



Australian Government

Department of Health

Therapeutic Goods Administration

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

Proprietary Product Name: Stribild

Sponsor: Gilead Sciences Pty Ltd

June 2017

About the Therapeutic Goods Administration (TGA)

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- An Australian Public Assessment Report (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; it provides 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.

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Common abbreviations

Abbreviation	Meaning
AE	adverse event
aGFR	actual GFR
ARV	antiretroviral
ATR	Atripla: EFV/FTC/TDF
ATV	atazanavir
ATV/r	ritonavir boosted atazanavir
BMD	bone mineral density
CD4	cluster determinant 4
CER	Clinical evaluation report
CG	Cockcroft-Gault
CI	confidence interval
CMI	consumer medicine information
COBI	cobicistat; GS-9350
CSR	clinical study report
CYP	cytochrome P450
CysC	cystatin C
EFV	efavirenz
EFV/FTC/TDF	efavirenz/emtricitabine/tenofovir disoproxil fumarate; Atripla
eGFR	estimated glomerular filtration rate
eGFR _{CG}	estimated glomerular filtration rate calculated using the Cockcroft-Gault method
EU	European Union
EVG	elvitegravir
EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; Stribild; STB

Abbreviation	Meaning
FAS	Full Analysis Set
FEPO ₄	fractional excretion of phosphate
FTC	emtricitabine
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate; Complera/Eviplera
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate; Truvada
GFR	glomerular filtration rate
HIV-1	human immunodeficiency virus (type 1)
INSTI	integrase strand-transfer inhibitor
LDL	Low density lipoprotein
MAH	Marketing authorisation holder
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse transcriptase inhibitor
PI	product information
PIn	protease inhibitor
PK	pharmacokinetic(s)
PRT	proximal renal tubulopathy
RAL	raltegravir
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SBR	staying on a baseline regimen
SD	standard deviation
STB	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; Stribild

Abbreviation	Meaning
STR	Single tablet regimen
TDF	tenofovir disoproxil fumarate; tenofovir DF; Viread
TVR	telaprevir
USA	United States of America

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	1 July 2015
<i>Date of entry onto ARTG</i>	17 July 2015 (for decision) 22/2/13
<i>Active ingredients:</i>	Tenofovir disoproxil fumarate / Emtricitabine / Elvitegravir / Cobicistat
<i>Product name:</i>	Stribild
<i>Sponsor's name and address:</i>	Gilead Sciences Pty Ltd Level 6/147 St Kilda Road MELBOURNE VIC 3004
<i>Dose form:</i>	Tablet
<i>Strength:</i>	Each tablet contains: 300 mg tenofovir disoproxil fumarate; 200 mg emtricitabine; 150 mg of elvitegravir and 150 mg of cobicistat
<i>Container:</i>	Bottle
<i>Pack size:</i>	30 tablets
<i>Approved therapeutic use:</i>	<p><i>Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naive adults. Stribild is also indicated in certain virologically suppressed (HIV1RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see Clinical Trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Stribild (tenofovir DF, emtricitabine or elvitegravir).</i></p> <p><i>Stribild is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.</i></p>
<i>Route of administration:</i>	Oral
<i>Dosage:</i>	1 tablet daily
<i>ARTG number:</i>	194081

Product background

This AusPAR describes an application by Gilead Sciences Pty Ltd to extend the indications for Stribild to include use in patients who have no known mutations associated with resistance to the individual components of Stribild.

The requested extension of indication is to (change is emphasised in bold):

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

Stribild is a fixed dose combination of one integrase inhibitor, one pharmacokinetic enhancer and two nucleos(t)ide HIV-1 reverse transcriptase inhibitors.

Stribild is a four drug combination of elvitegravir, an HIV integrase strand transfer inhibitor (HIV-1 INSTI), cobicistat, a cytochrome P450 (CYP) CYP3A inhibitor, and emtricitabine and tenofovir DF, both HIV nucleoside analog reverse transcriptase inhibitors (HIV NRTI). Stribild was registered by TGA in 2013 for the treatment of HIV infection in treatment naïve adults.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 22 February 2013.

At the time of this submission the approved indications for Stribild were:

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-1 reverse transcriptase inhibitors

Overseas status

The application had been submitted to United States of America (USA) FDA and EMA, at the time of application to TGA, and has subsequently been approved overseas. In USA the extension of indications has been approved with wording

“Stribild is a four-drug combination of elvitegravir, an HIV integrase strand transfer inhibitor (HIV-1 INSTI), cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir DF, both HIV nucleoside analog reverse transcriptase inhibitors (HIV NRTI) and is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild”.

The EMA wording for the EOI approval is

“Stribild is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years and over who are infected with HIV-1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild”.

At the time the TGA considered this application, the international regulatory status was as shown in Table 1.

Table 1: International regulatory status of Stribild tablets

Country	Submission Date	Approval Date	Approved Indication
European Union	6 Mar 2014	22 May 2014	Stribild is indicated for the treatment of human immunodeficiency virus 1 (HIV 1) infection in adults aged 18 years and over who are antiretroviral treatment naïve or are infected with HIV 1 without known mutations associated with resistance to any of the three antiretroviral agents in Stribild.
USA	20 Feb 2014	17 Dec 2014	Stribild is indicated as a complete regimen for the treatment of HIV-1 infection in adult patients who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.
Canada	28 May 2014	8 May 2015	Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) is indicated for use as a complete regimen for the treatment of adults aged 18 years and older infected with HIV-1 with no known mutations to the integrase inhibitor class, tenofovir or emtricitabine. The safety and efficacy of Stribild has not been established in patients with a prior history of virologic failure.

Product information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

This is a Category 1 Type C application to extend the indications and make changes to the Product Information (PI) and Consumer Medicine Information (CMI).

Contents of the clinical dossier

Clinical Study Report (CSR) of Extrinsic Factor pharmacokinetic (PK) Study x 1;

Reports of Efficacy and Safety Studies:

- 4 Controlled Clinical Studies Pertinent to the Claimed Indication
- 2 Uncontrolled Clinical Studies
- Reports of Analyses of Data from More than One Study: Integrated Summary of Safety, Integrated Summary of Efficacy.
- Integrated Virology Summary Report for Studies GS-US-236-0102 and GS-US-236-0103).

The information provided is adequate to undertake the evaluation. It is noted that the clinical expert is an employee of Gilead Sciences Pty Ltd.

Good clinical practice

It is stated in the clinical study reports that the studies were undertaken in accordance with good clinical practice.

Pharmacokinetics

Studies providing pharmacokinetic data

GS-US-236-0135 Pharmacokinetic drug interaction study

This was a randomised, open label, multiple dose, two part, multiple cohort study. Part 1 assessed the pharmacokinetics (PK) and drug interaction potential of telaprevir (TVR) and elvitegravir/cobicistat /emtricitabine/tenofovir disoproxil fumarate (Stribild (STB)). Part 2 assessed the PK and drug interaction of TVR and ritonavir (RTV) boosted atazanavir (ATV/r) + elvitegravir (EVG). It was conducted at one site in the United States (US) between January and March 2013.

For a full description of the clinical evaluation of the pharmacokinetics please see Attachment 2, extract from the clinical evaluation report (CER).

Evaluator's conclusions on pharmacokinetics

The sponsor concluded that:

- There were no clinically relevant drug interactions between the components of Stribild (STB) and TVR, and, between ATV/r + EVG 85 mg and TVR, and no dose adjustment is necessary when these are co-administered.

The sponsor's conclusions are accepted.

Efficacy

Studies providing efficacy data

The efficacy data provided in the dossier comprise CSRs for the following studies:

- GS-US-236-0102 and GS-US-236-0103 to support updates to the drug resistance subsection of the pharmacology section and the clinical trials section to include data from patients treated to 144 weeks.
- GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123 to support an update to the current approved indication to include the use of STB in virologically suppressed patients who have no known mutations associated with resistance to the individual components of STB.

Of note, studies GS-US-236-0102 and GS-US-236-0103 were provided to and evaluated by the Therapeutic Goods Administration (TGA) in the 2011-03533 application for initial marketing authorisation. CSRs for the other studies have not been previously been submitted to the TGA.

For a full description of the clinical evaluation of the efficacy please see Attachment 2, extract from the CER.

Evaluator's conclusions on efficacy

The results from Week 144 data in Studies GS-US-236-0102 and GS-US-236-0103 demonstrate continued efficacy of STB in treatment naïve subjects with HIV.

Data and information to support an extension of indications to include the use of STB in virologically suppressed human immunodeficiency virus (type 1) (HIV-1) infected subjects are provided in Studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123. In GS-US-236-0115 and GS-US-236-0121, subjects were switched to STB from the baseline regimens of protease inhibitor (Pin) + RTV + FTC/TDF and nonnucleoside reverse transcriptase inhibitor (NNRTI) plus emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) respectively and compared with subjects continuing on the baseline regimens. Results are presented showing that at Week 48 treatment with STB was non-inferior to continued treatment with the baseline regimens. Also, in both studies, there was no treatment emergent HIV-1 drug resistance in either treatment group. Efficacy of STB in this population was also demonstrated from the results of Study GS-US-236-0123. In this study, subjects were switched to STB from a regimen of raltegravir (RAL) + TVD. All subjects maintained virologic suppression and there was no development of drug resistance. It is considered that these data support the use of STB in virologically suppressed HIV-1 infected subjects.

Safety

Studies providing safety data

The safety data provided in the dossier that are relevant to the proposed PI changes in the precautions and adverse effects sections comprise:

- The CSR for Study GS-US-236-0118 to support an update to the adverse effects section to include 48 week safety data with use of STB in HIV-1 infected treatment naïve patients with mild to moderate renal impairment.
- CSRs for Studies GS-US-236-0102 and GS-US-236-0103 to support an update of safety information in the precautions and adverse effects sections to include Week 144 data.

- CSRs for Studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123 to support additional information in the adverse effects section to include data from the use of STB in virologically suppressed patients.

For a full description of the clinical evaluation of safety please see Attachment 2, extract from the CER.

Evaluator's conclusions on safety

The results of Study GS-US-236-0118 showed that in HIV-1 infected subjects with mild to moderate renal impairment, the renal safety profiles of cobicistat (COBI) containing regimens, STB or a regimen including a PI with or without TDF, were consistent with those from previous studies.

The Week 144 results from Studies GS-US-236-0102 and GS-US-236-0103 continued to show a favourable safety and tolerability profile. This included clinically relevant tolerability advantages over Atripla: EFV/FTC/TDF (ATR) and ATV/r + TVD as follows:

- Lower incidence of adverse events (AEs) considered related to study drug.
- Lower incidence of treatment emergent Grade 3 or 4 laboratory abnormalities.
- Smaller increases from baseline in fasting total cholesterol and low density lipoprotein (LDL) cholesterol versus ATR and smaller increases from baseline in fasting triglycerides versus ATV/r + TVD.
- Lower incidence of neurological and psychiatric AEs versus ATR.
- Lower incidence of rash AEs versus ATR.
- Lower incidence of liver-related laboratory abnormalities versus ATR or ATV/r + TVD.

Also:

- The renal events and changes from baseline in renal parameters were consistent with the known safety profile.
- The findings in relation to bone fractures and changes in bone mineral density (BMD) were consistent with data from other studies of TDF containing regimens.

In Studies GS-US-236-0115 and GS-US-236-0121, there were higher percentages of AEs with STB. This was considered to be expected when changing to a new treatment regimen. The higher % of subjects with AEs assessed as treatment related is consistent with this. Of note, there were few Grade 3 or 4 treatment related AEs. Serious adverse events (SAEs) were reported for a similar % of subjects in both groups in both studies and there were few discontinuations due to AEs. In Study GS-US-236-0115 no subject with STB experienced a clinically significant renal event, namely a renal SAE or AE resulting in discontinuation and there were no notable changes in renal laboratory parameters with STB. In Study GS-US-236-0121, 2 subjects receiving STB had renal AEs (acquired Fanconi syndrome and increased blood creatinine) resulting in discontinuation. Results for laboratory evaluations (in particular fasting glucose and lipids) and nervous system, psychiatric and rash events were consistent with known information.

An overview of AEs in these studies is presented below.

Table 2: GS-US-236-0115 and GS-US-236-0121: overall summary of adverse events (safety analysis set)

Subjects Experiencing Adverse Events by Category, n (%) ^{a,b}	GS-US-236-0115		GS-US-236-0121	
	STB (N=293)	SBR (PI+RTV+FTC/TDF) (N=140)	STB (N=291)	SBR (NNRTI+FTC/TDF) (N=143)
Any Treatment-Emergent Adverse Event	232 (79.2%)	104 (74.3%)	237 (81.4%)	107 (74.8%)
Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	133 (45.4%)	57 (40.7%)	111 (38.1%)	49 (34.3%)
Any Grade 3 or 4 Treatment-Emergent Adverse Event	12 (4.1%)	11 (7.9%)	19 (6.5%)	9 (6.3%)
Any Treatment-Emergent Study Drug Related Adverse Event	73 (24.9%)	9 (6.4%)	68 (23.4%)	9 (6.3%)
Any Grade 2, 3, or 4 Treatment-Emergent Study Drug Related Adverse Event	11 (3.8%)	2 (1.4%)	16 (5.5%)	2 (1.4%)
Any Grade 3 or 4 Treatment-Emergent Study Drug Related Adverse Event	2 (0.7%)	0	2 (0.7%)	0
Any Treatment-Emergent Serious Adverse Event	17 (5.8%)	9 (6.4%)	14 (4.8%)	6 (4.2%)
Any Treatment-Emergent Study Drug Related Serious Adverse Event	2 (0.7%)	0	0	0
Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	6 (2.0%)	4 (2.9%)	6 (2.1%)	1 (0.7%)
Treatment-Emergent Death ^c	0	1 (0.7%)	1 (0.3%)	0

The sponsor's conclusions summarised below are accepted: concluded that:

- STB and staying on a baseline regimen (SBR) were generally well tolerated as shown by infrequent discontinuations due to AEs and low incidence of study drug related SAEs.
- The renal safety profile was consistent with that seen in previous studies.
- No new safety issues were identified.

The results from Study GS-US-236-0123 in which subjects switched to STB from a RAL + FTC/TDF regimen showed that STB was well tolerated and that there were no new safety issues observed. Key findings were:

- The AEs and laboratory findings reported were consistent with the known safety profile of STB.
- 43 of 48 subjects (89.6%) experienced ≥ 1 AE; there were Grade 3 events in 2 subjects and no Grade 4.
- 2 SAEs were reported neither of which were assessed as treatment related.
- There were no discontinuations due to an AE and no deaths.
- Results for renal parameters were consistent with the known profile and there were no clinically significant renal AEs.

First round benefit-risk assessment

First round assessment of benefits

The Week 144 efficacy results for Studies GS-US-236-0102 and GS-US-236-0103 showed continued and similar rates of virologic success following on from the Week 48 results. Resistance development to ≥ 1 components of STB, ATR, or ATV/r + TVD occurred infrequently and the majority of emergent resistance was reported during the first 48 weeks of study drug treatment. As well as robust and durable efficacy, STB demonstrated a favourable safety and tolerability profile with clinically relevant advantages over both ATR and ATV/r + TVD.

In Studies GS-US-236-0115 and GS-US-236-0121, high rates of virologic suppression were maintained to Week 48 in subjects who switched to STB and in those who remained on their baseline regimens containing a PI + RTV + FTC/TDF or an NNRTI + FTC/TDF. In each study, results of the primary efficacy analysis using the FDA defined snapshot algorithm demonstrated that switching to STB was non-inferior to SBR. In Study GS-US-236-0115, statistical superiority of STB over SBR (PI + RTV + FTC/TDF) was established.

In the single group Study GS-US-236-0123, 100% of subjects who switched to STB from RAL + FTC/TDF had virologic success at Week 48.

There was no treatment emergent HIV-1 drug resistance in Studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123 either in subjects switching to STB or in those SBR through the 48 week treatment periods.

First round assessment of risks

Results from Studies GS-US-236-0102 and GS-US-236-0103 showed that the safety profile for STB at Week 144 was the same as that for the Week 48 data. There were no new adverse drug reactions (ADRs) though the frequency of some ADRs changed. Of note, the renal safety profile was consistent with existing information and there were only several bone events not related to trauma.

In Study GS-US-236-0118 with HIV-1 infected subjects with mild to moderate renal impairment there were no clinically relevant median changes from baseline in cystatin C (CysC) based estimates of glomerular filtration rate (GFR) for subjects who received STB, no clinically relevant changes in creatinine or CysC based estimates of GFR for subjects who switched RTV to COBI in the PI/co cohort, and no changes in actual GFR (aGFR) in either cohort. Also, there were no clinically relevant changes from baseline in median values for other renal endpoints (serum phosphorus; urine fractional excretion of phosphate (FEPO₄)), and few subjects had clinically relevant changes in urine glucose or urine protein. Overall renal safety results were similar for subjects in subgroups by baseline estimated glomerular filtration rate calculated using the Cockcroft-Gault method (eGFR_{CG}) (< 70 mL/min and \geq 70 mL/min).

In Studies GS-US-236-0115 and GS-US-236-0121, there were a higher % of subjects who switched to STB experiencing an AE assessed as treatment related. The AEs were consistent with the known profile. Only a few of these were Grade 3 events and there were no Grade 4 events. Discontinuations due to AEs were infrequent. Overall STB was generally well tolerated in subjects who switched and there were no new safety issues identified.

In Study GS-US-236-0123 STB was well tolerated. Nearly all AEs were Grade 1 or 2 in severity with only 2 Grade 3 and none Grade 4. No subject discontinued due to an AE.

First round assessment of benefit-risk balance

The results of Studies GS-US-236-0102 and GS-US-236-0103 support the benefit risk balance of use of STB in treatment naïve subjects. The results of Studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123 support the use of STB in virologically suppressed subjects.

First round recommendation regarding authorisation

It is recommended that the indications for use of STB are extended to include use in virologically suppressed subjects.

Clinical questions

It is requested that:

- The sponsor addresses the issues regarding the PI and provides an updated PI. In the updated PI it is requested that the spelling is consistent with Australian norms.
- Provide an update on the international regulatory status of STB.

Second round evaluation of clinical data submitted in response to questions

The sponsor did not provide an update on the regulatory status of STB. However it is noted that the US label dated December 2014 includes use of STB in virologically suppressed patients.

Apart from the international regulatory status update, there were no questions in relation to the clinical data and information. The first round recommendation that the indications for use of STB are extended to include use in treatment naïve and virologically suppressed subjects remains the same.

V. Pharmacovigilance findings**Risk management plan**

Information required for evaluation, including draft protocols for planned studies in the Pharmacovigilance Plan, had not been provided.¹ The sponsor was then asked to submit the current European Union (EU) RMP with an ASA and all attachments. Furthermore the sponsor was advised the ASA should identify and provided explanation for differences between the current EU-RMP and the previously accepted AU-RMP (Version: 0.1, dated 24 November 2011, to be revised as specified in the sponsor's correspondence dated 18 December 2012 and 16 January 2013).

The sponsor refused to comply with this request on the basis that such a request was procedurally unfair and the outlined concerns could be appropriately responded to after full evaluation of the key safety and efficacy data had been conducted by the TGA. This response was accepted by the TGA and it is in this context, with consideration of material changes to the previously accepted RMP, that these documents have been reviewed in this report.

¹ Clarification; as the protocols were not available, the sponsor provided an assurance that they would be provided to TGA when available.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 3.

Table 3: Summary of ongoing safety concerns

	Safety Concerns for STB	Attributable Component(s) of STB
Important Identified Risks	Renal toxicity	TDF
	Bone events due to proximal renal tubulopathy/loss of BMD	TDF
	Post-treatment hepatic flares in HIV/HBV coinfecting patients	FTC, TDF
	Interaction with didanosine	TDF
	Pancreatitis	TDF
	Lactic acidosis and severe hepatomegaly with steatosis	FTC, TDF
	Lipodystrophy	FTC, TDF
	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness	EVG
Important Potential Risks	Overdose (occurring through accidental concurrent use of STB with any other TDF-containing product)	TDF
	Concurrent use of drugs whose coadministration with STB is contraindicated	COBI, EVG
Missing Information	Long-term safety information	STB
	Safety in children	EVG, COBI, TDF
	Safety in elderly patients	EVG, COBI, FTC, TDF
	Safety in pregnancy	EVG, COBI, FTC, TDF
	Safety in lactation	EVG, COBI, FTC, TDF
	Safety in patients with renal impairment	STB (as a STR), COBI, TDF
	Safety in patient with severe hepatic impairment (CPT score C)	EVG, COBI
	Drug-drug interactions	COBI
	PK of EVG in subjects with UGT1A1 polymorphisms	EVG
Safety in patients with cardiac conduction disorders	COBI	

Table 4: Appendix 1: 'Summary of changes to Stribild AU-RMP (Version 0.1 dated November 2011 to Version 1.1 dated May 2014'

Safety Concern (Component)	Comment	AU-RMP Section
<i>Important Identified Risks</i>		
Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Bone events due to proximal renal tubulopathy/loss of BMD has been added as an important identified risk for the TDF component of STB for consistency with the EU-RMP.	Part II, Section 6.3.1
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (EVG)	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness has been added as an important identified risk for the EVG component of STB based on Week 96 data from EVG Study GS-US-183-0145 and STB Studies GS-US-236-0102 and GS-US-236-0103.	Part II, Section 6.3.1
<i>Important Potential Risks</i>		
Overdose (occurring through accidental concurrent use of STB with any other TDF-containing product) (TDF)	The important potential risk of 'overdose (occurring through accidental concurrent use of STB with any of its marketed active components)' has been changed to 'overdose (occurring through accidental concurrent use of STB with any other TDF-containing product)' as no particular safety concerns have been associated with overdose of EVG, COBI or emtricitabine (FTC), in accordance with the AU-RMPs for EVG, COBI and FTC.	Part II, Section 6.3.2
<i>Missing Information</i>		
PK of EVG in subjects with UGT1A1 polymorphisms (EVG)	New missing information added to align with the agreed EU-RMP for EVG. In a boosted state, EVG is metabolized primarily by glucuronidation via UGT1A1/3. Most genetic variants of UGT1A3 do not result in marked changes in activity. A PK study is ongoing to determine EVG exposures in patients with UGT1A1 polymorphism associated with decreased activity of UGT1A1 (UGT1A1*28/*28 genotype) (GS-US-183-1004).	Part II, Section 4.3.2.7
Drug-drug interactions (COBI)	New missing information added to align with the agreed EU-RMP for COBI.	Part II, Section 6.4
Safety in patients with cardiac conduction disorders (COBI)	New missing information added to align with the agreed EU-RMP for COBI. Clinical study data for COBI and STB do not support an increased risk of cardiac conduction disorders associated with the use of COBI. As patients with abnormal ECG results at screening that were deemed to be clinically significant by the investigator were excluded from COBI and STB studies, 'safety in patients with cardiac conduction disorders' has been added as a category of 'missing	Part II, Section 4.3.3.7

RMP evaluator comment

Notwithstanding the evaluation of the clinical aspects of the safety specification, the above summary of the ongoing safety concerns is considered acceptable.

Pharmacovigilance plan***Proposed pharmacovigilance activities***

Pharmacovigilance actions associated with the new safety concerns listed above have been added to the pharmacovigilance plan as follows:

Table 5: Pharmacovigilance actions associated with the new safety concerns

Safety Concern (Component)	Areas Requiring Confirmation or Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities (Objectives)
Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	<p>Information on BMD and bone events with long-term exposure to TDF</p> <p>Information on the relationship between BMD changes and proximal renal tubulopathy</p>	<p>Routine pharmacovigilance (including a bone events due to proximal renal tubulopathy/loss of BMD targeted follow-up questionnaire and close monitoring in PSURs)</p> <p>Clinical studies in HIV-1 and HBV infected adult and pediatric patients (GS-US-236-0103, GS-US-174-0102, GS-US-174-0103, GS-US-174-0115, GS-US-174-0121, GS-US-104-0321, GS-US-104-0352) (To collect information on BMD and bone events with long-term exposure to TDF)</p> <p>In vitro nonclinical studies on intestinal phosphate absorption (To collect information on whether TDF has an inhibitory effect on intestinal absorption of phosphate, which may contribute to the understanding of the observed effects of TDF on BMD)</p> <p>Clinical study in HBV infected pediatric patients (GS-US-174-0144) (To collect information on the relationship between BMD changes and proximal renal tubulopathy)</p>
	<p>Information on bone safety in pediatric patients</p> <p>Information on BMD loss with TDF use in patients at high risk for low BMD</p> <p>Information on BMD in HIV-1 infected women</p>	<p>Post-authorization safety studies of a representative sample of HIV-1 infected pediatric patients (To collect information on renal and bone safety in pediatric patients in the postmarketing setting)</p> <p>Cross-sectional study to assess BMD in HIV-1 infected patients at risk for BMD loss (GS-US-104-0423) (To collect information on the profile of low BMD in patients of interest who include those over 50 years of age, particularly women, and who have been exposed to TDF for at least 3 years)</p> <p>Clinical study of STB in HIV-1 infected women (GS-US-236-0128) (To collect information on BMD in HIV-1 infected women from a subset of subjects from Study GS-US-236-0128 in which DEXA scans will be performed with up to 96 weeks of STB therapy)</p>
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (EVG)	Information on the long-term risk of suicidal ideation and suicide attempt	<p>Routine pharmacovigilance (including close monitoring in PSURs)</p> <p>Clinical studies in HIV-1 infected patients (GS-US-236-0102, GS-US-236-0103) (To collect information on the long-term risk of suicidal ideation and suicide attempt)</p>
Drug-drug interactions (COBI)	Information on drug-drug interactions (EVG/co and antimycobacterials, EVG/co and anticonvulsants, and the effect of potent CYP3A4 inhibitors on COBI exposure)	<p>Routine pharmacovigilance (including close monitoring in PSURs)</p> <p>Clinical drug-drug interaction studies to evaluate the interaction of EVG/co and antimycobacterials (GS-US-216-0136) and EVG/co and anticonvulsants (GS-US-216-0137)</p> <p>Planned PBPK simulations of the effect of potent CYP3A4 inhibitors on COBI exposure (To collect information on drug-drug interactions as described above)</p>
PK of EVG in subjects with UGT1A1 polymorphisms (EVG)	Information on the PK of EVG in subjects with UGT1A1 polymorphisms	Planned PK study of EVG/co in subjects with UGT1A1*28/*28 genotype (GS-US-183-1004) (To determine EVG exposures in patients with UGT1A1 polymorphism associated with decreased activity of UGT1A1)

Routine pharmacovigilance will monitor the new important potential risk: 'Overdose (occurring through accidental concurrent use of STB with any other TDF-containing product)' and the missing information: 'Safety in patients with cardiac conduction disorders'.

Appendix 1: 'Summary of changes to Stribild AU-RMP (Version 0.1 dated November 2011 to Version 1.1 dated May 2014)' provides information in regard to other changes to the pharmacovigilance plan as shown in Table 6.

Table 6: Appendix 1: 'Summary of changes to Stribild AU-RMP (Version 0.1 dated November 2011 to Version 1.1 dated May 2014)'

Safety Concern (Component)	Changes to Pharmacovigilance Activities
Important Identified Risks	
Renal toxicity (TDF)	<p>The following activities have been added to the PV plan:</p> <p><i>Planned clinical study of STB, a TDF-containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected ARV treatment-naive patients (GS-US-236-0140; Category 4) (To collect information on renal function and markers of renal tubular function)</i></p> <p><i>Planned drug utilization study for STB (GS-EU-236-0141; Category 4) (To collect information on the effectiveness of the renal risk minimization measures for STB, factors potentially associated with the risk of proximal renal tubulopathy, and the reversibility of proximal renal tubulopathy)</i></p> <p><i>Monitoring of renal parameters in subjects enrolled in clinical studies of tenofovir DF-containing products in HIV-1 and HBV infected adult and pediatric patients who discontinue tenofovir DF due to renal tubulopathy (Category 3) (To collect information on the reversibility of renal tubulopathy following the discontinuation of tenofovir DF in adult and pediatric patients)</i></p> <p><i>Clinical study GS-US-236-0118 (Category 3) (To collect information on the renal safety profile of STB in patients with renal impairment [CL_{cr} 50-89 mL/min])</i></p> <p><i>Clinical study of STB in HIV-1 infected women (GS-US-236-0128; Category 4) (To collect information on the incidence and risk factors for renal adverse events in women)</i></p> <p><i>Post-authorization safety study of a representative sample of HIV-1 infected pediatric patients (Category 3) (To collect information on renal and bone safety in pediatric patients in the postmarketing setting)</i></p> <p>The following activities have been completed and removed from the PV plan:</p> <p><i>Study GS-US-104-0353 (see Part II Sections 2.5.1 and 6.3.1)</i></p>
Missing Information	
Safety in children (EVG, COBI, TDF)	<p>The following activities have been added to the PV plan:</p> <p><i>Clinical study GS-US-236-0112 (Category 4) (To collect information on the safety of STB in HIV-1 infected pediatric patients aged 12 to < 18 years)</i></p> <p><i>Clinical studies of EVG/r (GS-US-183-0160, CO-US-183-0165) and EVG/co (GS-US-183-0154) in HIV-1 infected children (Category 4) (To collect information on the safety of EVG/r and EVG/co in HIV-1 infected, antiretroviral treatment-experienced and treatment-naive pediatric patients aged < 18 years)</i></p>
Safety in pregnancy (EVG, COBI, FTC, TDF)	<p>The Antiretroviral Pregnancy Registry (APR) was included as a PV activity for FTC and TDF in version 0.1 of the AU-RMP. With the approval of STB, it has also been added as a PV activity for EVG and COBI</p>
Safety in patients with renal impairment (STB [as a STR], COBI, TDF)	<p>The following activities have been completed and removed from the PV plan:</p> <p><i>Clinical studies in HBV infected patients including patients with mild to moderate renal impairment (GS-US-174-0108 and GS-US-203-0107) (see Part II Section 4.3.5.5).</i></p>

RMP evaluator's summary in regard to the pharmacovigilance plan and appropriateness of milestones

There are no objections to the specified changes to the pharmacovigilance plan previously accepted for Stribild. However, the sponsor should correct the internal inconsistency regarding the categorisation of the planned post authorisation safety study of a representative sample of HIV-1 infected paediatric patients.

In addition the sponsor's correspondence dated 23 July 2012 stated: "Gilead provides an assurance that the protocols for planned Clinical Studies GS-US-174-0127, GS-US-216-0128

and GS-US-174-0144 will be provided to TGA as reference, when available.” To date it appears none of these protocols have been provided to the TGA, therefore it is assumed they are still not yet available. The sponsor should confirm the availability of these protocols and fulfil their obligation if the protocol of any of these studies is now available.

Given ‘Protocols for Proposed and Ongoing Studies in RMP Part IV’ of the AU-RMP has not been provided; draft protocols have not been submitted for the following new planned studies in the pharmacovigilance plan:

- GS-US-236-0140 - Clinical study of STB, a TDF containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected antiretroviral (ARV) treatment naïve patients
- GS-EU-236-0141 - A Prospective, Observational Drug Utilisation Study of Stribild in Adults With HIV-1 Infection, which is also meant to assess the effectiveness of additional risk minimisation activities conducted for the important identified risk: ‘Renal toxicity’
- Post authorisation safety study of a representative sample of HIV-1 infected paediatric patients
- PBPK simulations of the effect of potent CYP3A4 inhibitors on COBI exposure
- GS-US-183-1004 - A Phase I, Multiple Dose Study to Evaluate the Pharmacokinetics of Cobicistat Boosted Elvitegravir in Subjects with Decreased UGT1A1 Activity.

The sponsor should provide at least an electronic copy of the draft protocols for these studies to the TGA for review if they have not already been initiated. If they are not yet available the sponsor should provide an assurance that draft protocols for these studies will be provided to the TGA when they become available.

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 conducted; and the missing information: ‘Long-term safety information’, ‘PK of EVG in subjects with UGT1A1 polymorphisms’ & ‘Safety in patients with cardiac conduction disorders’ for which no routine risk minimisation is proposed.

The AU-RMP states: “UGT polymorphisms are not considered likely to result in clinically relevant differences in EVG exposures; therefore, no risk minimisation measures are considered warranted.”

For the missing information: ‘Safety in patients with cardiac conduction disorders’, the AU-RMP states: “No risk minimisation measures are considered necessary for this population at this time as although there is currently no specific data for COBI in this population, data from COBI and STB clinical trials do not support an increased risk of cardiac conduction disorders associated with the use of COBI.”

RMP evaluator comment

The above conclusion is similar to what was previously accepted for Stribild and continues to be acceptable.

Potential for medication errors

The ‘Potential for Medication Errors’ section of the AU-RMP previously accepted for Stribild has been removed from the updated AU-RMP.

RMP evaluator comment

The sponsor's handling of this matter using routine pharmacovigilance routine risk minimisation and additional risk minimisation activities was previously considered satisfactory. Consequently the sponsor should reinstate such a section in a revised AU-RMP, which relates to the important identified risk: 'Renal toxicity', including updating this section with post-marketing data.

Risk minimisation plan*Planned actions*

Routine risk minimisation activities will comprise product labelling, including contraindications, pharmacokinetic data, precautionary statements, instructions for use, drug interactions and/or notification of undesirable effects for all the specified ongoing safety concerns, except for the missing information: 'Long term safety information', 'PK of EVG in subjects with UGT1A1 polymorphisms' & 'Safety in patients with cardiac conduction disorders' for which no routine risk minimisation is proposed.

'Risk Minimization Measures for Important Identified Risks' of the AU-RMP outlines details of the additional risk minimisation activities conducted for the important identified risk: 'Renal toxicity'.

RMP evaluator comment

The sponsor's correspondence, dated 16 January 2013, states:

- Following TGA approval of Stribild, Gilead will be conducting commercial launch activities to introduce the efficacy and safety of Stribild to Australian health care providers in all States and Territories. Timing of launch will be established upon confirmation of PBS reimbursement.
- Gilead is committed to conducting educational programs for healthcare providers in Australia. The educational programs listed in the Stribild RMP include the ongoing 'HIV in the Body' Meetings which have been held on an annual basis since 2007. These meetings will be continued post launch and as such the next HIV in the Body meeting is proposed in July 2013. The effectiveness of these educational programmes has previously been measured by a clinical audit of 530 attending Physicians pre and post meeting. Previous results (specific to renal risk) show that 40% of physicians prior to attending an HIV in the body meeting assessed renal function in all patients by estimated glomerular filtration rate (eGFR). After attending an HIV in the body meeting 92% of physicians intended to assess renal function in all patients by eGFR. Subsequent clinical audits involving Physicians who attended the meetings showed 96% of patients had eGFR assessed. Results from this clinical audit have since been written in a manuscript which has been published in the Internal Medicine Journal, accepted for review by the Sexual Health Journal and submitted to the Medical Journal of Australia. [Information redacted]
- Further to the proposed HIV in the Body meetings, Gilead has recently planned to hold a number of state based educational meetings in March 2013. The objective being to educate HIV and HBV prescribers about the renal effects of tenofovir (TDF) and the appropriate guidelines for screening, monitoring and management of patients. The desired outcomes of these meetings is to increase the number of patients on a TDF containing regimen being screened by eGFR at baseline, monitoring of patients on a TDF containing regimen on a regular basis as per the Kidney Health Australia and relevant HIV and HBV guidelines and raise prescriber awareness of dose reduction requirements when managing patients with identified renal risks. Evaluation of these meetings will be conducted by a clinical audit of attendees at pre and post meeting.

- Gilead provides assurance that key results regarding renal messaging from the clinical audits conducted at the proposed HIV in the Body meeting and state based educational meetings will be communicated to the TGA within the next version of the Stribild RMP. Gilead is aware that the TGA has now adopted the EU Guideline Volume 9A – Guidelines on Pharmacovigilance for Medicinal Products for Human Use – of The Rules Governing Medicinal Products in the European Union, and as such will provide an updated RMP on an annual basis, or as required.

It does not appear that the key results regarding renal messaging from the clinical audits conducted at the proposed HIV in the Body meeting and state based educational meetings have been communicated to the TGA within the updated AU-RMP. Consequently the sponsor should now fulfil its obligation by revising the AU-RMP accordingly and include the above details of the additional risk minimisation activities conducted for the important identified risk: ‘Renal toxicity’ in Australia in this document.

In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information is considered satisfactory.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the first round evaluation of the RMP, the sponsor’s responses to issues raised and the RMP evaluator’s evaluation of the sponsor’s responses.

Table 7: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor’s response	RMP evaluator’s comment
<p>1. Safety considerations may be raised by the clinical evaluator through the consolidated request for further information and/or the clinical evaluation report (CER). It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p>The sponsor states: “Gilead provides confirmation that no Safety Considerations were raised by the clinical evaluator through the consolidated request for further information and/or the Clinical Evaluation Report”.</p>	<p>This is generally acceptable. However, in response to a CER query in relation to the PI, the sponsor proposed to amend the statement: “Additional adverse drug reactions observed with Stribild included suicidal ideation and suicide attempt (0.3%), all in subjects with a pre-existing history of depression or psychiatric illness” to “Additional adverse drug reactions observed with Stribild included suicidal ideation and suicide attempt (0.3%, 2 of 701), these two patients had a pre-existing history of depression or psychiatric illness” for clarity. This was accepted by the clinical evaluator, although this revision to the routine risk minimisation for the important identified risk: ‘Suicidal ideation/suicide attempt in</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
		<p>patients with a pre-existing history of depression or psychiatric illness' does not appear to be reflected in the revised AU-RMP. The sponsor should administratively correct this oversight when the RMP documentation is next updated. To this end it will be expected that the updated RMP documentation will be an unadapted EU-RMP, including V.B.8.6 RMP module SVI Additional EU requirements for the safety specification, and all RMP differences between the EU and Australia should be documented in the Australian-specific Annex (ASA) accompanying the EU-RMP as per the RMP Questions & Answers (Version 2.0, March 2015). In addition any updated RMP submission requires a summary table of changes between the updated RMP and the last RMP submitted to the TGA.</p>
<p>2. There are no objections to the specified changes to the pharmacovigilance plan previously accepted for Stribild. However, the sponsor should correct the internal inconsistency regarding the categorisation of the planned Post authorisation safety study of a representative sample of HIV-1 infected paediatric patients between Appendix 1 and Table 4-2 of the AU-RMP.</p>	<p>The sponsor states: "Gilead has updated Appendix 1 to state that the Post-authorisation safety study of HIV-1 infected paediatric patients to define the long-term safety profile of TDF (TDF, Viread) in HIV-1 infected paediatric patients is listed as a Category 4 study for consistency within Stated Additional Pharmacovigilance Activities (Category 4) of the AU-RMP".</p>	<p>This is acceptable.</p>
<p>3. The sponsor's correspondence dated 23 July</p>	<p>The sponsor states: "Clinical Studies GS-</p>	<p>For the missing information: 'Safety in patients with renal</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>2012 states: "Gilead provides an assurance that the protocols for planned clinical studies GS-US-174-0127, GS-US-216-0128 and GS-US-174-0144 will be provided to TGA as reference, when available." To date it appears none of these protocols have been provided to the TGA, therefore it is assumed they are still not yet available. The sponsor should confirm the availability of these protocols and fulfil their obligation if the protocol of any of these studies is now available.</p>	<p>US-216-0128 and GS-US-174-0144 are Category 4 studies. As per the new RMP format from the EMA, protocols are only provided in Annex 5 of the RMP for Category 1 to 3 studies only. Clinical study GS-US-174-0127 is no longer planned to be conducted and as such has been removed from the AU-RMP. In accordance with EMA Guideline² which has been adopted by the TGA, Gilead does not propose to provide protocols for Category 4 studies".</p>	<p>impairment', the removal of the planned clinical Phase II study (GS-US-174-0127) of use of tenofovir in HBV infected patients with moderate to severe renal impairment is acceptable as another more relevant Phase III study is ongoing. It is agreed the planned clinical studies GS-US-216-0128 and GS-US-174-0144 are Category 4 studies and corresponding protocols are not required.</p>
<p>4. Given Annex 7: 'Protocols for Proposed and Ongoing Studies in RMP Part IV' of the AU-RMP has not been provided, draft protocols have not been submitted for the following new planned studies in the pharmacovigilance plan:</p> <p>GS-US-236-0140 - Clinical study of STB, a TDF containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected ARV treatment naive patients</p> <p>GS-EU-236-0141 - A Prospective, Observational Drug Utilization Study of Stribild in Adults With HIV-1 Infection, which is also meant to assess the effectiveness of additional risk minimisation activities conducted for the important identified risk:</p>	<p>The sponsor states: "Annex 7 was not provided to the TGA as this Annex is specific to "Protocols for Proposed and Ongoing Studies in RMP Part IV". Part IV of the RMP is "Plans for Post Authorisations Efficacy Studies". As per Part IV of the RMP, there are no post authorisation efficacy studies planned and therefore no protocols are included in the Annex 7. The studies listed above by the RMP evaluator are Category 4 pharmacovigilance activities in the RMP, and as per the response to question</p>	<p>It is acknowledged that Annex 6 of the EU-RMP only requests 'Protocols for proposed and ongoing studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III'. However this EU guideline also states that Category 4 relates to: "Other studies conducted by MAH which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimisation activities". It is considered that such criteria do not apply to the planned Clinical Studies GS-US-236-0140 and GS-EU-236-0141. Consequently it is reiterated that the sponsor should provide at least an electronic</p>

² EMA/838713/2011, June 2012 guideline on good pharmacovigilance practices: Module V - Risk management systems.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>'Renal toxicity'</p> <p>Post authorisation safety study of a representative sample of HIV-1 infected paediatric patients</p> <p>PBPK simulations of the effect of potent CYP3A4 inhibitors on COBI exposure</p> <p>GS-US-183-1004 - A Phase I, Multiple Dose Study to Evaluate the Pharmacokinetics of Cobicistat-Boosted Elvitegravir in Subjects with Decreased UGT1A1 Activity</p> <p>The sponsor should provide at least an electronic copy of the draft protocols for these studies to the TGA for review if they have not already been initiated. If they are not yet available the sponsor should provide an assurance that draft protocols for these studies will be provided to the TGA when they become available.</p>	<p>3, only Category 1 to 3 studies are required to be provided".</p>	<p>copy of the draft protocols for these studies to the TGA if they have not already been initiated. If they are not yet available the sponsor should provide an assurance that draft protocols for these studies will be provided to the TGA when they become available.</p>
<p>5. The 'Potential for Medication Errors' section of the AU-RMP previously accepted for Stribild has been removed from the updated AU-RMP. The sponsor's handling of this matter using routine pharmacovigilance, routine risk minimisation and additional risk minimisation activities was previously considered satisfactory. Consequently the sponsor should reinstate such a section in a revised AU-RMP, which relates to the important identified risk: 'Renal toxicity', including updating this section with post marketing data.</p>	<p>The sponsor states: "Gilead has reinstated the 'Potential for Medication Errors' section of the AU-RMP within Section 6, Additional Requirements for the Safety Specification".</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>6. The sponsor's correspondence, dated 16 January 2013, states: (information relating to additional risk minimisation activities for the important identified risk: 'Renal toxicity'). It does not appear that the key results regarding renal messaging from the clinical audits conducted at the proposed HIV in the Body meeting and state based educational meetings have been communicated to the TGA within the updated AU-RMP. Consequently the sponsor should now fulfil its obligation by revising the AU-RMP accordingly and include the above details of the additional risk minimisation activities conducted for the important identified risk: 'Renal toxicity' in Australia in this document.</p>	<p>The sponsor states: "Gilead has updated Table 1-1.Risk Minimisation Measures for Important Identified Risks within Part V of the AU-RMP with key results from the HIV and the Body educational meetings and state based commercial launch meetings. Prior to commercial launch of Stribild in Australia in May 2014, Gilead has also undertaken additional risk minimisation measures related to the Important Identified Risk of Renal toxicity (TDF). As such, Table 1-2 has been updated accordingly".</p>	<p>This is acceptable, although it is noted that Annex 9. 'Details of additional risk minimisation measures' has been added rather than Table 1-2. 'Risk Minimisation Measures for Important Potential Risks' being updated.</p>

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

The sponsor was asked to respond to safety considerations raised by the clinical evaluator through the consolidated request for further information and/or the CER, in the context of relevance to the RMP. The sponsor states: "Gilead provides confirmation that no safety considerations were raised by the clinical evaluator through the TGA request for further information and/or the CER". This is generally acceptable. However, in response to a CER query in relation to the PI, the sponsor proposed to amend the statement: "Additional adverse drug reactions observed with Stribild included suicidal ideation and suicide attempt (0.3%, 2 of 701), these two patients had a pre-existing history of depression or psychiatric illness" for clarity. This was accepted by the clinical evaluator, although this revision to the routine risk minimisation for the important identified risk: 'Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness' does not appear to be reflected in the revised AU-RMP. The sponsor should administratively correct this oversight when the RMP documentation is next updated. To this end it will be expected that the updated RMP documentation will be an unadapted EU-RMP, including V.B.8.6 RMP module SVI Additional EU requirements for the

safety specification, and all RMP differences between the EU and Australia should be documented in the ASA accompanying the EU-RMP as per the RMP Questions and Answers (Version 2.0, March 2015). In addition any updated RMP submission requires a summary table of changes between the updated RMP and the last RMP submitted to the TGA.

It was noted that the draft protocols had not been submitted for the following new planned studies in the pharmacovigilance plan:

- GS-US-236-0140 - Clinical study of STB, a TDF containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected ARV treatment naïve patients.
- GS-EU-236-0141 - A Prospective, Observational Drug Utilisation Study of Stribild in Adults With HIV-1 Infection, which is also meant to assess the effectiveness of additional risk minimisation activities conducted for the important identified risk: 'Renal toxicity'.
- Post authorisation safety study of Viread (tenofovir) in a representative sample of HIV-1 infected paediatric patients.
- PBPK simulations of the effect of potent CYP3A4 inhibitors on COBI exposure.
- GS-US-183-1004 - A Phase I, Multiple Dose Study to Evaluate the Pharmacokinetics of Cobicistat Boosted Elvitegravir in Subjects with Decreased UGT1A1 Activity.

The sponsor was asked to provide at least an electronic copy of the draft protocols for these studies to the TGA for review. If they are not yet available the sponsor should provide an assurance that draft protocols for these studies will be provided to the TGA when they become available. The sponsor states: "The studies listed above by the RMP evaluator are Category 4 pharmacovigilance activities in the RMP, and as per the response to question 3, only Category 1 to 3 studies are required to be provided". It is acknowledged that Annex 6 of the EU-RMP only requests 'Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III'. However this EU guideline also states that Category 4 relates to: "Other studies conducted by the marketing authorisation holder (MAH) which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimisation activities". It is considered that such criteria do not apply to the planned clinical studies GS-US-236-0140 and GS-EU-236-0141. Consequently it is reiterated that the sponsor should provide at least an electronic copy of the draft protocols for these studies to the TGA if they have not already been initiated. If they are not yet available the sponsor should provide an assurance that draft protocols for these studies will be provided to the TGA when they become available.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

Clinical Evaluation Report

The safety concerns are accepted.

Key changes to the updated RMP

In their response to the TGA Requests for further information the sponsor provided an updated AU-RMP (Version 1.2, dated 19 January 2015). Key changes from the versions evaluated at Round 1 are summarised below.

Table 8: Key changes from the versions evaluated at Round 1

Key changes from the versions evaluated at Round 1	
AU-RMP	<p>Part II Section 6: 'Additional requirements for the safety specification' was added.</p> <p>Reference to the planned Clinical Study GS-US-174-0127 was removed.</p> <p>Part V Table 1-1. 'Risk Minimisation Measures for Important Identified Risks' was updated.</p> <p>Annex 9. 'Details of additional risk minimisation measures' was added.</p>

Suggested wording for conditions of registration***RMP***

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

"The Stribild Risk Management Plan for Australia (Version 1.2, dated 19 January 2015) must be implemented."

VI. Overall conclusion and risk/benefit assessment

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

This application, seeking approval to update the Stribild product information is supported by pharmacokinetic, efficacy, and safety data from the clinical studies; GS-US-236-0102, GS-US-236-0103, GS-US-236-0135, GS-US-236-0118, GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123.

In further analyses from the two pivotal Phase III studies; GS-US-236-0102 and GS-US-236-0103, the PI has been updated with the addition of 144 week efficacy, resistance, and safety data.

Studies GS-US-236-0115, GS-US-236-0121, and GS-US-236-0123 support an update to the current approved indication to include the use of Stribild in patients who have no known mutations associated with resistance to the individual components of Stribild.

Study GS-US-236-0118 supports an update to the adverse effects section with the addition of 48 week efficacy, resistance, and safety data in HIV-1 infected treatment-naïve patients with mild to moderate renal impairment.

The application also includes an update the pharmacokinetics section of the PI with the addition of drug-drug interaction data from the Phase I Study GS-US-236-0135 telaprevir + Stribild or ritonavir boosted atazanavir + elvitegravir.

The proposed product information was considered acceptable in the second round CER and RMP Evaluation, including Clinical Studies reporting of Week 96 and Week 144 analyses for GS-US-236-0102 and GS-US-236-0103, and clinical study reporting of GS-US-236-0115, a GS-US-236-0123 and GS-US-236-0125, and the proposed indications. The Delegate considers the proposed indications statement does not reflect the population included in clinical studies and the request for ACPM's advice is focused on the extension of indications component of the application.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Delegates' clinical overview

Efficacy

GS-US-236-0115

GS-US-236-0115 is a multi-centre Phase IIIb randomised, open label study to evaluate the efficacy, safety, and tolerability of switching from regimens consisting of a ritonavir boosted protease inhibitor (PI + RTV) plus FTC/TDF (TVD) to STB single tablet regimen in virologically suppressed, HIV-1 infected patients. The study is described in the CER (see Attachment 2).

The study was conducted at 86 sites in US, Canada, Puerto Rico and European countries in the years 2011 to 2013.

The primary objective was to evaluate the non-inferiority of switching to STB relative to staying on baseline regimen (SBR) in maintaining HIV-1 RNA < 50 copies/mL at Week 48 in virologically suppressed, HIV-1 infected subjects. The primary efficacy endpoint was the % of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot analysis.

Subjects were included who were receiving an antiretroviral regimen comprising an NNRTI + FTC/TDF for ≥ 6 consecutive months, with documented undetectable plasma HIV-1 RNA levels preceding the screening visit, and who had never experienced 2 consecutive HIV-1 RNA values above detectable levels after initially achieving virologic suppression on the 1st or 2nd regimen with no prior use of any approved or experimental integrase strand-transfer inhibitor (INSTI), no known resistance to TDF or FTC, and an estimated eGFR_{CG} ≥ 70 mL/min at screening. Documented historical genotype prior to starting initial ARV therapy shows no known resistance to TDF or FTC.

Study treatment in Group 1 was STB was administered orally 1 tablet daily with food at around the same time each day and in Group 2 FTC 200 mg/TDF 300 mg (TVD) plus PI + RTV administered orally in the same manner as before study entry (SBR). Subjects were randomised in a 2:1 ratio to Group 1 or Group 2. 438 randomised subjects received at least 1 dose of study drug (STB: 293; SBR: 140). Of these 433, 11.8% (51) prematurely discontinued study drug before the Week 48 analysis data cut-off (STB 8.5%, 25; SBR 18.6%).

Demographic and baseline characteristics were similar between the 2 treatment groups. The majority were male (85.7%), with a mean age of 41 years (range: 21 to 76); most were White (80.1%) or Black (14-15%). 79.0% (342) had received 1 ARV regimen, 19.2% (83) had received 2 regimens, and 1.8% (8) had received > 2 prior regimens. Atazanavir and darunavir were the most frequently used PI at screening. All subjects had HIV-1 RNA < 50 copies/mL at screening. The mean (standard deviation (SD)) baseline CD4 cell count was 610 (272.9) cells/ μ L.

Adherence to STB was high (median: 99.7%). Most had an adherence rate $\geq 95\%$ up to the Week 48 visit (93.2%). The adherence rate could not be calculated for the SBR Group as ARV drugs other than TVD were not provided by the sponsor.

Results for the primary efficacy endpoint are shown in Table 9. Full analysis set (FAS) virologic success rates at Week 48 were STB 93.8% (272 out of 290) and SBR 87.1% (121 out of 139); the difference in the % of subjects with virologic success (STB – SBR) was 6.7% (95% confidence interval (CI): 0.4 to 13.7); as the lower bound of the 2 sided 95% CI of the difference in response rate was > the prespecified –12% non-inferiority margin, switching to STB was determined to be non-inferior to SBR at Week 48. Statistical superiority of STB over SBR was established because the lower bound of the same 95% CI used to evaluate non-inferiority was > zero, and the difference in virologic success rates was statistically significant ($p = 0.025$). The %s of subjects with virologic failure at Week 48 were low and similar in both groups (STB 0.7%: 2/290; SBR 1.4%: 2 out of 139). A lower % receiving STB had no virologic data in the Week 48 window (STB 5.5%, 16 out of 290; SBR 11.5%, 16/139). Small increases from baseline in CD4 cell counts were seen in both groups. There was no treatment emergent HIV-1 drug resistance in either group.

Table 9: GS-US-236-0115: Analysis sets: virologic outcome at Week 48: HIV-1 RNA cut-off at 50 copies/mL, snapshot algorithm, FAS

HIV-1 RNA Category ^{a,b}	STB (N=290)	SBR (N=139)	STB vs. SBR	
			p-value ^c	Difference in Percentages (95% CI) ^d
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	272 (93.8%)	121 (87.1%)	0.025	6.7% (0.4% to 13.7%)
Virologic Failure at Week 48				
HIV-1 RNA ≥ 50 copies/mL	2 (0.7%)	2 (1.4%)		-0.7% (-4.3% to 1.5%)
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL ^e	0	1 (0.7%)		
No Virologic Data in Week 48 Window				
Discontinued Study Drug Due to AE/Death	5 (1.7%)	2 (1.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^e	11 (3.8%)	14 (10.1%)		
Missing Data During Window but on Study Drug	0	0		

GS-US-236-0121

GS-US-236-0121 is a multi-centre Phase IIb randomised, open label study to evaluate the efficacy, safety, and tolerability of switching from a SBR treatment comprising a NNRTI plus FTC and TDF to the STB single tablet regimen in virologically suppressed, HIV-1 infected patients.

The study is described in Attachment 2. The study was conducted at 72 sites in US, Canada, Puerto Rico and European countries in the years 2011-2013.

The primary objective was to evaluate the non-inferiority of switching to STB relative to staying on SBR in maintaining HIV-1 RNA < 50 copies/mL at Week 48 in virologically suppressed, HIV-1 infected subjects. The primary efficacy endpoint was the % of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot analysis.

Subjects were included who were receiving an antiretroviral regimen comprising an NNRTI + FTC/TDF for ≥ 6 consecutive months, with documented undetectable plasma HIV-1 RNA levels preceding the screening visit, and who had never experienced 2 consecutive HIV-1 RNA values above detectable levels after initially achieving virologic

suppression on the 1st or 2nd regimen with no prior use of any approved or experimental INSTI, no known resistance to TDF or FTC, and an estimated $eGFR_{CG} \geq 70$ mL/min at screening. Documented historical genotype prior to starting initial ARV therapy showing no known resistance to TDF or FTC.

Study treatment in Group 1 was STB was administered orally 1 tablet daily with food at around the same time each day and in Group 2 FTC 200 mg/TDF 300 mg (TVD) plus NNRTI (efavirenz, nevirapine and rilpivirine were the only allowed NNRTI) administered orally in the same manner as before study entry (SBR). Subjects were randomised in a 2:1 ratio to Group 1 or Group 2.

434 of 439 randomised subjects received at least 1 dose of study drug (STB: 291; SBR: 143). Of these 434, 9.2% (40 subjects) prematurely discontinued study drug prior to the Week 48 analysis data cut-off date (STB 7.6%/22; SBR 12.6%/18).

Demographic and baseline characteristics were generally similar in the 2 treatment groups. The majority of subjects were male (92.6%), with a mean age of 41 years (range: 20 to 72), most were White (76 to 80%) or Black (16 to 17%). All subjects had HIV-1 RNA < 50 copies/mL at screening. The mean (SD) baseline CD4 cell count was 588 (214.9) cells/ μ L. Before screening, 90.6% (393) had received 1 ARV regimen, 9.0% (39) 2 regimens, and 0.5% (2) > 2 regimens.

Adherence to STB was high (median: 99.7%). Most had an adherence rate $\geq 95\%$ up to the Week 48 visit (91.1%). The adherence rate could not be calculated with SBR as ARV components other than TVD were not provided by the sponsor.

Results for the primary efficacy endpoint are shown in Table 10. FAS virologic success rates were STB 93.4% (271 out of 290 subjects) and SBR 88.1% (126 out of 143). The difference in the %s of subjects with virologic success (STB – SBR) was 5.3% (95% CI: -0.5% to 12.0%). Because the lower bound of the 2 sided 95% CI of the difference in response rate was > the prespecified -12% non-inferiority margin, switching to STB was determined to be non-inferior to SBR at Week 48. %s of subjects with virologic failure at Week 48 were low and similar in the 2 groups: STB 1.0% (3 out of 290); SBR (0.7% 1 out of 143; difference [95% CI] in %s [STB – SBR] 0.3% [-2.8% to 2.5%]). A lower % of subjects receiving STB than SBR had no virologic data in the Week 48 window (STB 5.5%, 16 out of 290; SBR 11.2%, 16 out of 143). Small increases from baseline in CD4 cell counts were seen in both groups. There was no treatment emergent HIV-1 drug resistance in either group.

Table 10: GS-US-236-0121: Analysis sets: virologic outcome at Week 48: HIV-1 RNA cut-off at 50 copies/mL, Snapshot algorithm, FAS

HIV-1 RNA Category ^a	STB (N=290) ^b	SBR (N=143)	STB vs. SBR	
			p-value ^c	Difference in Percentages (95% CI) ^d
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	271 (93.4%)	126 (88.1%)	0.066 ^b	5.3% (-0.5% to 12.0%)
Virologic Failure at Week 48				
HIV-1 RNA ≥ 50 copies/mL	3 (1.0%)	1 (0.7%)		0.3% (-2.8% to 2.5%)
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL ^d	1 (0.3%)	0		
No Virologic Data in Week 48 Window				
Discontinued Study Drug Due to AE/Death	16 (5.5%)	16 (11.2%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^e	5 (1.7%)	1 (0.7%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL ^d	11 (3.8%)	13 (9.1%)		
Missing Data During Window but on Study Drug	0	2 (1.4%)		

GS-US-236-0123

GS-US-236-0123 is a Phase 3B open label pilot study to evaluate switching from a regimen comprising RAL plus FTC/TDF (TVD) to STB in virologically suppressed, HIV-1 infected patients. The Study is described in the CER (please see Attachment 2).

The study was conducted at 7 centres in the US between January 2012 and August 2013. The primary objectives was to evaluate the efficacy of STB after switching from a regimen consisting of RAL plus FTC/TDF at baseline in maintaining HIV-1 RNA < 50 copies/mL at Week 12.

Subjects were included HIV-1 infected adults who had been virologically stable on their current 1st ARV regimen comprising only RAL twice daily plus FTC/TDF continuously for ≥ 6 months before screening. Subjects were required to have documented undetectable plasma HIV-1 RNA levels for ≥ 6 months before screening, never to have experienced 2 consecutive detectable HIV-1 RNA levels after having achieved a confirmed undetectable HIV-1 RNA level on the 1st regimen, to have plasma HIV-1 RNA < 50 copies/mL at screening, and to have no known resistance to any of the study agents as demonstrated by HIV-1 genotyping at screening.

All subjects received STB orally, once daily, with a meal. 48 subjects were enrolled and all completed the study.

The majority of subjects were male (95.8%) and White (83.3%). The mean age was 44 years (range: 23 to 58). The majority (95.8%) had HIV-1 RNA < 50 copies/mL. Two subjects had HIV-1 RNA 50-< 200 copies/mL. The mean (SD) CD4 cell count was 711 (265.9) cells/μL. The mean duration for which subjects had received RAL was 31.6 months.

Results for the primary efficacy endpoint was that all subjects maintained virologic success at Week 12 and that in all, HIV-1 RNA was < 50 copies/mL. Data are provided showing that all subjects maintained virologic success at Weeks 24 and 48, and that in all, HIV-1 RNA was < 50 copies/mL. One subject had HIV-1 RNA ≥ 50 copies/mL during the study. This occurred at Week 8 and HIV-1 RNA was 59 copies/mL. At Week 48, mean (SD)

CD4 cell counts were 733 (270.1) cells/ μ L, and the mean (SD) change from baseline 23 (144.6) cells/ μ L. There was no development of drug resistance.

Safety

GS-US-236-0115

In Study GS-US-236-0115 the safety analysis set comprised 293 subjects receiving STB and 140 receiving SBR (ritonavir boosted Pin plus FTC/TDF). The majority of subjects in each group received study drug for \geq 144 weeks (STB: 82.6%, 242 out of 293; SBR: 78.6%, 110 out of 140).

Adverse events are summarised in Table 11. Higher %s in the switch group (STB) had any AE reported: STB 79.2%/232 of 293 subjects; SBR 74.3%, 104 out of 140) and any AE assessed as treatment related (STB: 24.9%, 73 out of 323; SBR 6.4%, 9 out of 140). The clinical evaluator considered this to be expected when changing to a new treatment regimen. STB and SBR were generally well tolerated as shown by infrequent discontinuations due to AEs and low incidence of study drug related SAEs. There were no clinically significant renal events (that is, SAEs or AEs leading to discontinuation) with STB. No new safety issues were identified.

Table 11: GS-US-236-0115: Overall summary of adverse events (safety analysis set)

Adverse Event Category, n (%) ^{a,b}	STB (N=293)	SBR (N=140)
Subjects Experiencing Any Treatment-Emergent Adverse Event	232 (79.2%)	104 (74.3%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	133 (45.4%)	57 (40.7%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	12 (4.1%)	11 (7.9%)
Subjects Experiencing Any Treatment-Emergent Study Drug Related Adverse Event	73 (24.9%)	9 (6.4%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug Related Adverse Event	11 (3.8%)	2 (1.4%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug Related Adverse Event	2 (0.7%)	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	17 (5.8%)	9 (6.4%)
Subjects Experiencing Any Treatment-Emergent Study Drug Related Serious Adverse Event	2 (0.7%)	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	6 (2.0%)	4 (2.9%)
Subjects who had Treatment-Emergent Death	0	1 (0.7%)

GS-US-236-0121

In Study GS-US-236-0121 the safety analysis set comprised 291 subjects receiving STB and 143 receiving SBR (NNRTI plus FTC and tenofovir DF). The median duration of exposure to study drug was 60.6 weeks (48.6 to 72.9 weeks) with STB and 61.0 weeks (48.1 to 73.7 weeks) with SBR. The majority of subjects in each group received study drug for \geq 48 weeks (STB 84.9%, SBR 81.8%).

Adverse events are summarised in Table 12. Higher %s in the switch group (STB) had any AE reported (STB 81.4%, 237 out of 291; SBR 74.8%, 107 out of 143) and any AE considered related to study drug by the investigator (STB 23.4%/68; SBR 6.3%/9). The clinical evaluator considered this to be expected when changing to a new treatment regimen. STB and SBR were generally well tolerated as shown by infrequent discontinuations due to AEs and low incidence of study drug related SAEs. 2 subjects

receiving STB had renal AEs (acquired Fanconi syndrome and increased blood creatinine) resulting in discontinuation. No new safety issues were identified.

Table 12: GS-US-236-0121: Overall summary of adverse events (safety analysis set)

Adverse Event Category, n (%) ^{a,b}	STB (N=291)	SBR (N=143)
Subjects Experiencing Any Treatment-Emergent Adverse Event	237 (81.4%)	107 (74.8%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	111 (38.1%)	49 (34.3%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	19 (6.5%)	9 (6.3%)
Subjects Experiencing Any Treatment-Emergent Study Drug Related Adverse Event	68 (23.4%)	9 (6.3%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug Related Adverse Event	16 (5.5%)	2 (1.4%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug Related Adverse Event	2 (0.7%)	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	14 (4.8%)	6 (4.2%)
Subjects Experiencing Any Treatment-Emergent Study Drug Related Serious Adverse Event	0	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	6 (2.1%)	1 (0.7%)
Subjects who had Treatment-Emergent Death	1 (0.3%)	0

GS-US-236-0123

In Study GS-US-236-0123 the safety analysis set comprised 48 subjects all of whom received STB. The median duration of exposure to study drug was 48.1 weeks. All subjects received study drug for > 44 weeks and 58.3% received study drug for > 48 weeks.

Adverse events are summarised in Table 13. Safety conclusions were that Stribild was well tolerated in this study, as evidenced by the absence of discontinuations due to AEs and study drug related SAEs. There were no clinically relevant changes from baseline in renal parameters. No subject had laboratory findings consistent with proximal renal tubulopathy (PRT).

Table 13: GS-US-236-0123: Overall summary of adverse events (safety analysis set)

Adverse Event Category, n (%) ^a	STB (N=48)
Subjects Experiencing Any Treatment-Emergent Adverse Event	43 (89.6%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	2 (4.2%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	16 (33.3%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug	12 (25.0%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug	0
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event Related to Study Drug	1 (2.1%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	1 (2.1%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event Related to Study Drug	0
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Permanent Discontinuation of Study Drug	0
Subjects Who Had Treatment-Emergent Death	0

Benefit risk assessment

The clinical evaluation benefit risk assessment is provided in Attachment 2.

In studies GS-US-236-0115 and GS-US-236-0121, high rates of virologic suppression were maintained to Week 48 in subjects who switched to STB and in those who remained on

their baseline regimens containing a PI + RTV + FTC/TDF or an NNRTI + FTC/TDF. In each study, results of the primary efficacy analysis using the FDA defined snapshot algorithm demonstrated that switching to STB was non-inferior to staying on the baseline regimen. In study GS-US-236-0115, statistical superiority of STB over SBR (PI + RTV + FTC/TDF) was shown.

In the single-group study GS-US-236-0123, 100% of subjects who switched to STB from RAL + FTC/TDF had virologic success at Week 48.

There was no treatment emergent HIV-1 drug resistance in studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123 either in subjects switching to STB or in those who stayed on their baseline regimen through the 48 week treatment periods.

In studies GS-US-236-0115 and GS-US-236-0121, there were a higher % of subjects who switched to STB experiencing an AE assessed as treatment related. The AEs were consistent with the known profile. Only a few of these were Grade 3 events and there were no Grade 4 events. Discontinuations due to AEs were infrequent. Overall STB was generally well tolerated in subjects who switched and there were no new safety issues identified.

In study GS-US-236-0123 STB was well tolerated. Nearly all AEs were Grade 1 or 2 in severity with only two Grade 3 and none Grade 4. No subject discontinued due to an AE.

Clinical evaluator's recommendation

The clinical evaluator's conclusion and recommendation was that the studies provided support the use of STB in virologically suppressed subjects.

Risk management plan

The second round RMP Evaluation notes an administrative oversight in the revised AU-RMP which does not include suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness.

The second round RMP Evaluation recommends that the sponsor should provide at least an electronic copy of the draft protocols, for new planned studies in the pharmacovigilance plan, to the TGA if they have not already been initiated.

ACSOM advice was not sought for this submission.

Risk-benefit analysis

The proposed PI in the sponsor's response including the proposed indication was considered acceptable in the second round clinical and RMP evaluation. The Delegate considers the proposed indications statement does not reflect the population included in clinical studies and the request for ACPM's advice is sought focused on the extension of indications aspect of the application.

Three clinical studies have been submitted virologically suppressed (HIV-1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen to support the extension of indications.

Stribild is indicated as a single tablet regimen for the treatment of HIV infection and reasons for a switch in regimen will include treatment simplification. HIV treatment guidelines emphasise that key principles of regimen switch in this setting is to maintain virological response without compromising future options and that a patient's prior

treatment history and responses to ART, resistance profiles, and drug tolerance should be considered when contemplating a regimen switch.

The ACPM considered an application for Eviplera³ (tenofovir DF/ emtricitabine/ rilpivirine single tablet regimen for an extension of indications based on clinical studies in virologically suppressed (HIV-1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen. The ACPM recommended

“Eviplera is indicated for the treatment of HIV-1 infection in treatment-naïve adult patients with plasma HIV-1 RNA < 100,000 copies/mL at the start of therapy.

Eviplera is also indicated in certain virologically suppressed (HIV-1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see CLINICAL TRIALS). Patients must not have a history of resistance to any of the components of Eviplera (tenofovir DF, emtricitabine or rilpivirine).”

Delegate’s considerations

The Delegate considered the current ‘Indications’ statement proposed in this application for Stribild should be amended as follows:

“Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment naive adults. Stribild is also indicated in certain virologically suppressed (HIV-1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see Clinical Trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the components of Stribild (tenofovir DF, emtricitabine or elvitegravir).”

The draft PI submitted with the sponsor’s response is considered acceptable except for proposed indications.

Summary of issues

This application proposes an extension of indications to include the use of Stribild in patients who have no known mutations associated with resistance to the individual components of Stribild.

The extension of indications is supported by Studies GS-US-236-0115, GS-US-236-0121, and GS-US-236-0123. These studies involve certain virologically suppressed (HIV-1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen.

The Delegate considers the proposed indications statement does not reflect the population included in clinical studies. A more appropriate extension of indications statement would be:

“Stribild is also indicated in certain virologically suppressed (HIV-1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see Clinical Trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the components of Stribild (tenofovir DF, emtricitabine or elvitegravir).”

³ ACPM considered the submission PM-2013-01524-1-2 for extension of indications of Eviplera in April 2014

Proposed action

The Delegate had no reason to say, at this time, that the application for Stribild should not be approved for registration, subject to finalisation of wording of the extension of indications.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. What is the view of ACPM on the proposed extension of indications statement “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”?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Gilead supports the proposed actions of the Delegate with regards to the approval of the application but disagree with the alternative wording proposed by the Delegate for the updated indication for Stribild tablets for inclusion to the Australian PI, as follows:

‘Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment naïve adults. Stribild is also indicated in certain virologically suppressed (HIV1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see Clinical Trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the components of Stribild (tenofovir DF, emtricitabine or elvitegravir)’.

For the reasons discussed further below, Gilead would like to propose the following indication for Stribild for consideration by the Delegate:

‘Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults or adults who have no known mutations associated with resistance to the individual components of Stribild (see CLINICAL TRIALS)’.

Gilead believes that this proposed indication states the therapeutic application of the medicine clearly and concisely, and includes the mandatory conditions of product usage with regards to patients with no known mutations associated with resistance to the individual components.

Summary

Stribild tablets were originally approved in Australia on 7 February 2013, and are currently indicated for the treatment of HIV-1 infection in treatment naïve adults.

More data have since become available in HIV-1 infected antiretroviral (ARV) treatment naïve patients in which Stribild has demonstrated potent and durable antiviral efficacy through 144 Weeks of treatment in Studies GS-US-236-0102 and GS-US-236-0103. New data has become available in virologically suppressed, HIV-1 infected adult patients who switched to Stribild from various ARV regimens including protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI), and INSTI (raltegravir; RAL) based regimens in Studies GS-US-236-0115, GS-US-236-0121, and GS-US-236-0123 (to 48 weeks), respectively. Collectively, the nature of switch studies support an integrated assessment of the benefits and risks of switching treatment to Stribild from PI, NNRTI, or INSTI (RAL) based ARV regimens.

As such, Gilead proposes to include data from these studies in the Stribild PI, and to extend the indication for Stribild to include patients who have no known mutations associated with resistance to the individual components of Stribild.

Gilead believes that our proposed extension of the Stribild indication is consistent with clinical decision making practice of selecting which antiretroviral agent(s) to use in patients from a resistance standpoint, which is primarily based on whether or not the virus has documented or suspected resistance, rather than whether the patient is treatment naive or experienced. In addition, our proposed indication has the potential to benefit the most patients with a treatment option that has been demonstrated to be efficacious, safe, and well tolerated, particularly for those patients who cannot tolerate their current regimen, or who wish to simplify their regimen.

The revised indication proposed by Gilead for the Australian PI is in line with the currently approved indication for Stribild in the EU.

Discussion of delegate's comments

Indication statement

The Delegate requests advice from the ACPM specifically with regard to the acceptability of the indication statement proposed by Gilead. The Delegate has noted that there is no reason, at this time that the application for Stribild should not be approved subject to finalisation of wording of the extension indications. The Delegate has recommended the indication to be amended as follows:

'Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults. Stribild is also indicated in certain virologically suppressed (HIV - 1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see Clinical Trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the components of Stribild (tenofovir DF, emtricitabine or elvitegravir).'

While Gilead agrees with the Delegates assessment that the application should be approved, the wording of the indication statement proposed by the Delegate is unnecessarily restrictive, and may result in patients who cannot tolerate their current ARV regimen, or who could benefit from ARV regimen simplification being deprived of a treatment option that has been demonstrated to be efficacious, safe, and well tolerated. The indication statement is critical in defining patient access, especially in a constantly evolving reimbursement environment and in providing patients who are in need of antiviral treatments with the best therapeutic options available.

The *'Form for providing product information for a restricted medicine or other medicine in relation to which the secretary requires product information to be provided'* (approved under subsection 7D(1) of the Therapeutic Goods Act 1989 (the Act)), states that the therapeutic application of the medicine should be stated clearly and concisely, include the mandatory conditions of product usage, where relevant, or be covered more appropriately in other parts of the PI.

As such, the indication section of the Australian PI should solely state the intended indication of the product, and information regarding the population included in clinical studies should be more appropriately presented within the clinical trials section of the Australian PI. Furthermore, HIV-1 RNA < 50 copies/mL is regarded as the optimal outcome of highly active antiretroviral therapy (HAART) and is the currently accepted threshold for complete suppression of HIV-1 replication therefore does not require inclusion within an indication statement.

As such Gilead maintains that the data presented in this application support extension of the Stribild indication to include patients who have no known mutations associated with resistance to the individual components of Stribild and proposes the following indication:

Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults or adults who have no known mutations associated with resistance to the individual components of Stribild (see CLINICAL TRIALS).

This proposed indication states the therapeutic application of the medicine clearly and concisely, and includes the mandatory conditions of product usage with regards to patients with no known mutations associated with resistance to the individual components.

As therapy with Stribild would be initiated by a physician who is experienced in the management of HIV infection, the reference to the CLINICAL TRIALS section of the PI will guide the physician to the data that supports the use of Stribild in the relevant populations to allow the appropriate prescribing choices.

The data provided within this application demonstrated in Studies GS-US-236-0115 and GS-US-236-0121, high rates of virologic suppression were maintained at Week 48 in patients who switched to Stribild and in those who remained on their baseline regimens containing a PI + RTV + FTC/TDF or an NNRTI + FTC/TDF. In each study, results of the primary efficacy analysis demonstrated that switching to Stribild was non-inferior to staying on the baseline regimen. In Study GS-US-236-0115, statistical superiority of Stribild over SBR (PI + RTV + FTC/TDF) was established. In the single group Study GS-US-236-0123, 100% of subjects who switched to Stribild from RAL + FTC/TDF had virologic success at Week 48. There was no treatment emergent HIV-1 drug resistance in studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123 either in subjects switching to Stribild or in those who stayed on their baseline regimen through the 48 Week treatment periods.

As such the clinical evaluation recommendation and RMP evaluator recommendation both agree that the clinical data presented by Gilead support an update to the indication to include use in patients who have no known mutations associated with resistance to the individual components of Stribild.

Gilead notes that the Delegate has drawn a direct comparison to the current TGA approved indication of Eviplera (tenofovir disoproxil fumarate 300 mg / emtricitabine 200 mg / rilpivirine 25 mg) tablets. Eviplera in addition to Atripla (tenofovir disoproxil fumarate 300 mg / emtricitabine 200 mg / efavirenz 600 mg) Tablets are NNRTI/NRTI⁴ based single tablet regimens (STRs) approved for once daily administration in the treatment of HIV-1 infection. However Stribild was the first approved INSTI based STR for the treatment of HIV-1 infection and has demonstrated both potent antiviral efficacy and a safety and tolerability profile that offer advantages over the currently recommended first line NNRTI and PI based ARV regimens:

- Potent and durable antiviral suppression regardless of baseline viral load.
- For a significant number of patients, NNRTIs (efavirenz (EFV) and rilpivirine (RPV)) are intolerable due to adverse reactions.
- A significant number of patients wish to avoid using EFV due to concerns about tolerability.

⁴ NRTI = nucleoside or nucleotide reverse transcriptase inhibitor

Stribild is a recommended initial ARV regimen in the US Department of Health and Human Services (DHHS)⁵, British HIV Association (BHIVA)⁶ guidelines and European AIDS Clinical Society (EACS) Guidelines.⁷ Stribild is thus a potential option for patients receiving ARV treatment who are unable to tolerate their current PI, NNRTI, or INSTI based ARV regimen, or who wish to simplify their regimen for the convenience of a once daily single tablet regimen (STR) that has been demonstrated to be efficacious, safe, and well tolerated.

A desire to simplify the current anti-HIV regimen was cited as a reason to enrol by a large majority of patients in Studies GS-US-236-0115 (85.7%) and GS-US-236-0123 (95.8%). Regimen simplification was cited by a lower percentage of patients in Study GS-US-236-0121 (48.2%), likely reflecting current use/availability of NNRTI based STRs. Higher percentages of patients in Study GS-US-236-0121 compared with Study GS-US-236-0115 cited reasons to enrol in relation to concern about the long-term side effects of the current anti-HIV regimen (19.8% and 12.2%, respectively), and intolerance of the current regimen because of side effects (13.6% and 3.2%, respectively). These differences likely reflect known differences in the tolerability profiles of agents in the NNRTI and PI classes.

Conclusion

Stribild provides an option for patients receiving ARV treatment but who cannot tolerate their current regimen, or who could benefit from regimen simplification. This application provides efficacy, safety, and tolerability data from virologically suppressed patients infected with HIV-1 who switched to Stribild from their baseline therapy of PI + RTV + FTC/TDF, NNRTI + FTC/TDF, or RAL + FTC/TDF based on the newly available data from the Studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123, respectively. In each of these studies, Stribild was well tolerated and high rates of virologic suppression were maintained for subjects following a switch to Stribild. Gilead maintains that the data presented in this application support extension of the Stribild indication to include patients who have no known mutations associated with resistance to the individual components of Stribild, which is consistent with the way ARV's are used in clinical practice.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (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 resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Stribild fixed dose combination tablet containing 300 mg tenofovir DF (which is equivalent to 245 mg of tenofovir disoproxil); 200 mg emtricitabine; 150 mg of elvitegravir; and 150 mg of cobicistat to have an overall positive benefit-risk profile for the amended indication;

Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment naive adults. Stribild is also indicated in certain virologically suppressed (HIV-1 RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen

⁵ Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Revised April 8 2015. Available at: <http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0>

⁶ Williams I et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). *HIV Med* 2014;15 Suppl 1:1-85.

⁷ European AIDS Clinical Society (EACS). Guidelines. Version 7.1. November 2014.

(see Clinical Trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the components of Stribild (tenofovir DF, emtricitabine or elvitegravir).

In making this recommendation the ACPM was of the view that the Delegate's amended indication is supported by the data presented.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *What is the view of ACPM on the proposed extension of indications statement "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"?*

The ACPM noted that the sponsor's proposed indication would extend use of Stribild to patients who had prior treatment failure, were treatment intolerant or wanted to change treatment for personal preference, without regard to virological control status. The ACPM noted that the data to support the proposed indication were derived from 'switching studies' which excluded salvage treatment that is patients failing their current regimens. The ACPM noted that patients failing other regimens but having no resistance to the three anti-retroviral components of Stribild could be considered analogous to naïve patients with respect to their likelihood of benefit from Stribild but no data were provided to support this. The ACPM considered that the wording of the FDA indication, which includes virologic status, reflected the absence of such data. The ACPM advised that the indication proposed by the Delegate was more appropriate as it targeted the population in whom efficacy had been demonstrated.

The ACPM advised that 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.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Stribild containing (combined 300mg tenofovir disoproxil fumarate, 200 mg emtricitabine, 150 mg elvitegravir and 150 mg cobicistat) tablet, indicated for:

Stribild is indicated as a single tablet regimen for the treatment of HIV infection in treatment-naïve adults. Stribild is also indicated in certain virologically suppressed (HIV RNA < 50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see Clinical Trials). Patients must not have a history of treatment failure or known mutations associated with resistance to the antiretroviral components of Stribild (tenofovir DF, emtricitabine or elvitegravir).

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 of registration applying to these goods

The Stribild containing (combined 300mg tenofovir disoproxil fumarate, 200 mg emtricitabine, 150 mg elvitegravir and 150 mg cobicistat) tablet, Risk Management Plan (RMP); Version: 2.0, dated 30 June 2015, included with submission PM2014- 01079-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Stribild approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

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