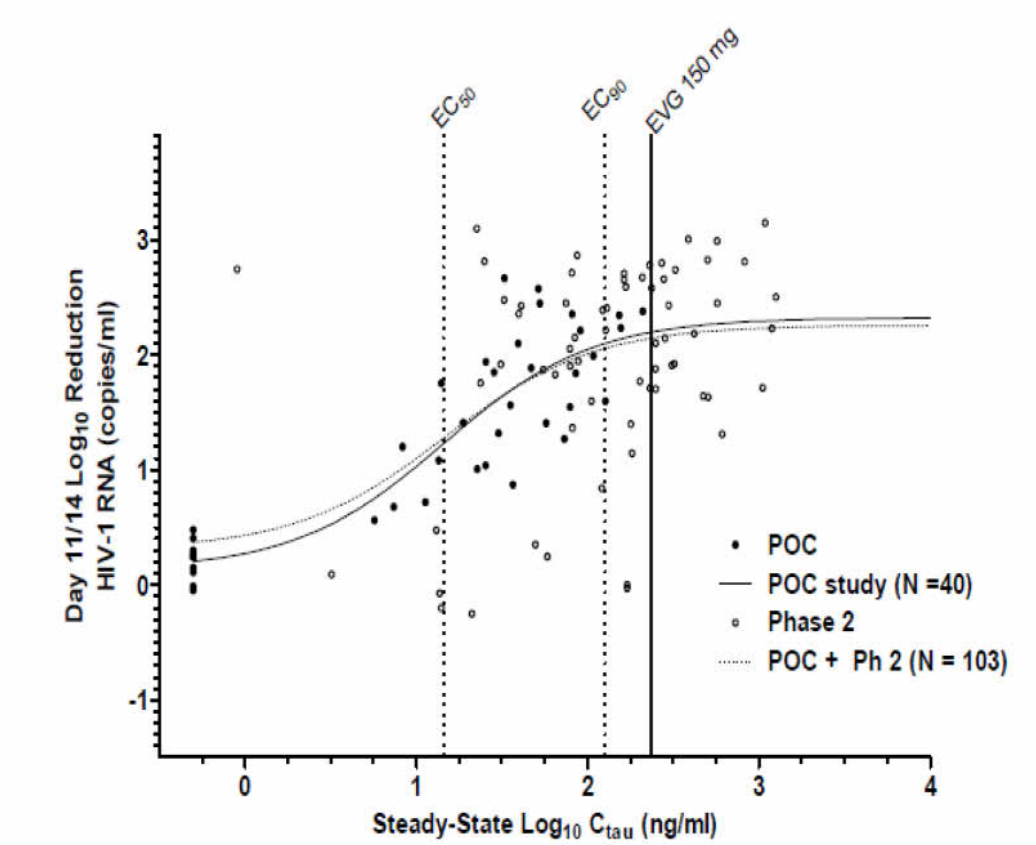
Study 183-0101 in HIV-1 patients (naïve or experienced but not on ART) was a placebo-controlled, dose ranging, proof of concept study in which EVR/r 50/100 mg (once daily; qd) was compared with EVG 200, 400, 800 mg (bid) and 800 mg (qd). The exposures obtained with EVG 800 mg (qd) was not consistent with those obtained with EVG (bid) dosing. The exposure and t½ obtained with EVG/r 50/100 mg was consistent with that

[15] Acceptable finished product release and expiry specifications that incorporated appropriate tests and limits were provided prior to the TGA decision concerning the registration of this product.

obtained with EVG/r 100/100 mg in a previous study (183-0102) and along with the effect on viral load seen in this study is the claimed basis for further testing of EVG/r dosing.

Study 183-0105 was a dose finding study using treatment-experienced HIV patients on ART which examined EVG/r 20/100, 50/100 and 125/100 mg doses compared with CPI/r control. The EVG exposures obtained with 50/100 mg and 125/100 mg EVG/r dosing were consistent with those seen in the previous 2 studies (102 and 101), and along with a dose response (change in viral RNA from baseline), supported the selection of EVG/r 125/100 mg doses (see Figure 2 below).

Figure 2. EVG Dose-response model based on monotherapy and Phase II dose-ranging studies (Combined data from Studies GS-US-183-0101 and GS-US-183-0105)



However, another Study 183-0121, which was provided in response to a TGA request for information and is stated to have been ongoing at the time of initial submission of this dossier, was a relative bioavailability (bioequivalence) study. This study showed that the EVG exposures (AUC) were nearly 10% lower with the proposed Formulation 2 (EVG/r 125/100 mg) compared to the Reference formulation (EVG/r 125/100 mg) which was also used in the previous Study 183-0105. The dose of EVG was thus increased to 150/100 mg in the Formulation 2 for subsequent testing.

The new formulation EVG/r 150/100 mg was examined in the multiple dose Study 18-0140 in healthy volunteers and compared with the previous 125/100 mg formulation. The 2 were found to be bioequivalent based on the acceptance criterion of 80-125% for EVG geometric means ratio with respect to both AUC and Cmax.

The PK of COBI was examined in Study 216-0101 in healthy volunteers with single and multiple dosing of COBI 50, 100 and 200 mg. The results indicated a non-linear rise in plasma exposure to COBI with falling clearance within this dose range. The study also

examined suppression of CYP3A by COBI using a midazolam probe as compared with suppression with RTV 100 mg. The suppression was effective as indicated by midazolam plasma exposure increasing by about 20 times with COBI 200 mg and with RTV 100 mg dosing compared with midazolam alone. Despite non-linearity of COBI plasma exposure in this dose range noted early in this study, the effect on CYP3A (midazolam clearance and plasma exposure) was indicative of dose response.

The bioequivalence of the Stribild formulation (TDF/FTC/EVG/COBI 300/200/150/150 mg) to its components is based on the steady state Study 236-0101 in healthy volunteers. This study is also the claimed link between EVG/COBI in Stribild and EVG/r. The study compared the PK of the constituent active drugs in TDF/FTC/EVG/COBI 300/200/150/150 mg (Stribild) against EVG/r 150/100 mg, TDF/FTC 300/200 mg and TDF/FTC/EVG/COBI 300/200/150/100 mg. The peak and total plasma exposures (Cmax and AUC) of COBI were significantly higher with TDF/FTC/EVG/COBI 300/200/150/150 mg compared to TDF/FTC/EVG/COBI 300/200/150/100 mg whereas the EVG peak and total exposures for TDF/FTC/EVG/COBI 300/200/150/100 mg versus EVG/r 150/100 mg were comparable (bioequivalent) in all respects. The peak and total plasma exposures for the 3 components (EVG, FTC, TDF) were "clinically comparable" for the TDF/FTC/EVG/COBI 300/200/150/150 mg against EVG/r 150/100 mg and TDF/FTC 300/200 mg comparators. However, a number of point estimates or upper sides of the 90% CI were above the 125% limit. These magnitudes are claimed to be clinically not important and similar to ART with boosted protease inhibitor use.

Overall, the data support EVG/COBI combination of 125/100 mg, 150/100 mg or 150/150 mg, of which 150/150 mg was selected for Stribild. This is not unreasonable but does indicate a known bias for picking relatively higher doses in drug development. Replacing RTV with COBI would have been a proprietary consideration.

Food effect with Stribild was studied in Study 236-0105. The results (ratio of means and 90% CI) are summarised in Table 1 of this AusPAR. Emtricitabine bioavailability is not affected; TDF bioavailability is increased slightly in the presence of food, while COBI bioavailability is decreased slightly in the presence of a high fat meal. Elvitegravir bioavailability is increased substantially with food, particularly with a high fat meal. The company considers the differences between a light meal and a high fat meal in respect of EVG bioavailability to be not clinically significant. The PI recommends that the tablets be taken with a meal, without specifying the type of meal.

Population pharmacokinetics

Based on mathematical modelling, apparent systemic clearance of EVG was estimated to be 6.55 L/h. A modest effect of body surface area on EVG apparent clearance was observed but was not considered clinically relevant. No other demographic variable was found to be significant. Note a reliable estimate of systemic clearance of EVG was otherwise not available from the EVG PK or pivotal efficacy studies due to non-linear behaviour.

PK studies in special population groups

Renal Study 216-0121 demonstrated the effect of COBI on GFR estimated based on CrCl (decrease of about 10 mL/min relative to baseline in both group of subjects with normal and with moderate renal impairment) after 7 days of dosing. The changes reversed after 7 days of cessation of treatment. In contrast, GFR estimated using extraneous inert substance iohexol was not affected by treatment with COBI. The effect on estimated GFR is consistent with inhibition of tubular secretion of creatinine. The mechanism has been elucidated to be a transporter mediated interaction between COBI and creatinine.

In Renal study 216-0124, the effect of EVG/COBI 150/150 mg multiple dose treatment in patients with severe renal impairment was examined and showed 33% and 25% lower

peak and total plasma exposure to EVG and 22% and 25% higher peak and total COBI exposures compared to patients with normal renal function.

In hepatic Study 183-0133, the effect of multiple dose treatment with EVG/COBI 150/150 mg in patients with moderate hepatic impairment was studied and showed 40% and 35% higher peak and total EVG exposures compared to the normal matched controls. The COBI plasma exposures were unaffected.

Pharmacokinetic interactions

Elvitegravir and COBI are metabolized by CYP3A. Cobicistat is also metabolized, to a minor extent, by CYP2D6. Hence an extensive number of interactions are expected and a number have been studied. In addition, EVG forms a complex with divalent cations at the active site of the integrase enzyme. Interaction with antacids in the gastrointestinal tract are thus expected. The relevant studies were183- (0106, 0108, 0116, 0119, 0104), 216- (0120, 0122, 0123), and 236- (0106).

Pharmacodynamics

The clinical studies include dedicated QT studies (EVG study 183-0128; COBI study 126-0107) and COBI cardiovascular safety study 126-0116.

Resistance

Reference was made to the following information extracted from the recently approved US label for Stribild:

In cell culture

Elvitegravir

HIV-1 isolates with reduced susceptibility to EVG have been selected in cell culture. Reduced susceptibility to EVG was associated with the primary integrase substitutions T66A/I, E92G/Q, S147G, and Q148R. Additional integrase substitutions observed in cell culture selection included D10E, S17N, H51Y, F121Y, S153F/Y, E157Q, D232N, R263K, and V281M.

Emtricitabine and Tenofovir DF

HIV-1 isolates with reduced susceptibility to FTC or tenofovir have been selected in cell culture. Reduced susceptibility to FTC was associated with M184V/I substitutions in HIV-1 RT. HIV-1 isolates selected by tenofovir expressed a K65R substitution in HIV-1 RT and showed a 2–4 fold reduction in susceptibility to tenofovir.

In treatment-naïve HIV-1 infected patients

Virus samples from Stribild -treatment failure patients in studies 236-0102 and 0103 who were viremic with HIV-1 RNA greater than 400 copies/mL at virologic failure, at Week 48, or at the time of early study drug discontinuation were evaluated for Stribild resistance (genotypic and phenotypic data available for 23 subjects [3%, 23/669]). The development of one or more primary substitutions associated with resistance to EVG, FTC, and/or tenofovir was observed in 57% (13/23) of the viremic subjects with evaluable genotypic data. The most common substitutions that emerged were M184V/I (N=12) in HIV-1 RT and the primary EVG resistance-associated substitutions T66I (N=2), E92Q (N=8), Q148R (N=3), and N155H (N=3) in integrase; K65R in RT was also detected (N=4). In isolates with primary EVG resistance substitutions, additional substitutions in integrase associated with resistance to EVG were H51Y, L68I/V, G140C, S153A, E157Q, V165I, and H183P. Failure isolates expressing primary EVG resistance-associated substitutions (N=11) had median decreases in susceptibility to EVG of 44-fold (range: 6 to > 198- fold) and 33-fold (range: 4 to >122-fold) compared to wild-type

reference HIV-1 and to the respective baseline isolates, respectively. Most subjects (N=10) who developed integrase substitutions associated with EVG resistance also developed the M184I/V RT substitutions, conferring reduced susceptibility to both EVG and FTC. In phenotypic analyses, 50% (11/22) of the viremic subjects with evaluable data had HIV-1 isolates with reduced susceptibility to EVG, 57% (12/21) had reduced susceptibility to FTC, and 10% (2/21) had reduced susceptibility to tenofovir.

Cross Resistance

Stribild-treatment failure subject isolates exhibited varying degrees of cross resistance within the INSTI and NRTI drug classes depending on the specific substitutions observed. These isolates remained susceptible to all NNRTIs and protease inhibitors.

Elvitegravir

Cross-resistance has been observed among INSTIs. Elvitegravir-resistant viruses showed varying degrees of cross-resistance in cell culture to RTG depending on the type and number of substitutions in HIV-1 integrase. Among the 4 primary EVG resistance-associated substitutions detected in the Stribild -treatment virologic failure isolates, E92Q, Q148R, and N155H individually conferred reduced susceptibility both to EVG (greater than 32-fold) and RTG (greater than 5-fold) when introduced into a wild-type virus by site-directed mutagenesis. The T66I substitution conferred greater than 14-fold reduced susceptibility to EVG but less than 3-fold to RTG. Among the 3 primary RTG resistance-associated substitutions (Y143H/R, Q148H/K/R, and N155H), all but one (Y143H) conferred significant reductions in susceptibility to EVG (greater than 5-fold).

Emtricitabine

Cross-resistance has been observed among NRTIs. Emtricitabine resistant isolates harbouring an M184V/I substitution in HIV-1 RT were cross-resistant to lamivudine. HIV-1 isolates containing the K65R RT substitution, selected *in vivo* by abacavir, didanosine, and tenofovir, demonstrated reduced susceptibility to inhibition by FTC.

Tenofovir DF

Cross-resistance has been observed among NRTIs. The K65R substitution in HIV-1 RT selected by tenofovir is also selected in some HIV-1infected patients treated with abacavir or didanosine. HIV-1 isolates with the K65R substitution also showed reduced susceptibility to FTC and lamivudine. Therefore, cross-resistance among these NRTIs may occur in patients whose virus harbours the K65R substitution. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated RT amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Subjects whose virus expressed an L74V RT substitution without zidovudine resistance-associated substitutions (N=8) had reduced response to VIREAD. Limited data are available for patients whose virus expressed a Y115F substitution (N=3), Q151M substitution (N=2), or T69 insertion (N=4) in HIV-1 RT, all of whom had a reduced response in clinical trials.

Clinical efficacy

The demonstration of clinical efficacy and safety was based on one Phase II Study 236-0104 and 2 Phase III pivotal Studies 236-0102 and 236-0103 in treatment-naïve HIV-1 adult patients (inclusion criteria included baseline plasma HIV-1 RNA >5000 copies/mL and normal renal function). All studies were randomised, double blind, placebo-controlled, non-inferiority trials comparing Stribild (TDF/FTC/EVG/COBI 300/200/150/150 mg) against TDF/FTC/EFV 300/200/600 mg (Studies 236-0102 and 236-0104) or against TDF/FTC 300/200 mg plus boosted ATV/r 300/100 mg (Study 236-0103). All regimes

were once daily. Stribild was administered with food. The dossier relied on double blinded 48 Weeks efficacy data.

The primary efficacy outcome was virologic success (proportion of patients achieving HIV-1 RNA <50 copies/mL at 4 Weeks of treatment. Non-inferiority (95% CI for the treatment difference from comparator to be no worse than -12%) was satisfactorily demonstrated in all trials. The treatment difference numerically favoured Stribild in both pivotal trials (approximately 3%).

The effect with respect to the primary variable was homogenous across various sub-groups including baseline viral load (≤ 100,000 copies/mL or >100 000 copies/mL; this was a stratification factor for randomisation) and baseline CD4 cell count (≤ 350 and > 350 cells/μL). Loss of power in some sub-groups, especially for the Phase II trial due to small number of patients, was notable. The results are summarised in Table 8, below.

Table 8. GS-US-236-0102, 0103, and 0104: Treatment difference in virologic success by subgroup at Week 48 (HIV-1 RNA cutoff at 50 copies/mL, Snapshot analysis, intention to treat (ITT) Analysis set)

		QUAD (N=749)	Control[a] (N=730)	Quad vs. Control -- Difference in Percentages (95% CI)[b]
Overall				
	236-0102	305/348 (87.6%)	296/352 (84.1%)	3.6% (-1.6% to 8.8%)
	236-0103	316/353 (89.5%)	308/355 (86.8%)	3.0% (-1.8% to 7.7%)
	236-0104	44/48 (91.7%)	19/23 (82.6%)	9.2% (-9.9% to 28.3%)
	Pooled	665/749 (88.8%)	623/730 (85.3%)	3.5% (0.1% to 7.0%)
Age (years)				
< 40	236-0102	171/200 (85.5%)	169/197 (85.8%)	-0.1% (-7.1% to 6.9%)
	236-0103	181/206 (87.9%)	163/193 (84.5%)	3.4% (-3.5% to 10.3%)
	236-0104	28/31 (90.3%)	12/16 (75.0%)	13.5% (-13.1% to 40.0%)
	Pooled	380/437 (87.0%)	344/406 (84.7%)	2.3% (-2.6% to 7.1%)
>= 40	236-0102	134/148 (90.5%)	127/155 (81.9%)	8.3% (0.4% to 16.1%)
	236-0103	135/147 (91.8%)	145/162 (89.5%)	3.1% (-3.4% to 9.7%)
	236-0104	16/17 (94.1%)	7/7 (100.0%)	-7.4% (-37.0% to 22.2%)
	Pooled	285/312 (91.3%)	279/324 (86.1%)	5.3% (0.3% to 10.3%)
Sex				
Male	236-0102	270/307 (87.9%)	266/316 (84.2%)	3.9% (-1.6% to 9.4%)
	236-0103	292/324 (90.1%)	276/316 (87.3%)	3.1% (-1.9% to 8.0%)
	236-0104	41/44 (93.2%)	17/21 (81.0%)	13.0% (-7.3% to 33.3%)
	Pooled	603/675 (89.3%)	559/653 (85.6%)	3.9% (0.3% to 7.5%)
Female	236-0102	35/41 (85.4%)	30/36 (83.3%)	2.3% (-15.5% to 20.1%)
	236-0103	24/29 (82.8%)	32/39 (82.1%)	-1.2% (-20.6% to 18.3%)
	236-0104[g]	3/4 (75.0%)	2/2 (100.0%)	-25.0%(-67.4% to 17.4%)
	Pooled	62/74 (83.8%)	64/77 (83.1%)	-0.2% (-13.3% to 12.8%)
Race				
White	236-0102	191/214 (89.3%)	199/227 (87.7%)	1.7% (-4.4% to 7.7%)
	236-0103	225/250 (90.0%)	240/277 (86.6%)	3.4% (-2.1% to 9.0%)
	236-0104	30/33 (90.9%)	15/18 (83.3%)	8.7% (-13.7% to 31.1%)
	Pooled	446/497 (89.7%)	454/522 (87.0%)	2.9% (-1.1% to 6.9%)
Nonwhite	236-0102	114/134 (85.1%)	97/125 (77.6%)	7.5% (-2.2% to 17.1%)
	236-0103	91/103 (88.3%)	68/78 (87.2%)	2.1% (-7.9% to 12.1%)
	236-0104	14/15 (93.3%)	4/5 (80.0%)	15.4% (-34.3% to 65.1%)
	Pooled	219/252 (86.9%)	169/208 (81.3%)	5.6% (-1.4% to 12.6%)

Table 8 continued. GS-US-236-0102, 0103, and 0104: Treatment difference in virologic success by subgroup at Week 48 (HIV-1 RNA cutoff at 50 copies/mL, Snapshot analysis, intention to treat (ITT) Analysis set)

		QUAD (N=749)	Control[a] (N=730)	Quad vs. Control -- Difference in Percentages (95% CI)[b]
Baseline HIV-1 RNA Level (copies/mL)				
<= 100,000	236-0102	206/230 (89.6%)	201/236 (85.2%)	4.4% (-1.6% to 10.4%)
	236-0103	188/203 (92.6%)	192/214 (89.7%)	2.9% (-2.5% to 8.3%)
	236-0104	35/37 (94.6%)	15/18 (83.3%)	11.3% (-7.4% to 30.0%)
	Pooled	429/470 (91.3%)	408/468 (87.2%)	4.1% (0.0% to 8.1%)
> 100,000	236-0102	99/118 (83.9%)	95/116 (81.9%)	2.0% (-7.6% to 11.6%)
	236-0103	128/150 (85.3%)	116/141 (82.3%)	3.1% (-5.4% to 11.5%)
	236-0104	9/11 (81.8%)	4/5 (80.0%)	1.8% (-40.0% to 43.6%)
	Pooled	236/279 (84.6%)	215/262 (82.1%)	2.6% (-3.8% to 9.0%)
Baseline CD4 Cell Count (/uL)				
<= 350	236-0102	129/155 (83.2%)	123/147 (83.7%)	-0.6% (-9.1% to 7.9%)
	236-0103	157/176 (89.2%)	143/163 (87.7%)	1.7% (-5.3% to 8.7%)
	236-0104	23/24 (95.8%)	6/8 (75.0%)	21.6% (-16.6% to 59.8%)
	Pooled	309/355 (87.0%)	272/318 (85.5%)	1.4% (-4.0% to 6.8%)
> 350	236-0102	176/193 (91.2%)	173/205 (84.4%)	6.8% (0.3% to 13.3%)
	236-0103	159/177 (89.8%)	165/192 (85.9%)	3.9% (-2.8% to 10.6%)
	236-0104	21/24 (87.5%)	13/15 (86.7%)	0.8% (-25.0% to 26.6%)
	Pooled	356/394 (90.4%)	351/412 (85.2%)	5.2% (0.6% to 9.8%)

Note: Week 48 window is between Day 309 and 378 (inclusive).

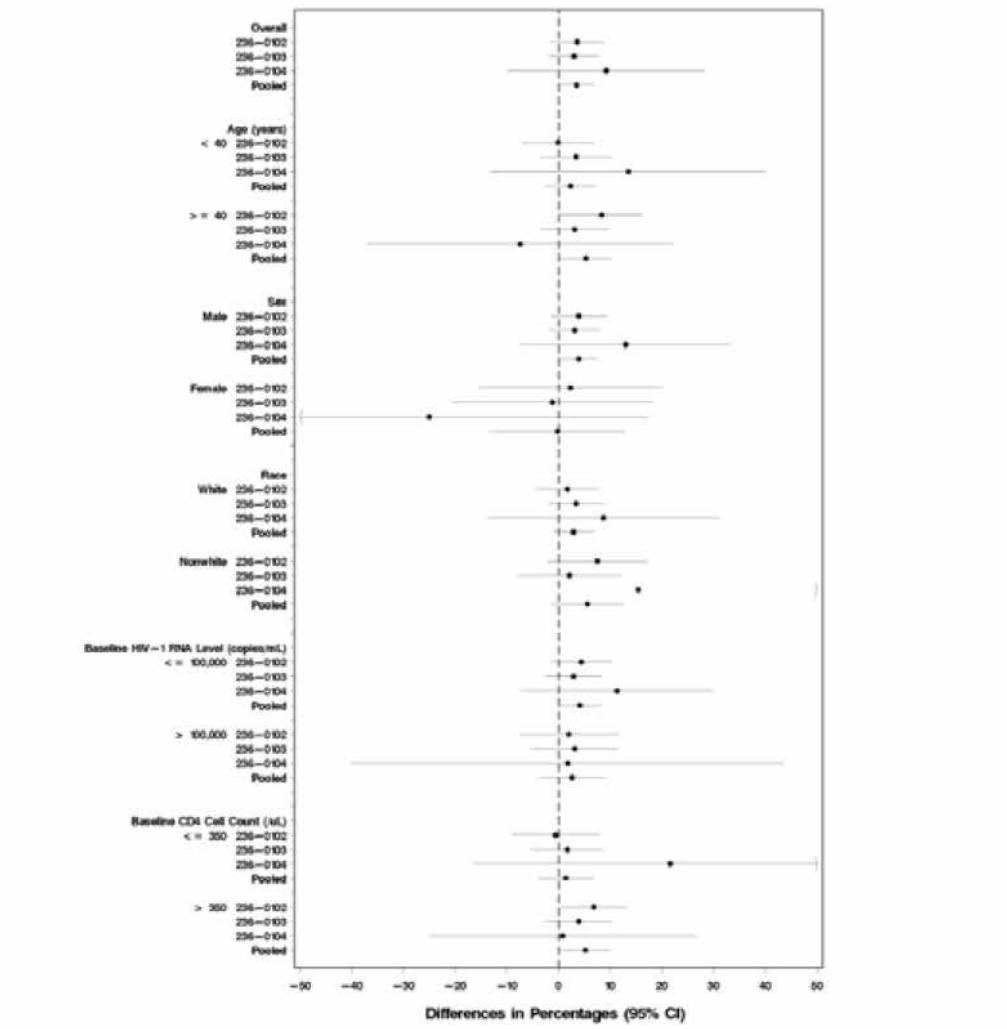
a Control groups are ATR in Studies GS-US-236-0102 and GS-US-236-0104, ATV/r+TVD in Study GS-US-236-0103, ATR and ATV/r+TVD in pooled analysis.

b Difference in response rate and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (if it is not the subgroup factor) and study (for pooled analysis).

c For Study GS-US-236-0104 female group, the proportions were not adjusted because no subjects had baseline HIV-1 RNA level > 100,000 copies/mL.

The results are shown graphically in Figure 3.

Figure 3. GS-US-236-0102, 0103, and 0104: Forest plot of treatment difference in virologic success by subgroup at Week 48 (HIV-1 RNA < 50 copies/mL, Snapshot analysis, ITT Analysis set)



Difference in response rate and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA stratum (if it is not the subgroup factor) and study (for pooled analysis).
For Study GS-US-236-0104 female group, the proportions were not adjusted because no subjects had baseline HIV-1 RNA level > 100,000 copies/mL.
Relative to the vertical line at 0, differences on the right favor the QUAD group and differences on the left favor the control group.
The 95% CI was truncated if it exceeded +/− 50%

The results using the PP population were consistent with the primary analysis.

Some of the other important results were as follows:

Stribild versus TDF/FTC/EFV at Week 48 (viral load <50 copies/ mL), Study 236 0102

- Virologic failure: 7.2% versus 7.1% ITT (6.9% versus 4.5% TLOVR)
- Mean change in HIV-1 RNA from baseline: -2.99 versus -3.00 log10 copies/mL
- Mean change in CD4 count from baseline: +239 versus +206 cells/µL
- Mean change in CD4% from baseline: 9.1% versus 9.9%

A total of 31/700 (4.4%) patients met the criteria for virologic failure for inclusion in the Resistance Analysis Population (RAP), with 14/348 (4.0%) in the Stribild and 17/352 (4.8%) in the Control group. In the Stribild group, 8/348 (2.3%) patients has emergent resistance to a study drug. All 8 patients developed RT-R mutations. Seven of these patients also developed INSTI-R mutations. In the Control group, 8/352 (2.3%) had

emergent resistance to a study drug. All 8 developed RT-R mutations. There were no INSTI-R mutations in this group. There was no development of primary protease inhibitor-resistance mutation in either group.

Stribild versus TDF/FTC+ATV/r at Week 48 (viral load <50 copies per mL), Study 236-0103

Virologic failure: 5.4% versus 5.4% ITT (5.4% versus 4.2% TLOVR)

Mean change in HIV-1 RNA from baseline: -3.09 versus -3.07 log10 copies/mL

Mean change in CD4 count from baseline: +207 versus +211 cells/μL

Mean change in CD4% from baseline: 9.4% versus 9.9%

A total of 20/708 (2.8%) patients met the criteria for virologic failure for inclusion in RAP: 12/353 (3.4%) in the Stribild and 8/355 (2.3%) in the Control group. In the Stribild group, 5/353 (1.4%) patients has emergent resistance to a study drug. Four of these 5 patients developed RT-R mutations. Four of these 5 patients also developed INSTI-R mutations. No patient developed primary protease inhibitor-resistance mutation in this group. No patients in the Control group developed emergent resistance to a study drug.

Extended open label experience available from study 236-0104

The results are summarised in Table 9, below.

Table 9. Results of analyses of virologic suppression in the open-label period.

Open label period- percentage of subjects with HIV-1 RNA < 50 copies/mL		
	QUAD/QUAD n/N (%)	ATR/QUAD n/N (%)
Baseline of open-label period (Study Week 60)		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	0/46 (0%)	13/14 (92.9%)
95% CI	0.0% to 7.7%	66.1% to 99.8%
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	0/46 (0%)	13/14 (92.9%)
95% CI	0.0% to 7.7%	66.1% to 99.8%
Missing = Excluded		
HIV-1 RNA < 50 copies/mL	0/46 (0%)	13/14 (92.9%)
95% CI	0.0% to 7.7%	66.1% to 99.8%
Open-label Week 24 (Study Week 84)		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	43/46 (93.5%)	12/14 (85.7%)
95% CI	82.1% to 98.6%	57.2% to 98.2%
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	43/46 (93.5%)	11/14 (78.6%)
95% CI	82.1% to 98.6%	49.2% to 95.3%
Missing = Excluded		
HIV-1 RNA < 50 copies/mL	43/45 (95.6%)	12/13 (92.3%)
95% CI	84.9% to 99.5%	64.0% to 99.8%
Open label Week 36 (Study Week 96)		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	NA	12/14 (85.7%)
95% CI	NA	57.2% to 98.2%
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	NA	12/14 (85.7%)
95% CI	NA	57.2% to 98.2%
Missing = Excluded		

Open label period- percentage of subjects with HIV-1 RNA < 50 copies/mL		
	QUAD/QUAD n/N (%)	ATR/QUAD n/N (%)
HIV-1 RNA < 50 copies/mL	NA	12/12 (100.0%)
95% CI	NA	73.5% to 100.0%
Open label Week 40		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	42/46 (91.3%)	NA
95% CI	79.2% to 97.6%	NA
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	40/46 (87.0%)	NA
95% CI	73.7% to 95.1%	NA
Missing = Excluded		
HIV-1 RNA < 50 copies/mL	42/44 (95.5%)	NA
95% CI	84.5% to 99.4%	NA

NA= not available. Note: 'QUAD' is the name formerly used for Stribild

Clinical safety

The results of pooled safety data from the 3 Phase II and III studies are provided below and indicate a similar profile of overall frequency of AEs in the 3 groups, including mortality (Table 10):

Table 10. GS-US-236-0102, 0103, and 0104: Overall summary of adverse events (Safety Analysis set)

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

a Treatment-emergent death refers to the death occurred between the first dose date and the last dose date plus 30 days (inclusive).

A system organ class based list of common treatment emergent AEs reported in the 3 trials is reproduced below (Table 11) and again indicates a similar profile among the 3 comparators:

Table 11. GS-US-236-0102, 0103, and 0104: Treatment-emergent adverse events reported for at least 5% of subjects in any treatment group (Safety Analysis set)

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

a Adverse events were coded using MedDRA 14.0.

b System organ class (SOC) and high level term (within each SOC) were presented alphabetically, and preferred term was presented by decreasing order based on the total frequencies.

c Multiple AEs were counted only once per subject for each SOC, high level term and preferred term, respectively.

The AEs according to laboratory abnormalities were also reported in similar frequencies across the 3 groups (Table 12):

Table 12. GS-US-236-0102, 0103, and 0104: Treatment-emergent Grade 3 and 4 laboratory abnormalities reported for at least 1% of subjects in any treatment group (Safety Analysis set)

Lab Panel, Lab Parameter, Grade[a, b]	QUAD 236-0102, 0103, 0104 (N=749)	ATR 236-0102, 0104 (N=375)	ATV/r + TVD 236-0103 (N=355)
Hematology			
Neutrophils	745	372	352
Grade 3	7 (0.9%)	9 (2.4%)	6 (1.7%)
Grade 4	3 (0.4%)	4 (1.1%)	0
Chemistry			
ALT	745	372	352
Grade 3	4 (0.5%)	8 (2.2%)	6 (1.7%)
Amylase	745	372	352
Grade 3	14 (1.9%)	6 (1.6%)	10 (2.8%)
AST	745	372	352
Grade 3	9 (1.2%)	9 (2.4%)	11 (3.1%)
Grade 4	6 (0.8%)	4 (1.1%)	3 (0.9%)
Creatine Kinase (CK)	745	372	352
Grade 3	26 (3.5%)	15 (4.0%)	10 (2.8%)
Grade 4	13 (1.7%)	25 (6.7%)	16 (4.5%)
GGT	745	372	352
Grade 3	5 (0.7%)	13 (3.5%)	2 (0.6%)
Grade 4	3 (0.4%)	5 (1.3%)	3 (0.9%)
Lipase[c]	62	36	33
Grade 3	5 (8.1%)	5 (13.9%)	6 (18.2%)
Grade 4	2 (3.2%)	1 (2.8%)	1 (3.0%)
Serum Glucose (Hyperglycemia)[d]	745	372	352
Grade 3	5 (0.7%)	1 (0.3%)	5 (1.4%)
Total Bilirubin (Hyperbilirubinemia)	745	372	352
Grade 3	3 (0.4%)	0	169 (48.0%)
Grade 4	1 (0.1%)	0	36 (10.2%)
Total Cholesterol (Fasting, Hypercholesterolemia)	707	340	328
Grade 3	5 (0.7%)	5 (1.5%)	0
Triglycerides (Fasting)	707	340	328
Grade 3	1 (0.1%)	0	4 (1.2%)
Urinalysis			
Urine Glucose (Glycosuria)	745	372	352
Grade 3	6 (0.8%)	2 (0.5%)	5 (1.4%)
Urine RBC (Hematuria, Quantitative)[e]	745	372	352
Grade 3	21 (2.8%)	5 (1.3%)	8 (2.3%)

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

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

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

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

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

Clearly, at this stage this is a small dataset and safety will critically depend on surveillance during the post-market phase, including further studies. The Delegate referred to the RMP evaluation report for this product (see above under *Pharmacovigilance Findings*).

Product Information

The Delegate noted that various TGA evaluation areas recommended changes be made to the initially proposed PI. Details of these and other revisions to the PI are beyond the scope of this AusPAR.

Clinical evaluator's recommendation

The clinical evaluator raised no objections to the registration of Stribild.

Risk management plan

See Section V *Pharmacovigilance Findings*, above.

Risk-benefit analysis

Delegate considerations

A full drug development programme was undertaken for Stribild. The dossier contained data in relation to pharmaceutical chemistry, manufacture, toxicology and the proposed clinical use. The latter included extensive data in relation to PK and PD of both new chemical components in this fixed dose combination of 4 drugs.

The 2 Phase III clinical efficacy and safety trials have shown the efficacy and safety profile of Stribild to be non-inferior and comparable, respectively, to the current standard of treatment in HIV-1 treatment-naïve patients. Note that randomised, controlled, double blind efficacy data are 48 weeks only at this stage and more purposeful outcomes such as TLOVR beyond this timepoint are still awaited. Similarly, the clinical safety dataset from the 3 Phase II and III studies is small, consisting of 749 Stribild treated patients.

However, in leading towards finalisation of this submission, the Delegate considered that the following points do not allow a firm assessment of the overall risk-benefit balance for this product at this stage; the advice of the ACPM would be requested on the following five issues:

1. This is the first instance of a fixed dose combination containing 4 active ingredients. Elvitegravir displays non-linear PK properties (clearance, half-life) which make it unsuitable for clinical use. It was investigated in conjunction with the PK booster RTV to allow clinical use of a lower dose of EVG. This was a useful approach as the results of the confirmatory clinical trials indicate.

   However, the inflexibility inherent in a fixed dose combination containing 4 active agents of which 2 are new chemical entities and have non-linear PK features could be an issue. A fixed dose dual combination of EVG with RTV or COBI may have been more appropriate.

   Currently there is one registered fixed dose combination of a protease inhibitor with RTV (lopinavir/RTV 200/50 mg and 100/25 mg).

2. This is also the first instance in which a fixed dose combination is being considered for registration before registration of its individual components. Elvitegravir and COBI are currently undergoing evaluation. The knowledge and experience with these constituents is not available to inform the decision making in relation to the proposed fixed dose It would be desirable to know how EVG has been investigated in its clinical testing programme and is being proposed for use as mono agent (in combination with ART), its dosing guidelines, and the use of PK enhancer. Such information can usefully contribute to assessment of risk-benefit balance for the fixed dose product.

3. Lack of absolute bioavailability studies for EVG and COBI is important missing information given that EVG biotransformation, systemic exposure and interactions are likely to be sensitive to changes in portal circulation and hepatic blood flow. The knowledge of the extent of systemic bioavailability of both EVG and COBI (as single agents) is highly desirable. The elucidation of metabolic pathway, faecal excretion

data, extent of biliary excretion is essentially incomplete without the knowledge of the fraction of the orally absorbed drug reaches the systemic circulation.

It is not known whether this information in available in the dossiers for EVG and COBI which are currently being evaluated. The sponsor is requested to provide comment on this in its pre-ACPM response.

4. The fixed dose product is being proposed for initiating treatment in *de novo* patients. However, the EVG mono agent currently under review is being proposed for the treatment experienced population. Is that approach acceptable?

5. Could there be an issue for allowing use of a new INSTI, that is, EVG with COBI in a fixed dose combination and its consequences for the use of the currently registered INSTI RTG which is not a CYP3A substrate and is available as a mono agent? Is an efficacy comparison between EVG/COBI and RTG desirable? The sponsor is requested to also comment whether this information is available in the dossier for EVG which is currently under evaluation.

Advice requested from ACPM

The Delegate sought general advice on this application from the ACPM, and requested in particular that the committee address issues 1 to 5, above.

Response from Sponsor

Gilead has co-formulated EVG (a novel HIV INSTI) and COBI (a pharmacoenhancer devoid of anti-HIV activity designed to boost EVG exposure to allow for once-daily dosing) with the standard-of-care NRTI backbone TDF/FTC into a single tablet regimen (STR). In 2 large and well-controlled clinical studies in treatment-naïve HIV-1 infected adults, Stribild has demonstrated potent, durable efficacy (up to 90% response rates) with a favourable safety profile. In contrast to RTG that requires administration twice-daily in combination with other ARV agents, Stribild provides a complete regimen within a single tablet that can be administered once daily in the treatment of adults with HIV-1 infection.

Clinical studies have clearly demonstrated high levels of adherence and treatment satisfaction with simple, once-daily highly active antiretroviral therapy (HAART) regimens, resulting in persistent suppression of HIV viral load.[16, 17, 18] The Stribild submission identified the inherent benefits of an STR compared to multiple tablet dosing and these benefits have continued to be further clarified in recent studies. In a US database review of more than 7073 HIV patients with commercial insurance, patients taking an STR were 59% more likely to achieve 95% adherence compared with those taking 3 or more pills per day. In addition, patients who received an STR were 24% less likely to have a hospitalization compared with those who received 3 or more pills per day.[19]

To date, there are 2 NNRTI/NRTI based-STRs (Atripla [EFV/FTC/TDF] and Eviplera (RPV/FTC/TDF)) approved for once-daily administration in the treatment of HIV-1 infection. There remains a need for alternative STRs to increase the availability of simple, safe and effective HIV regimens, and overcome limitation of the currently approved STRs.

[16] Maggiolo F *et al*. Once-a-day treatment for HIV infection: Final 48-week results. *8th Conf. on Retroviruses and Opportunistic Infections.* 2001 Feb 4-8; Chicago, IL. Abstract 320.
[17] Felizarta F *et al*. Adherence and efficacy with a once-daily efavirenz-based regimen: 48-week results from the Daily Antiretroviral Therapy II (DART II). Study [poster 5842]. *XV Int. AIDS Conf.* 2004 July 11-16; Bangkok, Thailand.
[18] Arribas JR *et al*. Adherence, treatment satisfaction and effectiveness of once-daily (QD) versus twice daily (BID) antiretroviral therapy (AT), in a large prospective observational cohort (CUVA Study) [poster WePeB5780]. *XV Int. AIDS Conf.*; 2004 July 11-16; Bangkok, Thailand.
[19] Sax PE, Meyers JL, *et al*. Adherence to antiretroviral treatment and correlation with risk of hospitalization among commercially insured HIV patients in the United States. *PLoS ONE* 2012;7(2):e31591.

Stribild provides an alternative to existing STRs.

No STRs exist that combine an INSTI with an NRTI backbone. Stribild provides an alternative for patients who cannot tolerate RTV-boosted protease inhibitors or NNRTIs and for patients who wish to simplify their regimen through a lower pill burden.

The Stribild application has been evaluated as a new fixed-dose combination product and deemed approvable by the PSC and clinical evaluators. The clinical evaluator noted that the overall benefit risk balance of Stribild is positive and meets the *Guidance on clinical development of medicinal products for the treatment of HIV infection* (EMEA/CPMP/EWP/633/02, 20 Nov 2008) which recommend that a *"convincingly demonstrated non-inferior benefit-risk at 48 weeks versus a well-recognized reference product may serve as a basis for approval"*.

The Delegate has noted that the phase 3 clinical efficacy and safety trials have shown the efficacy and safety profile of Stribild to be non-inferior to the current standard of care in treatment-naïve HIV-1 infected patients. However, the Delegate requests the ACPM's advice on 5 issues that would allow a firm assessment on the risk-benefit balance for Stribild to be made. The sponsor provided additional comment on each of these issues, below.

As the Stribild application contains only clinical studies that directly support the proposed PI, or that are relevant to the consideration of the combination of EVG, COBI, FTC and TDF, Gilead considers that this complete application should be viewed by the Delegate and ACPM independently of the 2 subsequent applications seeking registration of the single agents (EVG and COBI) as the development program and registration applications were designed to allow each therapeutic good to be evaluated as a stand-alone product. Data generated for the EVG and COBI single agent applications do not adversely impact the risk-benefit profile presented in the earlier Stribild submission.

The Delegate's overview states that the pivotal clinical data for Stribild were obtained in 'antiretroviral treatment-naïve HIV-1 infected adult patients' although the proposed indication statement does not make this explicit. The Delegates overview does not take into account Gilead's previous response to the clinical evaluation report in which an updated proposed indication statement was provided as follows:

> *Stribild is indicated as a complete regimen for the treatment of HIV-1 infection in ARV treatment naïve adults aged 18 years and over.*

The Delegate's overview states that the PSC recommended as a condition of registration that the dissolution test method and test limits for the product be as originally submitted. The Delegate's overview does not acknowledge that Gilead notified the TGA of an error within the TGA document *Evaluation of Replies to CMC*. A response document with the correct information was provided to the TGA and this highlighted errors in the report that lead to the inappropriate condition of approval regarding dissolution testing conditions. Gilead considers this issue important as the conditions proposed would have failed a batch of product found to be effective in clinical investigations; thus making the proposed conditions inappropriate and, as yet, not finalised in evaluation.

The remainder of this response is separated into 5 sections to address the issues raised under *Delegate considerations* in the Delegate's overview.

Discussion of Delegate's comments

(1) Inflexibility inherent in a FDC containing 4 actives, of which 2 are new and have non-linear pharmacokinetics

It is agreed there is an inherent inflexibility associated with STRs and that dose adjustments are not possible. However in the case of Stribild the inflexibility is warranted

given a) the therapeutic benefits associated with dosing simplicity and increased compliance, and b) linking the maximized boosting associated with COBI to the optimized antiviral activity seen with boosted 150 mg EVG dosing.

There remains a significant medical need for new, well-tolerated therapies in convenient dosing regimens that combine potent and sustained efficacy with acceptable tolerability and minimal long-term toxicity for the treatment of HIV infection. Incomplete adherence to ARV regimens is a critical factor contributing to the development of viral resistance and treatment failure, and thus a primary barrier to successful long-term treatment. Adherence is known to be paramount in maintaining viral suppression, as missing a small number of doses can result in viral rebound and risk of resistance development. Clinical studies and healthcare database reviews have clearly demonstrated high levels of adherence and treatment satisfaction with simple, once daily HAART regimens, resulting in persistent suppression of HIV viral load (see references at footnotes 14, 15 and 16).

The selected dose (150 mg) of EVG contained in Stribild , represents optimal antiviral activity, as compared with boosted protease inhibitors.[20, 21] Although, boosted EVG displays nonlinear PK properties, the effect is a less than proportional exposure increase. Therefore, there is little issue with regard to potentially higher EVG exposures should multiple tablets be taken. Also, reduced suboptimal EVG exposures as administration of lower doses are not possible. As such, coformulation within the STR minimizes potential risk associated with nonlinearity. With regards to COBI nonlinear PK properties, this is clinically insignificant because COBI 150 mg provides near maximal pharmacoenhancement (boosting) at this dose, resulting in targeted EVG trough concentrations approximately 10-fold above the protein binding-adjusted IC_{95}; further increases in COBI dose would not result in clinically relevant changes in EVG exposures. Higher COBI exposures would be expected in the setting of purposeful overdosage, however coformulation within the STR minimises potential risk associated with nonlinearity. The dose selection of EVG 150 mg and COBI 150 mg is confirmed by the results of the Phase II and Phase III studies with Stribild, as well as population PK and PK/PD modelling. As such, the combination of EVG and COBI within the single tablet regimen provides maximal antiviral activity and high rates of suppression. Furthermore, an extensive evaluation of the drug interaction potential of Stribild indicates that patient management is expected to be consistent with boosted protease inhibitors.

(2) This is also the first instance in which a fixed dose combination is being considered for registration before registration of the individual components.

The clinical development program and submission strategy for Stribild was discussed and considered acceptable at a pre-submission meeting with the TGA. A justification for the fixed-dose combination was accepted by the TGA. The sponsor believes that the Delegate's concerns are unwarranted as this is a complete, stand alone application seeking registration of a new fixed-dose combination therapeutic good that is supported by adequate efficacy, safety and quality information.

Unlike many therapeutic areas, current HIV treatment guidelines recommend that the treatment of HIV infection requires the use of a regimen including at least 3 active ARV agents. The clinical profile of ARVs in the target patient populations are therefore only ever established in combination with other ARVs. The risk-benefit of the single agents when combined with other active agents not included in Stribild (that is, other than TDF and FTC) are therefore of no consequence when compared to the risk-benefit established in the final product/regimen in a full clinical program consisting of 2 large and controlled

[20] DeJesus E *et al*. Antiviral activity, PK, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naïve and treatment-experienced patients. *JAIDS* 2006;43 (1):1-5.
[21] Zolopa AR *et al*. Activity of EVG, a once-daily integrase inhibitor, against resistant HIV Type 1: results of a phase 2, randomized, controlled, dose ranging clinical trial. *J Infect Dis* 2010;201 (6):814-22.

Phase III studies. Stribild is a stand alone registration package that provides sufficient data to support registration with the proposed indication. Gilead considers that this complete application should be viewed by the Delegate and ACPM independently of the 2 applications seeking registration of the single agents EVG and COBI. The Stribild application at the time of submission to the TGA presented all the relevant, known information necessary to assess the proposed STR.

HIV-1 infection is a life-threatening and serious disease, and the availability of STRs has been correlated with improved outcome in HIV infected patients (see response to Issue 1, above), thereby justifying an expedited approval of an STR containing 4 ingredients if, as in the case of Stribild, that STR is shown to provide efficacy non-inferior to current standard of care with differentiated safety benefits. The safety and efficacy of Stribild was established in 2 Phase III studies with the actual fixed-dose combination tablet in treatment-naïve subjects with HIV-1 infection.

Whilst this may be a novel regulatory precedent, the TGA is not the first regulatory agency to consider the issue. Stribild was approved by the US FDA on 27 August 2012. During review of this application in the USA, the FDA Advisory Committee was specifically requested by the FDA not to consider the merits of the single products as they were not necessary to allow a regulatory review of Stribild.

Gilead is attempting to make the STR available as soon as possible as this is the presentation that is going to likely have the greatest acceptance by patients that cannot tolerate the other available STRs. EVG and COBI are currently in the process of being registered as single agents which clearly demonstrates our drive to make all potential therapeutic options available for patients in need.

(3) Lack of absolute bioavailability studies for EVG and COBI is important missing safety information.

A justification for not conducting absolute bioavailability studies on EVG administered as part of the proposed four-active tablet was provided to the TGA prior to submission of the dossier. Upon submission of the following justification the application was considered complete and was accepted for evaluation. The same justification was also provided for evaluation within the Stribild application and no further questions or issues were raised by the clinical evaluator. Similar justifications were provided within the dossiers for the applications for EVG and COBI.

The solubility profile of EVG (approximately ≤1 µg/mL at pH 7 and below; US Pharmacopoeia classification: practically insoluble or insoluble) renders the development of a parenteral formulation particularly challenging for suitable evaluation of EVG PK after IV administration for an absolute bioavailability study.

The ADME properties, and the clinical pharmacology of EVG have been extensively characterised using *in vitro*/nonclinical studies and clinically, through PK, mass balance and drug interaction studies. EVG is expected to have very high/near-complete bioavailability when administered as the Stribild tablet. An early PK boosting study (clinical Study GS-US-183-0102) demonstrated a 20 fold increase in EVG AUC_{tau} (from approximately 719 ng.h/mL to approximately 14,300 ng.h/mL) following multiple coadministration with RTV 100 mg (another pharmacoenhancer) versus EVG dosing alone. This increase was mediated by a approximately 6-7 fold increase in bioavailability and a 3 fold reduction in EVG systemic clearance (based on EVG elimination t½ increase from approximately 3.5 to approximately 9.5 h). The resulting estimate of EVG apparent clearance (CL/F) is approximately 5-6 L/h, which is about 5% of the hepatic blood flow, indicating that bioavailabilty (F) is very high and approaches complete absorption. EVG exposures are comparable following administration of Stribild versus coadministration with RTV 100 mg (clinical Study GS-US-236-0101). Both clinical Studies GS-US-183-0102 and GS-US-236-0101 were submitted as part of this application.

The ADME properties, and the clinical pharmacology of COBI have been extensively characterised using *in vitro*/nonclinical studies and clinically, through dose ranging studies. COBI displays greater than dose proportional increases in plasma exposure due to a combination of reduced systemic clearance and higher bioavailability *via* autoinhibition of its own metabolism by CYP3A, which is related to the desired PD effect (boosting of coadministered agent). The bioavailability of COBI increases with dose from single dose to multiple dose administration (before reaching a plateau at 150 to 200 mg), consistent with autoinhibition and reduction in first pass metabolism (Studies GS-US-216-0101 and GS-US-216-0113), resulting in a low apparent clearance (CL/F approximately 10% to 15% of hepatic blood flow). At doses greater than 150 mg to 200 mg, increases in COBI exposures (AUC) following multiple dose administration corresponded to proportional increases in plasma half life due to reduction in systemic clearance, rather than substantial changes in bioavailability.

Based on Gilead's thorough understanding of the formulation challenges, clinical development programme and the estimation of bioavailability from available data, an absolute bioavailability study for EVG and COBI was not deemed necessary and therefore not performed.

(4) The fixed dose product is being proposed for initiating treatment in de novo patients. However EVG, the mono agent is being proposed for the treatment experienced population. Is that approach acceptable?

Gilead has submitted independent applications for Stribild - registration of a new fixed-dose combination product, and EVG - registration of a new chemical entity. Each stand alone-application contains quality, nonclinical and clinical data which directly supports the proposed PI and that are relevant to the benefit-risk assessment for use in the treatment populations in which they have been studied.

The proposed indication for Stribild is supported by clinical safety and efficacy data derived from 2 Phase III studies (GS-US-236-0102 and GS-US-236-0103) and one Phase II study (GS-US-236-0104) conducted in ARV treatment-naïve, HIV-1 infected subjects.

The proposed indication for EVG is supported by clinical safety and efficacy data derived from the pivotal Phase III Study GS-US-183-0145, and further supported by the Phase II Studies GS-US-183-0105 and GS-US-183-0130, which demonstrate the safety and efficacy of EVG tablets coadministered with a RTV-boosted PI and other ARV agents in treatment-experienced adults.

Stribild and the EVG single agent tablet are separate and distinct therapeutic goods with different data packages to support their use in different patient populations. The fact that they are proposed for registration in different patient populations is a situation that is clearly elaborated in their proposed PIs and Gilead considers that the PIs provide a suitable mechanism to inform prescribers of which populations each product have been demonstrated to provide acceptable safety and efficacy. In treatment-naïve patients, treatment guidelines call for the use of a regimen consisting of 2 NRTIs, such as TDF and FTC, and a third agent such as an NNRTI, protease inhibitor or INSTI. These treatment recommendations are suitable to the development of complete regimens within a single tablet. However, in treatment-experienced patients, an effective regimen needs to be constructed based on the patient's virus resistance profile and using available combinations of drugs to which the virus is susceptible. This approach to treatment requires the availability of single agent products to allow building a treatment regimen tailored to a specific patient. Accordingly, the development of an EVG-based STR for treatment-naïve patients, and of the EVG single agent for use in treatment-experienced patients is aligned with HIV treatment guidelines and medical practice.

(5) Possible issue for allowing use of a new INSTI in a FDC and its consequences for the use of the currently registered INSTI RTG which is not a CYP3A substrate and is available as a de novo agent. Is an efficacy comparison between EVG/COBI and RTG desirable?

Stribild is a complete treatment regimen which should not be coadministered with other ARV medications for treatment of HIV-1 infection. The *Precautions* section of the proposed Stribild PI adequately reflects this and will act as a suitable mechanism to inform prescribers. Gilead is uncertain why the Delegate has raised the consequences for the use of the currently registered INSTI RTG as a potential issue.

Current treatment guidelines suggest that initial therapy for ARV treatment-naïve HIV-1 infected patients consists of 2 NRTIs/NtRTIs and either a NNRTI - usually EFV, a boosted protease inhibitor, or the INSTI RTG. Treatment guidelines list FTC and TDF as a preferred NRTI/NtRTI backbone in an ARV regimen for initial therapy.[22, 23, 24, 25]

Raltegravir is currently the only INSTI approved for use in adults that requires twice daily dosing, a study of RTG administered once daily (QDMRK, *A Phase III Study of the Safety and Efficacy of Once Daily (QD) Versus Twice Daily (BID) Raltegravir (RAL) in Combination Therapy for Treatment-Naïve HIV-Infected Patients (Pts)*) was terminated early due to the increase in rates in virological failure in the RTG QD arm compared to the RTG BID arm. To reduce pill burden, a number of ARVs are available in fixed-dose combinations; however, with such combinations patients may take an incomplete regimen, leading to the development of viral resistance and treatment failure. This risk is reduced if a complete treatment, that is, including 2 NRTIs plus an agent from another class, is available in an STR. Elvitegravir within the Stribild STR, only requires once daily dosing, and is the first INSTI to have demonstrated non inferior efficacy, with differentiated tolerability, against EFV and RTV-boosted ATV in treatment-naïve patients (both combined with TDF and FTC).

No studies are currently available which have made a direct comparison between EVG/COBI and RTG.

Gilead has established the quality, safety and efficacy of Stribild and believes that this novel integrase-based STR will provide healthcare providers in Australia with an important new therapeutic option for administration once-daily in treatment-naïve patients with HIV-1 infection.

Advisory Committee Considerations

The ACPM provided the following advice in response to the TGA Delegate's request for comment on five specific issues (see *Delegate considerations*, above):

Issue 1.

The ACPM noted the Delegate's comment that this is the first instance of a fixed dose combination containing 4 active ingredients, 2 of which have non-linear kinetics. The ACPM did not see this as an issue. The ACPM noted that the clinical development program and submission strategy for Stribild was discussed and considered acceptable at a pre-submission meeting with the TGA on 2 August 2011.

[22] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Oct 14, 2011; 1–167.
[23] European AIDS Clinical Society (EACS) Guidelines for the Clinical Management and Treatment of HIV Infected Adults in Europe. Version 6.0 - Oct 2011 1-61.
[24] Thompson MA, *et al*. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA* 2010;304(3):321-33.
[25] Gazzard BG. British HIV Association Guidelines for the treatment of HIV-1- infected adults with antiretroviral therapy 2008. *HIV Med* 2008;9(8):563-608.

Current HIV treatment guidelines recommend that the treatment of HIV infection requires the use of a regimen including at least 3 active antiretroviral agents. Unlike combination therapies used to treat asthma or hypertension, no component dose titration is necessary. If TDM were to be used it would apply only to the EVG component and consideration of adjustment of the relative doses would not arise.

Issue 2:

While [the comments made by the Delegate at this point are] true, this is a complete, stand-alone Category 1 application of a fixed dose combination that is supported by adequate efficacy, safety and quality data. There are 3 antiretrovirals (ARVs) in the combination. Two are already in widespread use. The third, EVG, with its PK enhancer is new. There are sufficient trial data and other data provided to make the application supportable. A potential problem with the lack of individual safety data on the two new chemical entities is that it may be difficult to identify the causative component if there is a severe adverse event.

Issue 3.

A justification for not conducting absolute bioavailability studies was provided and PSC advice is that this should not preclude registration. The clinical evaluator was in agreement. The solubility profile of elvitegravir, in particular, renders the development of a parenteral formulation particularly challenging for suitable evaluation of its kinetics with IV administration for an absolute bioavailability study. The kinetics have been extensively characterised and suggest near complete absorption.

Issue 4.

The EVG component would be used when TDF and or FTC are not appropriate choices, usually either because of resistance or intolerance (or both). The approach is appropriate.

Issue 5.

Stribild has been studied in comparison with other once a day combination strategies. There does not seem to be particular need to compare EVG/COBI with RTG. Patients failing either of these for reasons of resistance would not be likely to consider the other as an option.

Advisory committee advice

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall positive benefit – risk profile for the indication;

> *Stribild is indicated as a fixed dose combination complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of Stribild.*

In making this recommendation, the ACPM expressed concern that 2 of the individual active ingredients in this fixed dose combination have not been evaluated and that while the applications for the individual active ingredients have been submitted to the TGA it may be some time before these evaluations are finalised.

The ACPM advised the following:

- The ACPM's standard advice on the need to titrate individual agents prior to commencement on a fixed dose combination does not apply in this instance, as the clinical context for combined medication regimens has been well established.

- That in the absence of individual assessment it will be difficult to determine the cause of an unusual side effect and this is a key consideration in the benefit-risk assessment for this product.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

The ACPM expressed significant concern about the regulatory processes that allow parallel assessment of new chemical entities and fixed dose combination products containing the new chemical entities and recommends that policies be developed with industry to prevent this in the future.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Stribild fixed dose combination tablets, containing 300 mg TDF, 200 mg FTC, 150 mg EVG and 150 mg COBI, indicated for:

> *Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults.*
>
> *Stribild is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-I reverse transcriptase inhibitors.*

Specific Conditions Applying to these Therapeutic Goods

The implementation in Australia of the Stribild -300 mg TDF, 200 mg FTC, 150 mg EVG and 150 mg COBI tablet Australian Risk Management Plan Version: 0.1, dated 24 November 2011, to be revised as specified in correspondence to the OPR dated 18 December 2012 and 16 January 2013 included with submission PM-2011-03533-3-2, and any subsequent revisions, as agreed with the TGA and its OPR.

Request for Review under Section 60 of the Therapeutic Goods Act 1989

On 7th May 2013, the sponsor requested review by the Minister for Health/Parliamentary Secretary to the Minister for Health of the decision (the initial decision), dated 7th February 2013 under section 25 of the *Therapeutic Goods Act 1989* [Commonwealth] (the Act), to approve the registration of Stribild with the indication statement as follows:

> *"STRIBILD is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naive adults.*
>
> *STRIBILD is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors."*

Delegate's Decision Being Appealed

The basis of the sponsor's request for the initial decision to be reviewed is as follows:

Gilead sought approval for the registration of Stribild tablets with the indication;

> *"Stribild is indicated as a complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of Stribild."*

Following evaluation of this application, the TGA Delegate approved Stribild tablets with the indication;

> *"STRIBILD is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naive adults. STRIBILD is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors."*

and failed to approve the following indication as proposed by the ACPM:

> *"Stribild is indicated as a fixed dose combination complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of Stribild".*

While Gilead agrees with the TGA decision to approve Stribild tablets, it disagrees with the wording of the TGA approved indication and believes the Delegate did not give due consideration to the indication as proposed by the ACPM. The ACPM arrived at their recommendation following review of the data package, the pre-ACPM response, the comments made by the evaluators and the concerns outlined by the Delegate. The ACPM noted that the pivotal Phase III studies demonstrated clinical efficacy and safety within treatment naïve patients, however, the ACPM did not recommend a restriction of the indication to the naïve population for Australian Prescribers.

The sponsor believes that the ACPM recommended indication is more appropriate as it leaves the choice of whether to use Stribild in this patient population in the hands of the prescribers.

Gilead therefore requests reconsideration of the wording of the approved indication, to reflect the ACPM recommendation, taking into account subsequent negotiations with the TGA Delegate, as follows:

> *"Stribild is indicated as a single tablet regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of Stribild."*

Basis of the Appeal

Gilead believes in providing patients who are in need of antiviral treatments with the best therapeutic options available. The Indication statement is critical in defining patient access, especially in a constantly evolving reimbursement environment. As such Gilead considers that the differences in the TGA approved indication compared to the ACPM recommended indication for Stribild could inappropriately deprive patient access to important therapies.

Gilead therefore disagrees with the wording of the indication for Stribild tablets approved by the Delegate on the basis of:

- The TGA Delegate has not given due consideration to the ACPM recommendation and wishes to seek reconsideration of the ACPM recommended indication statement as possible under Section 60 (3) (b) of the *Act.*

Review by the Delegate of the Minister

Materials on which the findings of fact were based

In making a decision on this matter, the Delegate of the Minister has taken account of the following:

- The EU *Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection* (Rev 2, 2008).
- The sponsor's appeal letter dated 7 May 2013.

- The clinical evaluation report(s) for Stribild, dated 30 May 2012 and 19 September 2012.
- The approval letter of the initial decision maker dated 7 February 2013.
- The pre-ACPM response of Gilead Sciences Pty Ltd (noting the indication statement at that time).
- All other documents contained in the sponsor's submission dated 7 May 2013 but not individually named immediately above.

Conclusions

Having reviewed the above material, the following conclusions are made:

- The Delegate of the Minister does not believe that the utility of Stribild in patients who are treatment-naïve is in dispute. There appears no real dispute about the clinical data *per se*.
- The EU *Guidance on the Clinical Development of Medicinal Products for the Treatment of HIV Infection* states that for use in treatment-experienced patients, relevant data should be generated. These data do not appear to be in the submission.
- Even were this product approved for use in those who do not have mutations associated with resistance, the sponsor has not outlined via data and justification what the place in therapy of this drug might be, that is, for example, for whom would it provide benefit? In combination with anything else? These questions require clinical data to answer them and in any case have not been addressed in the sponsor's appeal documentation.
- As stated in the sponsor's pre-ACPM response, treatment-experienced patients have their medication tailored on the basis of their virus resistance profile, and a fixed combination such as Stribild would, in the Delegate of the Minister's view, make this difficult or not possible. In addition, the sponsor has not detailed with supporting evidence how this product might figure in such 'tailoring', nor provided clinical data to substantiate its safety and effectiveness were it so used.

In summary, on review of the appeal documentation, the sponsor presents no arguments based upon the submitted clinical data, as far as is evident to the Delegate of the Minister, to substantiate safety and efficacy in a patient population beyond treatment-naïve subjects. Hence the patient population and potential benefits (and risks) beyond this patient group are entirely unclear and non-specific. Thus the conclusion of the Delegate of the Minister can only be that quality, safety and efficacy for this broader indication statement have not been satisfactorily established as is necessary under s 25 of the Act.

Result of the Delegate of the Minister's reconsideration of the initial decision

Pursuant to section 60 of the Act, and for the reasons referred to above, the Delegate of the Minister decided to confirm the initial decision (see *Outcome*, above).

Reasons for the Delegate of the Minister's decision

The above decision was made on the basis that:

In the view of the Delegate of the Minister, the appeal does not involve any dispute about the results of the pivotal clinical trials. The product has been shown to be non-inferior and comparable to the current standard of treatment in HIV-1 infected treatment naïve patients, over a 4 year time period, both in efficacy and safety profile. The sponsor has not disputed the presentation or critique of the clinical data beyond the indication statement which the sponsor now disputes subsequent to the ACPM meeting and the TGA Delegate's decision, and it is noted the indication statement was not disputed in the pre-ACPM

response. Indeed, argument was presented in the sponsor's pre-ACPM response to state that treatment-experienced patients required individual tailoring of medications. It is specifically stated, *'This approach to treatment requires the availability of single agent products to allow building a treatment regimen tailored to a specific patient'.* If the sponsor believes that Stribild has a role in this, it has not been detailed or supported by clinical data presented to the Delegate of the Minister.

What is disputed in this appeal is solely whether there is any evidence for efficacy and safety for Stribild in use beyond the treatment-naïve subset.

The Delegate of the Minister could find no clinical trials in the sponsor's submission for treatment-experienced patients to support such use as the broader indication might allow. Furthermore, apart from claiming that the current treatment-naïve indication might 'deprive patient access to important therapies', there appears to be no detail of whom such patients are, how they would be deprived and when Stribild would be indicated in the management of such patients. As a result, the sponsor's claim of uniqueness based on combining an INSTI with an NRTI backbone does not address, if that is the case, what the advantages are of such a combination and circumscribe the patient population the sponsor intends might benefit from receiving it. Also, there is no technical justification for the lack of clinical trials in treatment-experienced patients that the EU *Guidance on the Clinical Development of Medicinal Products for the Treatment of HIV Infection* otherwise requires.

On reviewing the advice of the ACPM, the Delegate of the Minister considered the ACPM did not specifically address the issue of use beyond treatment-naïve patients and as such, the sponsor's claim that the ACPM addressed the TGA Delegate's concerns in full does not, in the Delegate of the Minister's view, pertain directly to this appeal issue.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>

Attachment 2. Extract from the Clinical Evaluation Report

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