



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for tenofovir disoproxil fumarate / emtricitabine

Proprietary Product Name: Truvada

Sponsor: Gilead Sciences Australia Pty Ltd

November 2016

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Common abbreviations

Abbreviation	Meaning
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ART	antiretroviral therapy
ASHM	Australasian Society for HIV Medicine
BMD	bone mineral density
CASI	computer-assisted structured interview
CDC	Centre for Disease Control
CI	confidence interval
DAIDS	NIH Division of AIDS
DEXA	dual-energy X-ray absorptiometry
DSMB	Data Safety Monitoring Board
EAE	expedited adverse event
FDA	Food and Drug Administration (US)
FDC	fixed dose combination
FTC	emtricitabine
FTC/TDF	emtricitabine and tenofovir disoproxil fumarate (Truvada®)
GCP	Good Clinical Practice
GMSM	gay men who have sex with men
HBsAg+	hepatitis B surface antigen positive
HBV	hepatitis B virus
HIV-1	human immunodeficiency virus (type 1)
HR	hazard ratio
HSV-2	herpes simplex virus type 2

Abbreviation	Meaning
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Index subject	HIV-1 infected subject in a serodiscordant heterosexual couple
iPrEx	Pre-exposure Prophylaxis Initiative (Study CO-US-104-0288)
IQR	interquartile range
ITT	intent to treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MSM	men who have sex with men
N/A	not applicable
NIH	National Institute of Health (US)
NNDSS	Australian National Notifiable Disease Surveillance System
NRTI	nucleoside reverse transcriptase inhibitor
Partners PrEP	Partners Pre-exposure Prophylaxis Study (CO-US-104-0380)
Partner subject	HIV-1 uninfected subject in a serodiscordant heterosexual couple
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
PSUR	periodic safety update report
PT	preferred term

Abbreviation	Meaning
REMS	Risk Evaluation and Mitigation Strategy
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
SIV	simian immunodeficiency virus
SOC	system organ class
STD	sexually transmitted disease
TDF	tenofovir disoproxil fumarate
TFV-DP	tenofovir diphosphate
ULN	upper limit of normal
URAI	unprotected receptive anal intercourse
US	United States
WHO	World Health Organization

Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	2 May 2016
<i>Date of entry onto ARTG</i>	6 May 2016
<i>Active ingredient(s):</i>	Tenofovir disoproxil fumarate/emtricitabine
<i>Product name(s):</i>	Truvada
<i>Sponsor's name and address:</i>	Gilead Sciences Pty Ltd Level 6 / 417 St Kilda Road Melbourne VIC 3004
<i>Dose form(s):</i>	Film coated tablet
<i>Strength(s):</i>	300 mg tenofovir disoproxil fumarate / 200 mg emtricitabine
<i>Container(s):</i>	High-density polyethylene (HDPE) bottle
<i>Pack size(s):</i>	30 tablets
<i>Approved therapeutic use:</i>	<i>Pre-Exposure Prophylaxis</i> <i>Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples (see CLINICAL STUDIES)</i>
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	One tablet daily
<i>ARTG number (s):</i>	107072

Product background

This AusPAR describes a submission by the sponsor (Gilead Sciences) to register Truvada for a Human Immunodeficiency Virus type-1 (HIV-1) pre-exposure prophylaxis (PrEP) in HIV negative adults with high risk of acquiring infection. In addition, the sponsor proposes modifications of the currently approved indication to bring the product into line with other Gilead Sciences HIV-1 products approved in Australia. A number of additional changes to the PI are also proposed.

Truvada is a fixed dose combination product containing tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg. TDF and FTC belong to the nucleotide and nucleoside reverse transcriptase inhibitor (NRTI) group of anti-HIV drugs.

In Australia, Truvada has been approved as a treatment for HIV-1 infection since 2005 with the Australian Register of Therapeutic Goods (ARTG) number 107071 for the following indication:

Truvada is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of VIREAD and EMTRIVA in treatment-naïve and treatment-experienced adults.

The proposed modification of the current indication removes the qualifier statement:

Truvada is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.

The proposed new indication of HIV-1 pre-exposure prophylaxis is:

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples (see CLINICAL STUDIES).

The proposed Truvada dosing in PrEP is one tablet daily. This dosing regimen (TDF/FTC 300 mg/200 mg one tablet daily) is the same as that currently approved in the treatment of HIV-1 infection (in combination with other antiretroviral agents). The submission does not include any study or data examining an optimal dosing regimen specifically for PrEP.

TDF and FTC have long half-lives enabling once daily dosage. The mean plasma half-life ($t_{1/2}$) of FTC and TDF is 10 and 17 hours respectively. TDF is an inactive pro-drug of tenofovir diphosphate (TFV-DP) that in turn has a mean plasma $t_{1/2}$ in peripheral blood mononuclear cells (PBMCs) of 87 to 150 hours. Both drugs are also stated to achieve high concentrations in male and female genital tracts.

In Australia, in 2014, the estimated HIV population prevalence in persons ≥ 15 years of age is 0.14%. Over the last 5 years, the incidence of new HIV infection was 4.2 (2010), 4.5 (2011), 4.7 (2012), 4.5 (2013) and 4.7 (2014) cases per 100,000 of population.¹

According to the information provided by the sponsor (based on Kirby Institute data) PrEP is currently used by 2,568 MSM and bisexual men in Australia. It is estimated that 5,611 are likely to use PrEP in the near future (Table 1).

Table 1: Sponsor provided estimate of number of men who currently use and are likely to use PrEP in the near future

Indicator	Estimated number		
	Among gay/ homosexual GMSM	Among bisexual/ other GMSM	Total
Current PrEP use			
Estimated number of men who reported any use of ARVs before sex to prevent them from getting infected with HIV ¹	1,914	648	2,568
Potential PrEP use in the near future			
Estimated number of likely users	3,739	1,871	5,611

¹ This is not an estimated number of daily PrEP users, but rather of men who have ever tried an antiretroviral drug for PrEP (off-label use of medication). This number is based on the indicator of off-label PrEP use in GCPS and is prone to bias and over-reporting due to a poor knowledge of GCPS participants about PrEP and common confusion with postexposure prophylaxis (PEP).

¹ HIV, viral hepatitis and sexually transmissible infections in Australia. Kirby Institute, UNSW Sydney: *Annual Surveillance Report 2015*

No estimates were available for use in heterosexual, HIV discordant couples which is also the identified high risk group in the proposed indication in addition to MSM.

Regulatory status

Australian regulatory history

Truvada was first registered in Australia for use in the treatment of HIV-1 infection in adults on 22 September 2005. The product had its indication revised to include PrEP on the Australian Register of Therapeutic Goods (ARTG) on 6 May 2016.

Overseas regulatory history

At the time the TGA considered this application, a similar application had been approved by the US FDA on 16 July 2012 for the following indication:

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples [See Clinical Studies (14.2, 14.3)].

This followed a request by the FDA to Gilead to make a submission for the PrEP indication. Truvada has also been approved for the PrEP indication in France (November 2015), South Africa (November 2015), Canada (February 2016) and Peru (April 2016).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared 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>.

Quality findings

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

Nonclinical findings

Introduction

The relevant nonclinical dossier studies consisted of a series of primary pharmacology 'proof of concept' studies involving HIV infection in humanised BLT² mice and simian immunodeficiency virus (SIV) or simian-human immunodeficiency virus (SHIV) (susceptible and antiviral resistant strains) infection in macaques. In general, worst case infectious challenge doses were used (infectious challenge roughly consistent with semen viral load during primary HIV viraemia). However, overall the nonclinical primary

² Humanised BLT (Bone Marrow-Liver-Thymus) mice are an immunodeficient NOD/SCID mice strain that undergo human CD34+ haematopoietic stem cell, human liver and thymus tissue transfer, subsequently developing a human haemato-lymphoid system that provides a good model for the study of HIV and other viral-induced human immune responses.

pharmacology studies are somewhat biased in favour of efficacy since infectious challenge was typically timed to coincide with time taken for maximum drug plasma concentration (T_{max}).

The prophylactic use of Truvada provides imperfect protection from transmission of HIV, SIV and SHIV in animal models. The most common overall effect was to delay the onset of detectable infection following repeated infectious challenge over time (generally once per week for 14 weeks). Truvada does not provide absolute protection from infection in every study in the animal models examined; however, there are examples of 100% efficacy in some studies. It is notable that the experimental power of the available nonclinical primary pharmacology studies was often low. Overall, the nonclinical primary pharmacology provides good proof of concept that pre-exposure prophylaxis will achieve the general aims of the requested extension of indication to prophylactically reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

In some of the nonclinical studies, the combined prophylactic use of both tenofovir disoproxil fumarate and emtricitabine often has greater efficacy than the use of either agent alone. The combination of two different NRTIs also appears to retain adequate efficacy in the presence of NRTI-resistant viral strains.

The oral doses used in the monkey studies (typically emtricitabine 20 mg/kg/day with tenofovir disoproxil fumarate 22 mg/kg/day) achieved plasma and intracellular drug levels comparable to those seen clinically in humans undergoing oral treatment with Truvada, however, it should be noted that the nonclinical studies have relied upon SHIV and SIV infection in monkeys and various HIV isolates in humanised mice. The strict quantitative relationships between these models and human HIV infection are uncertain. Accordingly the nonclinical pharmacology data should be regarded mostly as a 'proof of concept' rather than a strictly quantitative predictor of the human clinical situation.

While it is difficult to draw definitive conclusions from the available nonclinical data, the timing of prophylaxis relative to infection and route of prophylactic dosing appear to be important. Optimal prophylaxis in macaques at risk of SHIV_{SF162P3} infection appears to result from either daily subcutaneous (SC) dosing with emtricitabine (20 mg/kg/day) in combination with tenofovir disoproxil fumarate (22 mg/kg/day) starting between 7 to 9 days before the first viral exposure and continuing for 28 days following the last viral exposure or SC dosing with emtricitabine (20 mg/kg/day) in combination with tenofovir disoproxil fumarate (22 mg/kg/day) 2 h before and 24 h after weekly intra-rectal viral exposure. Both SC dosing regimens provided 100% protection after 14 weeks of once per week intra-rectal viral exposure. In this model, daily oral prophylaxis using emtricitabine (20 mg/kg/day) in combination with tenofovir disoproxil fumarate (22 mg/kg/day) starting 7 to 9 days before the first viral exposure and continuing for 28 days after the last viral exposure was less effective than either of the SC dosing regimens. Presumably, this reflects lower systemic bioavailability following oral (PO) dosing however the statistical power of these studies is relatively small.

In one study most (but not all) breakthrough infections were associated with infectious challenge occurring during a period of low plasma drug concentrations. Based on the nonclinical data, breakthrough infections can rarely occur even in the presence of high plasma drug concentrations. Notably, tenofovir disoproxil fumarate is a pro-drug. The potential issues regarding metabolism and breakthrough infection were not explored in the nonclinical studies.

Nonclinical summary and conclusions

Overall, the available nonclinical data provide good proof of the concept that Truvada can reduce the risk of HIV transmission in humanised mice and intra-rectal SIV and SHIV

transmission in monkeys in the face of biologically plausible infectious doses. In some studies, prevention of transmission is possible over relatively short periods (up to 14 weeks with weekly infectious exposure). Prophylaxis is dependent on timing, and dosing regimen. SC dosing appears to be more efficacious than PO dosing. There are no nonclinical objections to the proposed extension of indications for emtricitabine/tenofovir disoproxil fumarate (Truvada) to HIV-1 pre-exposure prophylaxis.

Clinical findings

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

Introduction

Clinical rationale

Up to 3 million new cases of HIV are diagnosed worldwide each year. The prevalence of HIV-1 infection remains high despite widespread public health campaigns which promote the use of safer sex practices and condoms. Combination antiretroviral therapy (ART) can now effectively suppress viral replication and maintain good health for extended periods, and it has the potential to reduce transmission to uninfected sexual partners. The value of post-exposure prophylaxis (PEP) with ART has been established in macaque monkeys infected with SIV, with occupational exposure to HIV-1 in healthcare workers, and with mother-to-child transmission. However, until recently, prevention of infection following sexual exposure in humans has not been demonstrated in large controlled clinical studies.

Truvada is given as a once daily tablet in combination with other agents for the treatment of HIV-1 infection. Studies in macaques have shown that the FTC/TDF combination prevents or delays viraemia better than either individual component when administered before or shortly after rectal inoculation with SIV.³ Pre exposure combined with post exposure was also highly effective in preventing viral transmission in this animal model. NRTIs such as Truvada are potent but well tolerated with long half-lives enabling once daily dosage. They also achieve high concentrations in male and female genital tracts.

Truvada was approved by the FDA for PrEP in July 2012 following the publication of two significant controlled trials. Based on this approval, and efficacy in preventing mother-to-child transmission, the *Centers for Disease Control and Prevention* (CDC) in the USA amended its guidelines to include PrEP in May 2014. Currently tenofovir plus emtricitabine is the only HIV prophylactic treatment recommended by the WHO. The WHO guideline suggests that PrEP might be valuable for:

1. Couples wishing to conceive a child where one partner is HIV positive;
2. People who are unable to insist on condom use, in particular victims of coercion or violence; and
3. High risk populations such as men who have sex with men (MSM), female partners of MSM, and IV drug users.

In 2013, there were 1236 new cases of HIV-1 infection reported in Australia with a cumulative total of 33,287 reports. Truvada is not approved for PrEP in Australia but demand is growing. The Australasian Society for HIV Medicine (ASHM) has updated the Melbourne Declaration in April 2015 to strongly support access to PrEP for at-risk

³ Garcia-Lerma JG, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Medicine* February 2008

subjects in Australia.⁴ The Victorian Pre-Exposure Prophylaxis Project (VicPrEP) and the Queensland Pre-Exposure Prophylaxis Project (QPrEP) are on-going pilot clinical trials in at risk subjects sponsored by Monash University, Queensland Department of Health and the HIV Foundation of Queensland, respectively. The Treatment Options to Reduce Chances of HIV (TORCH) Study sponsored by the Kirby Institute, University of New South Wales is a survey of gay men to assess the feasibility of PrEP in an Australian setting.

Gilead has been lobbied by these and other academic, medical and patient advocacy groups to support a submission for tenofovir disoproxil fumarate plus emtricitabine for PrEP in Australia.

Contents of the clinical dossier

The submission included the following clinical information:

- Two pivotal efficacy/safety studies
 - CO-US-104-0288
 - CO-US-104-0380
- Integrated Summary of Efficacy, Integrated Summary of Safety and safety update supplemental New Drug Applications (sNDA)
- Interim reports from an ongoing prospective observational study of individuals who seroconvert while taking Truvada for PrEP (GS-US-276-0103)
- Truvada Periodic Safety Update Reports (PSUR) covering 3 April 2013 to 2 April 2014

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical studies were conducted in accordance with ICH (International Conference on Harmonisation) GCP (Good Clinical Research Practice) guidelines.

Pharmacokinetics

No new studies were submitted.

Pharmacodynamics

No new studies were submitted.

Dosage selection for the pivotal studies

The selected dosage was the same as that approved for the treatment of HIV-1 infection.

Efficacy

Studies providing efficacy data

The following studies provided evaluable efficacy data:

⁴ Crooks L et al. ASHM Position Statement: Pre Exposure Prophylaxis (PrEP). ASHM, April 2015

- Study CO-US-104-0288 (iPrEx Study)
 - This was a randomised, double-blind, placebo-controlled, Phase III study of the safety and efficacy of FTC/TDF for prophylaxis in seronegative MSM at high risk of acquiring HIV-1 infection.
- Study CO-US-104-0380 (Partners PrEP Study)
 - This was a randomised, double-blind, placebo-controlled, Phase III study of the safety and efficacy of PrEP with either TDF or FTC/TDF for prophylaxis in seronegative subjects in a known serodiscordant partnership (infected index subject and uninfected partner subject).

For more information on efficacy data and an in-depth analysis of these studies, please refer to Attachment 2 *Extract from the Clinical Evaluation Report*.

Evaluator's conclusions on efficacy

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

Two pivotal studies have been submitted to support the proposed indication. In the double-blind, placebo-controlled iPrEx Study, 2,499 HIV-uninfected MSM were randomised and received FTC/TDF or placebo for a median of 62 weeks. In the modified intention-to-treat (mITT) population, HIV-1 seroconversions were reported in 2.9% of the FTC/TDF group compared with 5.3% of subjects receiving placebo. There was a 44% relative risk reduction for the FTC/TDF group compared with placebo. This benefit in favour of FTC/TDF in the mITT population was statistically significant ($p = 0.005$) although it did not exclude the null hypothesis of 30% efficacy or less (95% CI: 15%, 63%). There was a clear relationship between efficacy and compliance with drug therapy. In subjects with $\geq 50\%$ self-reported compliance, the relative risk reduction was 50% (95% CI: 18%, 70%, $p = 0.006$). In subjects with $\geq 90\%$ self-reported compliance, the relative risk reduction was 73% (95% CI: 41%, 88%). In subjects with detectable TFV-DP drug levels, the relative risk reduction was 92% (95% CI: 40%, 99%).

In the double-blind, placebo-controlled Partners PrEP study, 4,758 heterosexual HIV-discordant couples received TDF, FTC/TDF or placebo for a median of 23 months.

Post-randomisation HIV-1 infections were reported in 17, 13, and 52 partner subjects in the respective study drug groups, representing incidence rates of 0.65, 0.50, and 1.99 per 100 person-years. TDF and FTC/TDF were significantly more effective than placebo ($p < 0.0001$) but not different from each other. In the TDF group, there was a 67% reduction in the risk of HIV-1 acquisition (95% CI: 44%, 81%), and in the FTC/TDF group there was a 75% reduction (95% CI: 55%, 87%). Based on tablet counts, 97% of study medication was taken although 15% of subjects reported missing at least one dose of study medication in the preceding month. Compared with subjects with undetectable TFV-DP levels, subjects with detectable levels had a 90% reduction in the risk of HIV-1 acquisition (95% CI: 56%, 98%, $p = 0.002$). Sex without condom use decreased from 27% overall at Baseline to 13% and 9% at 12 and 24 months, respectively.

Both pivotal studies enrolled large subject numbers in the different populations at risk. In both studies the primary endpoint of HIV-1 seroconversion was confirmed by repeat testing and adjudication. Both studies used a double-blind, placebo-controlled design and both studies confirmed highly significant reductions in the risk of HIV-1 acquisition compared with placebo. Compliance with study drug was carefully monitored in both studies by tablet counts, self-reported estimates and plasma TFV-DP levels. Efficacy was

directly related to compliance in both studies, and approximately 90% risk reduction for HIV-1 acquisition was observed in subjects with detectable TFV-DP levels.

Subject numbers in subgroups were too low to permit statistical analysis, although efficacy rates were comparable with the overall populations in both studies. There were no meaningful gender differences in the Partner PrEP study. Continuous counselling was provided and condom use increased in both studies. This was probably a factor in the observation that risk reduction was highest in older and more educated subjects. Drug resistance to FTC/TDF was not observed in subjects who acquired HIV-1 infection during the iPrEx Study, and it was observed in only one subject in the Partners PrEP Study. In both studies, resistant strains were detected in subjects with pre-existing infection.

However, the resistant variants declined during the follow-up period when the study drugs were discontinued.

The studies were conducted largely in South American and East African populations with lower educational and healthcare standards compared with Australia. However, the overall efficacy rates were outstanding in patients who complied with drug and safer sex practices. There is no reason to expect less in the Australian context with appropriate counselling and monitoring.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- Two pivotal efficacy studies:
 - Study CO-US-104-0288 (iPrEx)
 - Study CO-US-104-0380 (Partners PrEP)
- Interim analyses of two post-marketing safety studies:
 - GS-US-276-0101
 - GS-US-276-0103

In addition, the following evaluable safety information was submitted:

- Latest Periodic Benefit Risk Evaluation Report (PBRER) of Truvada (3 April 2013 to 2 April 2014)

For more information on evaluable safety data and an in-depth analysis of these studies, please refer to Attachment 2.

Patient exposure

In the iPrEx Study, median exposure in the FTC/TDF group was 62.3 weeks. Subjects were followed for one day to 145 weeks with a total exposure of 3,324 person-years. In the Partners PrEP Study no formal analysis of exposure was performed. The median follow-up time was 23 months and 7,830 person years of follow-up were reported.

Post-marketing data

Post-marketing safety has been assessed in:

1. Data from the Antiretroviral Pregnancy Registry, including an interim report from 1 January 2011 to 31 January 2014 (Study GS-US-276-0101).

2. An observational study of subject receiving Truvada for PrEP who seroconvert during follow-up (Study GS-US-276-0103).
3. The latest Periodic Benefit Risk Evaluation Report (PSUR/PBRER) for Truvada dated 3 April 2013 to 2 April 2014.
4. An updated summary of literature data since submission of the sNDA to 30 November 2014.
5. Additional reports submitted to the FDA after the sNDA with a cut-off date of 24 July 2013.

For more information on post-marketing safety for each of the above, please refer to Attachment 2.

Evaluator's conclusions on safety

Safety data to support the new proposed indication are derived primarily from the two pivotal Phase III studies of FTC/TDF used for PrEP in two high risk populations, MSM and heterosexual HIV-1 discordant couples. Supportive data were provided from published studies of MSM in the US, and African women and heterosexual adults. Routine recording of adverse events (AEs) and laboratory abnormalities was performed and compared with data in the Gilead Core Data Sheet. In addition, AEs of interest were identified including renal dysfunction and changes in bone mineral density, both related to the known effects of TDF on the proximal renal tubule.

In the iPrEx study in 2,499 randomised MSM, FTC/TDF was well tolerated with a safety profile comparable to placebo. AEs of any severity were reported in 55% of the FTC/TDF group compared with 56% in the placebo group (Gilead analysis). A similar incidence of Grade 3 or 4 AEs (9% versus 9%) and serious adverse events (SAEs) (4% versus 4%) were reported in the respective groups. Deaths occurred in < 0.1% of each group. Clinical and laboratory AEs leading to drug discontinuations were reported in 2% and < 0.1% of each group, respectively. The most commonly reported AEs by system organ class (SOC) were related to Infections and Infestations (36% in each group) and Psychiatric Disorders (8% versus 9%). The frequency of AEs related to gastric disturbance was similar in each group although nausea was more common in the group receiving FTC/TDF (2% versus < 1%).

Bone fractures were reported in 1% of the FTC/TDF group compared with < 1% in the placebo group. However, all fractures were traumatic and none were considered drug related. Overall, serum creatinine elevations above the upper limit of normal (ULN) were reported more commonly in the FTC/TDF group (25 versus 14 subjects, $p = 0.08$) but no Grade 3 or 4 events were reported in the FTC/TDF group. Decreased serum phosphate levels were comparable in each group but Grade 3 elevations were more common in the FTC/TDF group (11 versus 7 subjects, $p = 0.66$).

In the Partner PrEP study, FTC/TDF and TDF were well tolerated with a safety profile comparable to placebo. AEs of any severity were reported in 86%, 85%, and 85% of the FTC/TDF, TDF, and placebo groups, respectively. Grade 4 events were reported in 37%, 26%, and 32% of the respective groups, and SAEs were reported in 7% of each group. Deaths were reported in 6%, 5%, and 6% of the respective groups. The most common AEs reported by preferred terms in the overall population were decreased neutrophil count (39%), blood phosphorus decreased (29%), malaria (19%), haemoglobin decreased (15%), decreased platelet count (12%), and upper respiratory infections (9%). Diarrhoea was reported in 2% to 3% of the study drug groups but nausea was reported in < 1% of any group. Grade 1 or higher increases in serum creatinine were reported in < 1% of each group. Bone fractures occurred in < 1% of subjects in each study drug group. All were traumatic and not considered drug related.

In the overall populations, PrEP with FTC/TDF was well tolerated with a safety profile comparable to placebo. No obvious differences in subgroups (in particular gender) were identified although subject numbers in some categories were too small to identify possible differences. No new safety signals have been detected in the pivotal studies or supportive studies of PrEP using FTC/TDF or TDF alone. The rates of AEs, laboratory AEs, severe AEs (SAEs) and deaths were generally similar in the active and placebo study groups. The overall data were also comparable with the known safety profile of Truvada used as treatment for HIV-1 infection.

AEs of interest were identified based on the known effects of Truvada. As expected, gastrointestinal adverse events (in particular nausea and vomiting) were more common in subjects receiving FTC/TDF compared with placebo. However, most events occurred in the first month and resolved with continued exposure.

Renal events associated with TDF renal tubulopathy were generally mild. Increased serum creatinine was reported more commonly in subjects receiving FTC/TDF but no Grade 3 or 4 events were reported and most elevations resolved with cessation of treatment. There was a low incidence of pre-emptive renal transplantation associated with the use of TDF and non-steroidal anti-inflammatory drugs (NSAIDs) and most events occurred in subjects with predisposing renal risk factors.

Hypophosphataemia was also reported more commonly in subjects receiving FTC/TDF or TDF alone. Compared with placebo, there was a mean 0.5% to 1% loss of bone mineral density (BMD) in subjects receiving FTC/TDF over observation periods of 24 to 96 weeks. Most of the observed bone loss occurred in the first six months of drug administration but further minor progression was observed over the remaining period. Overall, changes in BMD were modest and there was no evidence of an increased rate of bone fractures in subjects receiving FTC/TDF. However, in the iPrEx study, BMD loss of $\geq 5\%$ in the spine measured at any visit was observed in more subjects receiving FTC/TDF (14% versus 6%). This observation was confirmed in Study CDC4323 in which loss of BMD was higher in the FTC/TDF group (13% versus 6%). The subjects in these BMD sub-studies were male and no PrEP studies have been performed in women, or in women receiving depot medroxyprogesterone acetate. There was no evidence of an increased rate of bone fractures with the use of FTC/TDF or TDF alone. However, more long-term data are required to exclude progressive and damaging bone loss following extended periods of chemoprophylaxis.

No hepatic viral flares during or after treatment with FTC/TDF or TDF were reported in subjects with chronic or acute hepatitis B virus (HBV) infection. However, subject numbers infected with HBV were low and the risk of potentially serious hepatic events cannot be discounted.

Pregnancy outcomes in the FTC/TDF and placebo groups were comparable with no unexpected increase in birth defects. The pregnancy and foetal outcome data were comparable to data from other ART drug registries.

Sexual disinhibition is a significant safety concern as PrEP alone will not prevent HIV-1 transmission in all cases. The perception that PrEP is a 'chemical condom' might lead to a reduction in safer sex practices and actually increase the risk of infections, particularly in subjects with poor drug compliance. However, opposite trends were apparent in the pivotal studies with increased self-reported condom use and a decrease in the number of sexual partners.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Truvada in the proposed usage are:

- Reduced risk of HIV-1 infection in high risk MSM.
- Reduced risk HIV-1 infection in sexually active, HIV-1 discordant partnerships.
- Well tolerated with safety profile comparable to placebo.
- Adverse events related to tenofovir disoproxil fumarate well understood and predictable.
- Improved safer sex practices associated with counselling and close medical supervision.

First round assessment of risks

The risks of Truvada in the proposed usage are:

- Reduced but still significant risk of acquiring HIV-1 infection.
- Potential viral resistance in subjects with unrecognised HIV-1 infection.
- Adverse events related to tenofovir disoproxil fumarate, in particular reduced bone mineral density.
- Risk of post-treatment viral flares in subjects with HBV infection.
- Efficacy dependent almost entirely on good drug compliance and safer sex practices.
- Reduced efficacy if not closely supervised by experienced HIV healthcare providers.
- The value of PrEP not yet fully evaluated in the Australian context.

First round assessment of benefit-risk balance

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

There is a statistically significant and clinically meaningful benefit for Truvada in MSM and HIV-1 discordant couples. With appropriate counselling, education, and medical supervision of selected and motivated individuals, efficacy rates of up to 90% are possible. However, as demonstrated in the FEM PrEP study in African women, chemoprophylaxis is virtually worthless unless compliance is encouraged and closely monitored. Cultural factors and the public health environment are important and PrEP has not yet been evaluated as part of an overall risk reduction strategy in the Australian context. However, PrEP has been endorsed by the ASHM and limited free access schemes are currently available in Queensland, New South Wales and Victoria.

The risks of chemoprophylaxis are generally recognised. ART requires triple therapy and the use of Truvada in infected individuals will inevitably lead to viral resistance. However, in practice and with frequent HIV-1 testing, the rate of viral resistance is low and it resolves when the drug is discontinued. Discontinuation of therapy may lead to viral hepatic flares in HBV positive individuals. This does appear to be common although the number of subjects studied with HBV is limited. The adverse event profile of Truvada is characterised by gastrointestinal disturbance in some subjects in the first month of prophylaxis. Renal effects including increased serum creatinine and proteinuria are often observed but severe renal AEs are unusual. Modest reductions in bone mineral density can be expected. This appears to occur in the first year with lesser reductions thereafter.

However, long-term studies of PrEP have not been performed, and dual-energy X-ray absorptiometry (DEXA) studies in healthy females have not been conducted. The fear that PrEP might lead to reduced safer sex practices has not been observed in trials to date. With appropriate education and counselling, condom use may increase and the number of sexual partners may decrease.

First round recommendation regarding authorisation

Authorisation is recommended for the proposed new indications:

Truvada is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.

The proposed modification brings the indication into line with other Gilead HIV-1 products approved in Australia.

The proposed new indication for pre-exposure prophylaxis is:

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk.

This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples.

Clinical questions

There were no questions needing additional expert input or questions relating to pharmacokinetics, pharmacodynamics or safety, however the clinical evaluator had the following questions concerning *efficacy*:

1. Reported in the primary publication but not in the iPrEx CSR, seroconversion rates were similar in both treatment groups during an undefined follow-up period after discontinuation of study drug (161 FTC/TDF versus 159 placebo). Please provide the duration of this follow-up period, with a Kaplan-Meier plot if it is available.
2. In the iPrEx CSR, relative effectiveness in subjects with $\geq 50\%$ tablet usage is reported as 50% (95% CI: 18%, 70%). In the text, it is stated that tablet usage was based on pill counts, self-report, and dispensation records. However, in the supporting table (see Table 2) *Study CO US 104 0288: Relative effectiveness: primary analysis by self-reported level of pill use (iPrEx mITT analysis)* relative effectiveness in the $\geq 50\%$ usage group is identical but described as self-reported only. Please clarify this discrepancy. For the same table, please state which method of calculation was used to report relative effectiveness in the $\geq 90\%$ usage group.
3. In the iPrEx CSR, the relative risk reduction after adjustment for high-risk sexual practice (specifically unprotected receptive anal intercourse (URAI)) was stated to be 95% (95% CI: 70%, 99%) compared with placebo. However, it is not explained how this statistic was calculated. Please clarify.
4. Approximately 50% of MSM in the iPrEx study consumed ≥ 5 alcoholic drinks per day. Has an analysis been made of the influence of alcohol on compliance and efficacy rates? If not, can this be provided?
5. It appears that only 35/288 pregnancies occurring in Partners PrEP were reported in Study GS-US-276-0101. Please confirm that this was related to the overlapping timeframes of the two studies. Expedited AEs for newborns are reported in the Partners PrEP CSR. However, the incidence of birth defects does not appear to have been reported. Please provide these data if they are available. In addition, please

confirm that all pregnant women had study drug withdrawn and provide exposure data if they are available.

Table 2: Study CO-US-104-0288: Relative effectiveness: primary analysis by self-reported level of pill use (iPrEx mITT analysis)

	Placebo	FTC/TDF	P-value ^a
Subjects Self-Reporting ≥ 50% Pill Use	47 events	23 events	0.006 ^a
Subjects With Seroconversion Events			
Relative Effectiveness (2-sided 95% CI)	50% (18%, 70%)		
Subjects Self-Reporting ≥ 90% Pill Use	30 events	8 events	< 0.001 ^a
Subjects With Seroconversion Events			
Relative Effectiveness (2-sided 95% CI)	73% (41%, 88)		

a p-values by Wald test from Cox model.

Second round evaluation of clinical data submitted in response to questions

The clinical evaluator deemed the responses and data submitted for the all the clinical questions as satisfactory. For further details of the sponsor's responses to the Clinical questions please see Attachment 2 *Second round evaluation of clinical data submitted in response to questions*.

Specifically to Question 4: '*Approximately 50% of MSM in the iPrEx study consumed ≥ 5 alcoholic drinks per day. Has an analysis been made of the influence of alcohol on compliance and efficacy rates? If not, can this be provided?*' the evaluator felt the sponsor has not addressed the question of compliance; however, this is not important given the lack of interaction in the efficacy analysis.

Second round benefit-risk assessment

No new clinical information was submitted in response to questions. Accordingly, the benefits and risks of Truvada are unchanged from those identified in the first round assessment of benefit-risk balance.

Pharmacovigilance findings

Risk management plan

The sponsor submitted a the following Risk Management Plan which was reviewed by the RMP evaluator: EU-RMP (Version: 8, dated 27 June 2014) with an Australian Specific Annex (ASA) Version: 0.1, dated February 2015

Safety specification

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

Table 3: Sponsor's summary of ongoing safety concerns

	Truvada EU-RMP V8.0 date June 2014	Truvada ASA V0.1 dated January 2015
Important identified risks		HIV-1 acquisition (TVD PrEP)
		Development of resistance (TVD PrEP)
	Post-treatment hepatic flares in HIV-1/HBV co-infected patients (FTC, TDF)	Post-treatment hepatic flares in HIV-1/HBV co-infected patients (FTC, TDF)
	Lactic acidosis and severe hepatomegaly with steatosis (FTC, TDF)	Lactic acidosis and severe hepatomegaly with steatosis (FTC, TDF)
	Lipodystrophy (FTC, TDF)	Lipodystrophy (FTC, TDF)
	Renal toxicity (TDF)	Renal toxicity (TDF)
	Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Bone events due to proximal renal tubulopathy/loss of BMD (TDF)
	Interaction with didanosine (TDF)	Interaction with didanosine (TDF)
	Pancreatitis (TDF)	Pancreatitis (TDF)
Missing information	Safety in children (including long term safety)	Safety in children (including long term safety)
	Safety in elderly patients (FTC, TDF)	Safety in elderly patients (FTC, TDF)
	Safety in pregnancy (FTC, TDF)	Safety in pregnancy (FTC, TDF)
	Safety in lactation (FTC, TDF)	Safety in lactation (FTC, TDF)
	Safety in patients with renal impairment (TDF)	Safety in patients with renal impairment (TDF)

BMD=Bone mass density; FTC=emtricitabine; HBV=hepatitis B virus; HIV-1=human immunodeficiency virus type 1; TDF=tenofovir disoproxil fumarate (tenofovir DF)

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified safety concerns and missing information, including the use of targeted follow-up questionnaires for the important identified risks: 'HIV-1 acquisition',

'Renal toxicity' and 'Bone events due to proximal renal tubulopathy/loss of BMD'.

Additional pharmacovigilance activities in the form of clinical trials, a seroconversion study, a resistance study, a post-authorisation safety study, a Phase IV cross-sectional study and an Antiretroviral Pregnancy Registry are proposed to further characterise the important identified risks: 'HIV-1 acquisition', 'Development of Drug Resistance', 'Renal toxicity' and 'Bone events due to proximal renal tubulopathy/loss of BMD', and the missing information: 'Safety in children (including long-term safety)', 'Safety in pregnancy' and 'Safety in patients with renal impairment'.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all the specified safety concerns and missing information. Additional risk minimisation activities in the form of educational materials are proposed for the important identified risks: 'HIV-1 acquisition', 'Development of Drug Resistance' and 'Renal toxicity'.

Reconciliation of issues outlined in the RMP report

Table 4 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and an evaluation of the sponsor's responses.'

Table 4: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, 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.	The sponsor states: <i>'No safety considerations were raised by the nonclinical and clinical evaluators. In addition, the nonclinical and clinical evaluators did not request any additional changes to the Product Information'.</i>	This is acceptable.
2. The typographical error which refers to the Truvada ASA being dated 'January 2015' rather than 'February 2015' in the Table: 'Summary Table of Safety Concerns (Differences between Europe and Australia)' of the ASA should be corrected.	The sponsor states: <i>The Table 'has been updated to reflect the date of the most recent ASA (version 0.2, dated October 2015), that is being submitted as part of this response to TGA RMP questions'.</i>	This is acceptable, however under 'History of RMPs submitted in Australia' of the updated ASA it states: <i>'This is the first ASA proposed for Truvada'.</i> This is not the case and this section of the ASA should be revised in accordance with the ASA template, as found on the TGA website as of 4 May 2015.
3. A number of	The sponsor states:	The entry for the important

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>discrepancies in regard to detail have been observed between the relevant pharmacovigilance plan information in the ASA and the EU-RMP. Consequently the sponsor should consolidate Table 7: 'Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan (Categories 1-3) for Australia' and Table 8: 'Table of New/Ongoing PrEP Studies Referenced in Category 1 application and Not Referenced in EU-RMP' of the ASA, in accordance with Section 2.4: 'Studies referenced in the Pharmacovigilance Plan of the RMP' of the Australian-Specific Annex template, as found on the TGA website as of 4 May 2015, and any errors of fact should be corrected. The planned dates for submission of associated data should also be updated, as several of these dates as stated in the EU-RMP have already passed.</p>	<p><i>'Gilead reviewed the EU-RMP (section 8.1), Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan Table 5-1, and identified the discrepancy TGA noted, as such Gilead has incorporated Interventional Study (Category 3) GS-US- 236-0103 to the ASA. The submission dates for all studies mentioned, were updated as needed'.</i></p>	<p>identified risk: 'Bone events due to proximal renal tubulopathy/loss of BMD' in Table 6: 'Routine and Additional Pharmacovigilance Activities in Australia and Europe' of the updated ASA does not make reference to Study GS-US-236-0103. Furthermore the entries for the important identified risks: 'Renal toxicity' and 'Bone events due to proximal renal tubulopathy/loss of BMD'; and the missing information: 'Safety in children (including long-term safety), still refer to the EU 'Post-authorization safety study of a representative sample of HIV-1 infected pediatric patients (GS-EU- 104-1402)', despite Table 2-5: 'Summary of Changes to the Risk Management Plan' of the EU-RMP stating: 'A planned post-authorization safety study of HIV infected pediatric patients, GS-US- 104-1402, has been removed from the post authorization development plan following agreement from the CHMP to waive the commitment to conduct this study (EMA/H/C/000419/MEA/265.3; assessment report dated 24 November 2014)'. The sponsor should amend Table 6 of the ASA accordingly, and then revise Table 11: 'Summary Table of Pharmacovigilance and Risk Minimisation activities proposed in Australia' of the ASA to maintain internal consistency, preferably before this application is approved.</p>
<p>4. The column: 'Pharmacovigilance activities (routine and additional) proposed for Australia' in Table 12: 'Summary Table of Pharmacovigilance and Risk Minimisation activities proposed in Australia' of the ASA should be revised to be consistent with Table 6: 'Routine and Additional</p>	<p>The sponsor states: <i>'As requested, the columns Pharmacovigilance activities and Risk Minimisation Activities have been updated to be consistent with Table 6: Routine and Additional Pharmacovigilance Activities in Australia and Europe. In addition, Gilead made a minor edit to the column heading Safety</i></p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Pharmacovigilance Activities in Australia and Europe' of the ASA.	<i>Concerns, to align with the TGA ASA template as found on the TGA website on 4 May 2015, Section 4'.</i>	
5. For the important identified risk: 'Post-treatment hepatic flares in HIV-1/ HBV co-infected patients (FTC, TDF) and HBV monoinfected individuals (TVD PrEP)', Table 9: 'Summary Table of Risk Minimization Measures' of the ASA states: ' <i>Additional risk minimization activities proposed due to differing indications</i> '. This entry should be corrected as no additional risk minimisation activities are proposed for this safety concern.	The sponsor states: ' <i>As requested, Gilead has made this change</i> '.	This is acceptable.
6. For the important identified risk: 'Renal toxicity', Table 10: 'Differences in Additional Risk Minimization Measures for Renal toxicity (TDF) between EU-RMP and ASA' of the ASA should be updated with the information provided in Table 1-1: 'Risk Minimization Measures for Important Identified Risks' of the STRIBILD Risk Management Plan for Australia (Version: 2.0, dated 30 June 2015).	The sponsor states: ' <i>Gilead made some editorial updates to the important identified risk 'Renal toxicity' in Table 10, to align with the STRIBILD AU-RMP, version 2.0, dated 30 June 2015</i> '.	This is acceptable.
7. In regard to 'Criteria for judging the success of the proposed risk minimization measures' and 'Planned dates for assessment', Table 11: 'PrEP Indication Healthcare Provider Training and Education Program in Australia' of the ASA states: ' <i>Feedback forms will provide information to judge physician knowledge levels regarding the use of Truvada for PrEP</i> ' and ' <i>Ongoing</i> ' respectively. This table should be revised to	The sponsor states: ' <i>Gilead updated the 'Criteria for judging the success of the proposed risk minimization measures' to include further details on the review period, how the feedback forms will be implemented and how results will be reported to TGA</i> '.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
include the specific review period, the specific criteria used to verify success and how the results of HCP testing will be reported to the TGA.		
8. Table 11: 'PrEP Indication Healthcare Provider Training and Education Program in Australia' of the ASA does not appear to provide any detail as to how the effectiveness of the patient educational materials as a risk minimisation activity will be evaluated. Consequently this table should be revised to state how the effectiveness of this additional risk minimisation activity will be measured, the specific criteria used to verify success and how the results of such testing will be reported to the TGA.	The sponsor states: <i>'See response to Question 7 above for further details regarding the Australian PrEP Indication Healthcare Provider Training and Education Program have been added to the table.'</i>	This information was in relation to the proposed educational materials for HCPs, not the educational materials for patients. Consequently this issue remains outstanding and Table 10: 'PrEP Indication Healthcare Provider Training and Education Program in Australia' of the ASA should be revised to state how the effectiveness of the patient educational materials will be measured, the specific criteria used to verify success and how the results of such testing will be reported to the TGA, preferably before this application is approved.

Summary of recommendations

Issues in relation to the RMP

The sponsor's attention was drawn to a number of discrepancies in regard to detail observed between the relevant pharmacovigilance plan information in the ASA and the EU-RMP. The sponsor was asked to correct any errors of fact and update the planned dates for submission of associated data as required.

The sponsor states: *'Gilead reviewed the EU-RMP: Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan and identified the discrepancy TGA noted, as such Gilead has incorporated Interventional Study (Category 3) GS-US-236-0103 to the ASA. The submission dates for all studies mentioned, were updated as needed.'*

However, the entry for the important identified risk 'Bone events due to proximal renal tubulopathy/loss of BMD' in the 'Routine and Additional Pharmacovigilance Activities in Australia and Europe' of the updated ASA does not make reference to Study GS-US-236-0103. Furthermore, the entries for the important identified risks 'renal toxicity' and 'bone events due to proximal renal tubulopathy/loss of BMD' and the missing information 'safety in children (including long-term safety), still refer to the EU 'post-authorization safety study of a representative sample of HIV-1 infected paediatric patients (GS-EU-104-1402)' despite the 'Summary of Changes to the Risk Management Plan' of the EU-RMP stating: *'A planned post-authorization safety study of HIV infected paediatric patients, GS-US-104-1402, has been removed from the post authorization development plan following agreement from the CHMP to waive the commitment to conduct this study (EMA/H/C/000419/MEA/265.3; assessment report dated 24 November 2014).'*

The sponsor should amend the ASA accordingly, and then revise the *'Summary Table of Pharmacovigilance and Risk Minimisation activities proposed in Australia'* of the ASA to maintain internal consistency, preferably before this application is approved.

The sponsor was asked to provide detail as to how the effectiveness of the patient educational materials as a risk minimisation activity would be evaluated. The sponsor states: *'See response [in the Table above] for further details regarding the Australian PrEP Indication Healthcare Provider Training and Education Program have been added to the table'*. However, this information was in relation to the proposed educational materials for HCPs, not the educational materials for patients. Consequently this issue remains outstanding and *'PrEP Indication Healthcare Provider Training and Education Program in Australia'* of the ASA should be revised to state how the effectiveness of the patient educational materials will be measured, the specific criteria used to verify success and how the results of such testing will be reported to the TGA, preferably before this application is approved.

In addition in the *'History of RMPs submitted in Australia'* of the updated ASA states: *'This is the first ASA proposed for Truvada'*. This is patently not the case and this section of the ASA should be revised in accordance with the Australian-Specific Annex template, as found on the TGA website as of 4 May 2015.

Key changes to the updated RMP

In their response to the TGA the sponsor provided an updated ASA (Version 0.2, dated October 2015). Key changes from the versions evaluated in the first round are summarised below (Table 5).

Table 5: Key changes to the ASA

Document	Key changes
ASA	<p>Details of Study GS-US-236-0103 as an additional pharmacovigilance activity for the important identified risk: 'Bone events due to proximal renal tubulopathy/loss of BMD' have been added.</p> <p>Table 7: 'Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan (Categories 1-3) for Australia' has been revised and Table 8: 'Table of New/Ongoing PrEP Studies Referenced in Category 1 application and Not Referenced in EU- RMP' has been removed.</p> <p>Table 9: 'Differences in Additional Risk Minimization Measures for Renal toxicity (TDF) between EU-RMP and ASA' has been revised.</p> <p>Table 10: 'PrEP Indication Healthcare Provider Training and Education Program in Australia' has been revised.</p> <p>Table 11: 'Summary Table of Pharmacovigilance and Risk Minimisation activities proposed in Australia' has been revised</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. At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

Overall conclusion and risk/benefit assessment

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

Quality

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

Nonclinical

The following comment from the nonclinical evaluator is noted:

'The prophylactic use of Truvada® provides imperfect protection from transmission of HIV, SIV and SHIV in animal models. The most common overall effect was to delay the onset of detectable infection following repeated infectious challenge over time (generally once per week for 14 weeks). Truvada® does not provide absolute protection from infection in every study in the animal models examined. However, there are examples of 100% efficacy in some studies. It is notable that the experimental power of the available nonclinical primary pharmacology studies was often low. Overall the nonclinical primary pharmacology provides good proof of concept that pre-exposure prophylaxis will achieve the general aims of the requested extension of indication i.e. to prophylactically reduce the risk of sexually acquired HIV-1 infection in adults at high risk.'

Overall, there are no nonclinical objections to the proposed use of Truvada for PrEP in humans.

Clinical

Clinical efficacy

Truvada was approved by the FDA for PrEP in July 2012 following publication of 2 controlled trials. The same 2 trials (iPrEX and Partners PrEP) form the pivotal evidence of efficacy in support of this submission.

Clinical data included in the dossier is briefly discussed below. Please see the clinical evaluation report (CER) for details.

Study CO-US-104-0288 (iPrEx)

This was a randomised, double-blind, placebo-controlled, Phase III study of TDF/FTC (300/200) for pre exposure prophylaxis (PrEP) of HIV in seronegative MSM population. The study took place between 2007 and 2009 in 6 countries (Peru, Ecuador, Brazil, USA,

Thailand, and South Africa) and results were published in 2010⁵. The key inclusion criteria were:

- HIV-1 seronegative, males aged ≥ 18 years.
- Evidence of high risk for acquiring HIV based on protocol defined behaviours.
- Normal renal and hepatic function and haematology.

A number of exclusion criteria were aimed at excluding serious concurrent illness.

A total of 2,499 subjects were randomised (1,251 and 1,248 in TDF/FTC and placebo groups respectively) and followed for 3,324 person-years (median 1.2 years; maximum 2.8 years). Two subjects in TDF/FTC group and 8 in placebo group were HIV seropositive at baseline. The study was event-driven until accumulation of at least 85 seroconversion events based on earlier power calculations. HIV-1 testing was performed for additional 8 weeks after the last dose of study drug to capture late seroconversions.

Hepatitis B negative subjects at baseline were offered HBV vaccination and 94% accepted. All participants were provided regular counselling on risk reduction and sexually transmitted disease (STDs). Compliance was assessed at each study visit.

TFV-DP (active form of TDF) levels in plasma and peripheral blood mononuclear cell (PBMCs) were tested in a pre-specified subgroup (10% of sample). A sub-study of bone mineral density in about 500 subjects was also performed.

Overall, subject demographics were comparable in the 2 groups at baseline. The mean age was about 27 years in both groups (range 18 to 67 years). The results were as follows:

At the end of a median exposure of 62 weeks to the two study drugs, a total of 100 treatment-emergent HIV seroconversions were reported in the modified ITT population (36 in TDF/FTC, 64 in placebo) indicating a HIV infection acquisition rate of 2.4 and 4.2 per 100 Person-Years (PY) in TDF/FTC and placebo groups respectively.

Thus the relative risk reduction (RRR)⁶ in favour of TDF/FTC was 44% (95%CI 15%, 63%). RRR was comparable using the full ITT set (47%; 95%CI 22%, 64%).

However, the trial failed to achieve pre-defined level of efficacy of at least 30% RRR at the lower bound of 95%CI.

RRR was 43% (95%CI 18%, 60%) at 8 weeks after the end of treatment using mITT population. Information provided by the sponsor in the second round indicates that, off-treatment, a total of 161 subjects in TDF/FTC group were followed for a total of 62.2 PY during which there were 2 HIV seroconversions (3.2 per 100 PY). In placebo group, 159 subjects were followed, off-treatment, for a total of 49.2 PY during which there were 3 HIV seroconversions (6.1 per 100 PY). The log rank test was not significantly different with a hazard ratio of TDF/FTC to placebo of 0.48 (95%CI 0.08, 2.9).

In subjects with high level of compliance with study drug ($\geq 90\%$), RRR was 73% (95%CI 41%, 88%).

In subjects with quantifiable levels of plasma drug, RRR was 92% (95%CI 40%, 99%). It was estimated that four TDF doses per week could confer 97% efficacy (95%CI 90%, 99.9%) and seven doses per week could confer 99% efficacy (95%CI 97%, 99.9%).

In general, pre-specified subgroup analyses indicated protective effect consistent with the overall effect. However, RRR in URAI (unprotected receptive anal intercourse) subgroup

⁵ Grant *et al* (2010). [Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.](#) *NEJM*. 2010;363(27):2587-99.

⁶ 1 minus Relative Risk x 100

was 58% (95%CI 32%, 74%) compared with lower effect in non-URAI subgroup (-59%; 95%CI -284%, +34%).

For changes in sexual practice please see Attachment 2 to this AusPAR.

No drug resistant variants were detected in a post hoc analysis of subjects in TDF/FTC group who had seroconverted.

Study C0-US-104-0380 (Partners PrEP)

This was a randomised, double-blind, placebo-controlled, Phase III study of PrEP in seronegative subjects in heterosexual, HIV serodiscordant (uninfected partner subject/infected index subject) relationship.

Uninfected partner subjects in each couple were randomised 1:1:1 to receive one of the 3 study medications, that is, TDF alone (300mg daily), TDF/FTC fixed dose combination (300/200 mg daily) or placebo.

Partner subjects were adults (18 to 65 years), HIV-1 uninfected based on negative HIV-1 rapid test, have adequate renal function, LFTs and haematology and not infected with HBV.

Index subjects were required to have documented (positive enzyme immunoassay) but untreated HIV-1 infections with a CD4+ count of at least 250 cells/mm³. They must not have qualified for ART under the national treatment guidelines. Index subjects with current use of ART or with a history of clinical AIDS defining diagnoses were excluded.

The study took place between 2008 and 2011 at 9 centres in Kenya and Uganda and results were published in 2012.⁷

A total of 4,758 couples were randomised (1589, 1583 and 1586 to TDF, TDF/FTC and placebo groups respectively) to be followed until accumulation of 191 seroconversions based on earlier power calculations.

The demographic characteristics for the partner and index subjects were comparable in each study drug group. The majority of partner subjects were male (61 to 64%) with a median age of 33 to 34 years.

In index subjects, the median baseline CD4+ count was 491 to 499 cells/mm³ and the median plasma HIV-1 RNA was 3.9 log₁₀ copies/mL.

The couples had lived together for a median 7 years and their discordant HIV status had been known for a median of 0.5 years. In the month before enrolment, sexual intercourse was reported on a median 4 occasions, and this was unprotected on 26 to 28% of occasions. STDs other than HIV were reported in 6 to 9% of partner and index subjects.

The subjects were followed-up for a median 23 months with a total exposure of 7,830 PY. When the study was stopped by the Data Safety Monitoring Board (DSMB), 99 seroconversions had been reported. Of these, 3 were determined to be false positives and 14 were considered to be present at enrolment.

A total 17/1579, 13/1576, and 52/1578 treatment-emergent seroconversions occurred in TDF, TDF/FTC and placebo groups respectively, indicating HIV acquisition rates of 0.65, 0.50, and 1.99 per 100PY in the 3 groups respectively. The placebo corrected protective effect was RRR of 67% (95%CI 44%, 81%) in TDF group and RRR of 75% (95%CI 55%, 87%) in TDF/FTC group. The difference between TDF and TDF/FTC groups was not significant.

In general, the pre-specified subgroup analyses (Table 6) were consistent with the overall protective effect.

⁷ Baeten *et al* (2012). [Antiretroviral prophylaxis for HIV prevention in heterosexual men and women.](#) *NEJM.* 2012; 367(5):399-410.

Table 6: Partners PrEP. CO-US-104-0380: Hazard ratio comparisons of HIV-infection risk by subgroup (mITT)

Gender	Hazard Ratio (CI)		P-Value
	Female	Male	
TDF compared with placebo	0.29 (0.13, 0.63)	0.37 (0.17, 0.80)	0.65
FTC/TDF compared with placebo	0.34 (0.16, 0.72)	0.16 (0.06, 0.46)	0.24
FTC/TDF compared with TDF	1.18 (0.45, 3.06)	0.43 (0.13, 1.39)	0.18
Circumcision (male only)	Yes	No	
TDF compared with placebo	0.46 (0.17, 1.20)	0.28 (0.08, 1.00)	0.54
FTC/TDF compared with placebo	0.22 (0.06, 0.79)	0.09 (0.01, 0.68)	0.42
FTC/TDF compared with TDF	0.49 (0.12, 1.97)	0.31 (0.03, 3.01)	0.73
Country	Kenya	Uganda	
TDF compared with placebo	0.32 (0.14, 0.74)	0.33 (0.16, 0.68)	0.94
FTC/TDF compared with placebo	0.31 (0.13, 0.74)	0.20 (0.08, 0.48)	0.46
FTC/TDF compared with TDF	0.99 (0.35, 2.82)	0.60 (0.22, 1.64)	0.50
Age	18–24 years	≥ 25 years	
TDF compared with placebo	0.28 (0.08, 1.01)	0.34 (0.18, 0.61)	0.79
FTC/TDF compared with placebo	0.59 (0.21, 1.61)	0.17 (0.07, 0.37)	0.06
FTC/TDF compared with TDF	2.12 (0.53, 8.48)	0.49 (0.20, 1.22)	0.08
Unprotected sex	No	Yes	
TDF compared with placebo	0.47 (0.25, 0.89)	0.13 (0.04, 0.44)	0.05
FTC/TDF compared with placebo	0.27 (0.12, 0.58)	0.22 (0.08, 0.58)	0.77
FTC/TDF compared with TDF	0.56 (0.24, 1.35)	1.68 (0.40, 7.02)	0.19
Viral load (index partner at Enrollment)	< 50,000 copies/mL	≥ 50,000 copies/mL	
TDF compared with placebo	0.40 (0.21, 0.76)	0.23 (0.08, 0.69)	0.39
FTC/TDF compared with placebo	0.28 (0.13, 0.58)	0.23 (0.08, 0.68)	0.79
FTC/TDF compared with TDF	0.69 (0.29, 1.61)	0.99 (0.25, 3.96)	0.66
CD4 cell count (index partner at Enrollment)	250–349 count/mm ³	≥ 350 count/mm ³	
TDF compared with placebo	0.79 (0.31, 2.01)	0.21 (0.10, 0.44)	0.03
FTC/TDF compared with placebo	0.39 (0.12, 1.26)	0.21 (0.10, 0.44)	0.39
FTC/TDF compared with TDF	0.50 (0.15, 1.65)	0.99 (0.39, 2.50)	0.36

Abbreviation: CI = 95% confidence interval

Note: Efficacy (risk reduction) is 1 minus the HR. P-values for heterogeneity of effect.

Plasma TFV-DP was measured in all 17 partner subjects who had seroconverted in the TDF group, and in 12 of 13 subjects in TDF/FTC group who had seroconverted. These were compared with 200 randomly selected subjects (100 in each active study drug group) who did not seroconvert. In the infected subjects, detectable TFV-DP levels were present in 35% TDF subjects and 25% TDF/FTC subjects, whereas in uninfected subjects, TFV-DP was detected in 83% TDF subjects and in 81% TDF/FTC subjects.

For partner subjects in TDF group (Table 7), detectable TFV-DP was associated with an 86% RRR (95%CI 67%, 95%) compared with subjects with no detectable levels.

For partner subjects in TDF/FTC group (Table 7), detectable TFV-DP was associated with 90% RRR (95%CI 56%, 98%).

Table 7: Partners PrEP. CO-US-104-0380: Detection of tenofovir in plasma and HIV-1 prophylactic effects

	Number/ Total Samples (%) with Tenofovir Detected		Risk Estimate for HIV-1 Protection: Detection versus No Detection of Tenofovir	
	Case	Cohort	Hazard Ratio (95% CI)	p-value
TDF group	6/17 (35.3)	363/437 (83.1)	0.14 (0.05, 0.33)	<0.001
FTC/TDF group	3/12 (25.0)	375/465 (80.6)	0.10 (0.02, 0.44)	0.002

Abbreviations: CI = confidence interval

In the compliance substudy of 1,147 subjects, HIV-1 infections were acquired by 14 subjects, all of which were in the placebo group.

For changes in sexual behaviour, please see Attachment 2 to this AusPAR.

In subjects with treatment-emergent HIV acquisition, one resistant mutation was observed in TDF/FTC group.

Additional studies

CDC 4323 (CO-US-104-0277): Phase II, randomised, double-blind, placebo-controlled study in HIV-1 negative MSM population (n = 400) at 3 centres in the US. The study assessed safety of TDF (300 mg for up to 24 months) including delayed TDF (TDF 300 mg daily from 9 month onward). Only safety outcomes were reported.

FHI PrEP: Phase II⁸, randomised, double-blind, placebo-controlled, study of TDF (300 mg once daily for 12 months) for PrEP in women (N = 936) at high risk for HIV in Ghana, Cameroon, and Nigeria. Two subjects in TDF group (0.86/100PY) and 6 subjects in placebo group (2.48/100PY) acquired HIV infection yielding a relative risk of 0.35 (95%CI 0.03, 1.93).

CDC TDF2: Phase III⁹, randomised, double-blind, placebo-controlled study (N =1200) in male and female Botswanans at high risk of acquiring HIV. Treatment-emergent HIV-1 seroconversion occurred in 9 subjects in TDF/FTC group compared with 24 subjects in placebo group representing a RRR of 62% (95%CI 22%, 83%).

FEM PrEP: Randomised¹⁰, double-blind, placebo controlled study of FTC/TDF compared with placebo in African women (Kenya, South Africa, Tanzania) over 52 weeks. The study was stopped after an interim analysis showed no prospect of demonstrating chemoprotection with TDF/FTC. The incidence of HIV infection in TDF/FTC group was 4.7/100PY compared with 5.0/100PY in placebo group indicative of RRR of 6% (95%CI -52%, +42%). In TDF/FTC group, TFV-DP was detected in fewer than 50% of infected subjects and uninfected matched controls.

Clinical safety

The safety data supporting the PrEP indication is mainly based on the 2 pivotal studies in 2 high risk populations (MSM and heterosexual HIV discordant couples).

Additional safety data were available from published studies of MSM and heterosexual adults noted earlier i.e. studies CDC 4323, FHI PrEP, CDC TDF2 and FEM PrEP.

Post-marketing safety data included interim report from Antiretroviral Pregnancy Registry (Study GS-US-276-0101), another interim report (GS-US-276-0103) of an observational study of subjects receiving Truvada for PrEP in the US, latest PSUR/PBRER for Truvada and safety data updates from the sponsor.

In iPrEx (N = 2,499 MSM) AEs were reported in 55% TDF/FTC and 56% placebo subjects. A similar incidence of Grade 3 or 4 AEs (9%) and SAEs (4%) were reported in the 2 groups. Five deaths (1 in TDF/FTC, 4 in placebo) were reported.

Clinical and laboratory AEs leading to drug discontinuations were reported in 2% and <0.1% subjects in TDF/FTC and placebo groups respectively.

⁸ Peterson *et al* (2007). Tenofovir disoproxil fumarate for prevention of HIV infection in women: A phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clin Trials* 2(5): e27. doi:10.1371/journal.pctr.0020027.

⁹ Thigpen *et al* (2012). TDF2 Study Group. [Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana](#). *NEJM*. 2012;367(5):423-34.

¹⁰ Van Damme *et al* (2012). Preexposure prophylaxis for HIV infection among African women. *NEJM*. 2012;367:411-22.

Grade 4 alanine aminotransferase (ALT) abnormalities were recorded in 4 subjects in each group.

Overall, serum creatinine elevations above ULN were reported more commonly in TDF/FTC subjects compared to placebo subjects (25 versus 14 subjects respectively).

Bone fractures were reported in 36 subjects in the context of trauma (21 (2%) in TDF group compared with 15 (1%) placebo group).

At Week 24, there were statistically significant decreases in BMD in the TDF/FTC group compared with placebo (total hip $p=0.0004$, spine $p=0.0007$). The decreases in BMD ranged from approximately 0.5% to 1% but no further reductions were apparent at subsequent visits to Week 96.

Total hip osteopaenia (T-score of -1.0 to -2.5) at any post-baseline visit was reported in 19% TDF/FTC group compared with 18% placebo subjects. No subjects in either group had a marked reduction in BMD ($>7.0\%$ at ≥ 2 consecutive visits).

A decrease of $\geq 5\%$ in BMD in the spine was reported in 14% subjects in TDF/FTC group compared with 6% placebo subjects. Marked decreases ($>5\%$ at 2 consecutive visits) were observed in 3% and 2% subjects in the 2 groups respectively.

No hepatic flares were observed in 12 subjects with HBV at baseline or 4 subjects who acquired HBV during the study.

In Partner PrEP (heterosexual HIV discordant couples; $N = 4,758$), AEs were reported in 86%, 85%, and 85% TDF, TDF/FTC and placebo groups respectively. Grade 4 AEs were reported in 37%, 26%, and 32% subjects in the 3 groups respectively.

Overall, SAEs were reported in 7% partner subjects. A total of 25 deaths were reported with 8 in TDF, 8 in TDF/FTC group and 9 in placebo group. Two deaths (TDF/FTC group) (pulmonary embolus and influenza) were considered drug-related by the investigator. In an update, one more fatal event (cerebrovascular event) was reported but was not considered study drug-related.

No more than 2% of any study group experienced AEs related to ALT and alanine aminotransferase (AST) abnormalities. Two subjects in TDF/FTC group experienced a Grade 4 ALT elevation.

Any increased serum creatinine was reported in 5%, 7%, and 5% partner subjects in TDF, TDF/FTC and placebo groups respectively. One subject (TDF group) had a Grade 2 elevation. There was no Grade 3 or 4 elevations.

Bone fractures were reported in $<1\%$ subjects in each study drug group in the context of trauma. BMD was not assessed.

A total of 1,785 female partners (598, 566 and 621 in TDF, TDF/FTC and placebo groups respectively) were randomised in Partners PrEP. A total of 288 pregnancies (112, 80 and 96 in TDF, TDF/FTC and Placebo groups respectively) were reported in 267 women and 178 were completed.

The distribution of various outcomes was as follows (Table 8):

Table 8: CO-US-104-0380 Summary of pregnancy outcomes in partner subjects (ITT)

	TDF	FTC/TDF	Placebo	Total
Pregnancies reported, n	112	80	96	288
Pregnancies completed, n (%) ^a	70 (63)	54 (68)	54 (56)	178 (62)
Live births, n (%) ^b	42 (60)	23 (43)	25 (46)	90 (51)
Loss of pregnancy, n (%) ^b	28 (40)	31 (57)	29 (54)	88 (49)
Spontaneous abortion, n	21	28	21	70
Loss at < 20 weeks gestation, n	18	27	20	65
Loss at 20–36 weeks gestation, n	1	1	0	2
Loss at ≥ 37 weeks gestation, n	0	0	1	1
Gestation age at loss unknown, n	2	0	0	2
Induced abortion, n	7	3	8	18

a Percentage based on the number of pregnancies reported.

b Percentage based on the number of pregnancies completed.

A total of 4 birth defects were reported in TDF/FTC group.

Study GS-US-276-0101 (Antiretroviral Pregnancy Registry) [APR]

This is an interim report (1 January 2011 to 31 January 2014) of an observational study of maternal and foetal outcomes in HIV-uninfected women receiving Truvada for PrEP prior to conceiving.

At the interim analysis cut-off point, 36 pregnant women with Truvada prescriptions were identified in the database, of which 35 were enrolled in the Partners PrEP study which required discontinuation of drugs upon diagnosis of pregnancy. The subjects entering to this database are matched 1:1 with a comparison group of HIV-1-infected pregnant women receiving any other ART.

All subjects (36 in Truvada for PrEP group and 36 matched controls) were exposed during the first trimester and all but one patient discontinued Truvada. The mean exposure to Truvada was 6.61 weeks (range 0.1 to 31.4 weeks). Exposure was 12.9 weeks in a single individual who continued treatment during her pregnancy.

In Truvada for PrEP group of women (n=36), there was one birth defect in 19 live births indicating a prevalence of 0.05 (95%CI 0.01, 0.26).

In the matched control group (n=36) of women (HIV positive on any ART), there was one birth defect in 28 live births indicating a prevalence of 0.04 (95%CI 0.01 – 0.18). See Table 9.

Table 9: Study 0101 Prevalence of birth defects

	Truvada for PrEP, HIV- (N=36)			Any Treatment, HIV+ (N=36)		
	Birth Defects (n)	Live Births (n)	Prevalence (95% CI)	Birth Defects (n)	Live Births (n)	Prevalence (95% CI)
Total	1	19	0.05 (0.01-0.26)	1	28	0.04 (0.01-0.18)
Age (years)						
≤19	0	0	-	0	5	0.00 (0.00-0.52)
20-34	1	11	0.09 (0.01-0.41)	0	14	0.00 (0.00-0.23)
≥35	0	0	-	1	8	0.13 (0.01-0.53)
Geographical Region						
Africa	1	18	0.06 (0.01-0.28)	1	24	0.04 (0.01-0.21)
United States	0	1	0.00 (0.00-0.98)	0	4	0.00 (0.00-0.60)
Clinical Study Enrollment						
Yes	1	18	0.06 (0.01-0.28)	1	24	0.04 (0.01-0.21)
No	0	1	0.00 (0.00-0.98)	0	4	0.00 (0.00-0.60)
Prenatal Testing						
Yes	0	1	0.00 (0.00-0.98)	1	11	0.09 (0.01-0.41)
No	1	18	0.06 (0.01-0.28)	0	17	0.00 (0.00-0.20)

* Prevalence estimates were based on the number of live births. Defects include those meeting the Centers for Disease Control and Prevention Criteria (CDC) definition only. Excludes reported defects in abortions < 20 weeks.

¹¹ Prevalence estimates were based on the number of live births.

The prevalence of Adverse Pregnancy Events (spontaneous abortion, induced abortion and still births) was as follows (Table 10):

Table 10: Prevalence of Adverse Pregnancy Events

APR database (interim report)	Truvada for PrEP			Any ART (HIV positive)		
	Events	Prevalence	95% CI	Events	Prevalence	95% CI
Total	17/36	0.47	0.30, 0.65	8/36	0.22	0.10, 0.39
Spontaneous abortions	11/36	0.31	0.16, 0.48	4/36	0.11	0.03, 0.26
Induced abortions	6/36	0.17	0.06, 0.33	2/36	0.06	0.01, 0.19
Still births	0/36	0.00	0.00, 0.10	2/36	0.06	0.01, 0.19

Prevalence estimates were based on the number of live births.

Note that as Partners PrEP and the Registry study overlapped in time so that the majority of pregnancies in Partners PrEP were not eligible for inclusion in the APR.

Study GS-US-276-0103

This is an ongoing observational study of subjects who seroconvert while taking Truvada for PrEP in various demonstration projects (USA) or studies of Truvada for PrEP.

As of cut-off date (August 2014), a total of 34 evaluable seroconversions have been reported in 2190 subjects. All were male with a mean age of 28 years.

The total exposure to Truvada was 1,925 PY with an estimated HIV seroconversion rate of 1.77/100 PY. Viral resistance testing was performed in 14 cases. All cases were wild type virus and no resistance mutations were identified.

Truvada PSUR/PBRER

Since its international birthdate in 2004, the cumulative exposure to Truvada is estimated at 3,032,901 PY including 461,395 PY (5,814 in Australia and New Zealand) in the latest reporting period (3/4/2013 to 2/4/2014).

During the latest reporting period, approximately 3,305 subjects received Truvada in HIV (n=2,955) and HBV (n=350) clinical trials. In addition, there were 56 ongoing clinical trials with a cumulative exposure of 20,559 PY.

A total of 139 reports relating to renal toxicity were reported in the latest PSUR, corresponding to 2.5 events/10,000 PY exposure. This is comparable with that reported in the previous PSUR (2.2/10,000 PY).

A total of 51 reports relating to bone events were reported in the latest PSUR. Of these 20 events were related to osteopaenia/osteoporosis.

At the request of the FDA, Gilead provided an analysis of its Drug Safety and Public Health database for bone/muscle events (such as rhabdomyolysis, osteomalacia, muscular weakness, and myopathy) due to proximal renal tubulopathy (PRT)/loss of BMD.

There were 11,786 TDF events in the database of which PRT events were reported in 6.6% and bone/muscle events in 3.0% cases. Approximately 24% cases with a bone/muscle

event also reported a PRT event, whereas about 11% PRT cases also reported a bone/muscle event. A total of 0.7% cases in the database reported both PRT and bone/muscle event. The cases which reported both PRT and NSAID use accounted for 0.6% of all cases.

NSAIDs were used before a diagnosis of PRT in 4.3% of PRT cases and high doses of NSAIDs were reported in 26.5% of these. All reported cases are stated to have occurred in patients with risk factors for renal dysfunction.

A disproportionality analysis did not show increased likelihood of PRT with NSAIDs and TDF.

A multivariate analysis showed that NSAID use before or after a bone/muscle event did not increase the risk of PRT with or without exposure to TDF.

In a separate Renal Tubulopathy Reversibility review, data from various sources indicated that PRT was reversible in 81% to 93% of cases following cessation of TDF.

Overall, in safety database relating to the use of TDF/FTC for PrEP, increased serum creatinine was reported more commonly in subjects receiving FTC/TDF but most resolved with cessation of treatment.

Similarly, there was a mean 0.5% to 1% loss of BMD in subjects receiving FTC/TDF over observation periods of 24 to 96 weeks compared to placebo. Most of the observed bone loss occurred in the first 6 months but further minor progression was observed over the remaining period. In the iPrEx study, BMD loss of $\geq 5\%$ in the spine measured at any visit was observed in more subjects receiving FTC/TDF (14% vs. 6%). This observation was also seen in study CDC4323 in which loss of BMD was higher in the FTC/TDF group (13% versus 6%).

No hepatic viral flares during or after treatment with FTC/TDF or TDF were reported in subjects with chronic or acute HBV infection. The number of subject with HBV was low and the risk of potentially serious hepatic flare on treatment withdrawal cannot be discounted.

Risk management plan

The TGA's Advisory Committee on Safety of Medicines (ACSOM) advice was not sought for this submission.

EU-RMP for Truvada (Version: 8, dated 27 June 2014) with an Australian Specific Annex (ASA) as Annex 13 (Version: 0.1, dated February 2015) apply to this submission and will be a condition of approval including any further negotiations and finalisation of the outstanding issues with the RMP evaluation area of the TGA.

Risk-benefit analysis

Delegate's considerations

In the dossier submitted by the sponsor, the pivotal evidence of efficacy for the use of Truvada (TDF/FTC 300/200) for PrEP is derived from 2 clinical trials that were conducted largely in countries where the baseline risk (absolute risk) of acquiring HIV infection is different (higher) from that in Australia based on population prevalence.

The first trial (iPrEX) was a randomised double blind, placebo controlled trial (N=2,499) in seronegative MSM subjects in Peru, Ecuador, Brazil, USA, Thailand and South Africa who were considered at high risk of acquiring HIV infection according to protocol-defined sexual behaviours.

After a median exposure of 62 weeks (3,324PY) to the 2 study drugs (TDF/FTC 300/200 or placebo once daily dosing), the Relative Risk Reduction (RRR) versus placebo was 44% (95%CI 15% to 63%) in mITT population.

In subjects with high level ($\geq 90\%$) of compliance with the study drugs (self-reports; pill counts), RRR was 73% (95%CI 41% to 88%).

In subjects with detectable levels of the study drug in plasma (tenofovir-DP), RRR was 92% (95%CI 40% to 99%).

The second trial (Partners PrEP) was a randomised, double blind, placebo controlled trial in heterosexual, HIV serodiscordant (HIV negative Partner subject/HIV positive index subject not on ART) couples (N=4,758) in Kenya and Uganda in which participants were exposed to the 3 study drugs (TDF 300mg alone or TDF/FTC 300/200 mg or placebo once daily dosing) over a median of 23 months.

In TDF group, RRR (vs placebo) was 67% (95%CI 44% to 81%).

In TDF/FTC group, RRR (vs placebo) was 75% (95%CI 55% to 87%). The difference between TDF and TDF/FTC groups was not significant.

In a substudy, compliance was noted to be associated with efficacy.

In a case-cohort study in partner subjects with detectable plasma drug (tenofovir DP), RRR was 86% (95%CI 67% to 95%) in TDF group and 90% (95%CI 56% to 98%) in TDF/FTC group.

In general, the predefined subgroup analyses, including circumcision, were consistent with the overall protective effect in both studies.

The importance of drug compliance was further demonstrated in a failed study FEM PrEP (included in the dossier) and elsewhere.¹²

In the reported trials of PrEP13, overall observed efficacy of Truvada for PrEP has ranged from 6% to 92% in combination with safe sex practices, counselling and clinical oversight.

The dose and duration of prophylaxis with Truvada has not been optimised. As expected, the protective effect appears to be limited to the period of use of drug as noted in the off-treatment period in iPrEX (hazard ratio 0.48, 95%CI 0.08 to 2.9).

Alternative regimes have been investigated.¹⁴ Anecdotal information from prescribing doctors in New South Wales (NSW) indicates that short-term Truvada prescribed for post-exposure prophylaxis may end up being used for PrEP in a myriad of ways influenced by social media.

Changes in sexual behaviours over time were variable in the clinical studies of PrEP including the 2 pivotal trials. Regular counselling for drug compliance, safe sexual practices and STDs was provided in both pivotal studies.

A concern in practice is the perception of Truvada as alternative to the use of condoms ('chemical condom') sometime assisted unwittingly. A drop in the use of condoms will not only reduce efficacy of Truvada for PrEP but also leave exposure to other STIs unprotected.

A rise in STIs (particularly syphilis and gonorrhoea) has been noticeable since 2012 in overseas jurisdictions although association with PrEP is not implied.

¹² Marrazzo *et al* (2015). Tenofovir-based preexposure prophylaxis for HIV infection among African women. *NEJM*. 2015;372:509–18.

¹³ Spinner *et al* (2015). HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. *Infection*. 2015, DOI 10.1007/s15010-015-0850-2.

¹⁴ Molina *et al* (2015). On-Demand Preexposure Prophylaxis in Men at High Risk of HIV- 1 infection. *NEJM*. 2015;373:2237-46. DOI:10.1056/NEJMoa1506273

The currently known adverse effects profile of TDF/FTC in the treatment of HIV was confirmed during the clinical trials of its use in PrEP. No new signals were reported.

The established effects include proximal renal tubulopathy, effect on bone mineral density, risk of hepatic B flare in co-infection on treatment withdrawal, pancreatitis, lactic acidosis, hepatomegaly with steatosis, lipodystrophy and drug interactions.

Long-term data are currently lacking on renal and bone toxicity following extended periods of use of Truvada for PrEP in otherwise healthy individuals.

[information redacted]

In iPrEX study, no drug resistant variants were detected (after the even analysis) in subjects in TDF/FTC group who had seroconverted, whereas in Partners PrEP one resistant mutation was observed in TDF/FTC group.

Spinner et al (2015)¹³ report a HIV mutation resistance emergence of 5.9% (18/305) in all documented cases of HIV seroconversion in PrEP studies for TDF or TDF/FTC PrEP.

The submission is supported by an EU RMP and ASA. Identified risks include HIV acquisition, development of viral resistance and renal/bone toxicity.

Both pharmacovigilance and risk minimisation activities are proposed mainly as part of EU-RMP. Note PrEP-user Registry or restricted access is not proposed.

No epidemiological data relevant to PrEP use in Australia is currently available for regulatory purposes. Limited access schemes ('demonstration projects') are currently being administered in various Australian jurisdictions. A large demonstration project (EPIC trial) is about to get underway (March 2016) in NSW aiming at inclusion of about 4000 MSM over two years.

Public interest in this submission is also noted. ASHM supports PrEP.

In summary, the use of Truvada for PrEP was shown to be efficacious in clinical trials in combination with use of condoms, counselling, compliance and close supervision. The studied populations were MSM and HIV discordant heterosexual couples.

Given the lack of formal investigation of an optimum dosing strategy, daily use over undefined periods in MSM and HIV discordant heterosexual population is supported by the submitted clinical trials data. In practice, no doubt, it will be informed by the evolving clinical guidelines from the relevant bodies and the accumulating clinical experience.

Summary of issues

- Adequacy of dataset for applicability in Australian context.
- Advice in respect of post-market surveillance

Proposed action

The Delegate had no reason to say, at this time, that the application for Truvada should not be approved for the proposed extension of indication for use in PrEP.

Pending advice from the ACPM, the proposed use of Truvada (TDF/FTC 300/200 once daily) for PrEP is supported in the 2 identified high risk population groups that is, MSM and HIV discordant heterosexual populations.

Submitted for advice from the TGA's ACPM.

Request for ACPM advice

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

1. Does the committee consider the supporting evidence for the use of TDF/FTC (300/200mg once daily) for PrEP in the identified high risk populations appropriately applicable in Australian context to allow approval?
2. Does the committee propose any additional recommendations with regard to the proposed indication, Dosage and Administration and precautions to further facilitate correct and effective use of the medicine?
3. Does the committee propose any additional pharmacovigilance or risk minimisation activities in the post market phase?
4. The committee is also requested to provide advice on any other issue that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

This application for an extension of indication of Truvada is based on information generated by other study sponsors for the evaluation of emtricitabine/ tenofovir disoproxil fumarate (FTC/TDF) as pre exposure prophylaxis of HIV-1 infection (PrEP). The principal data source to support the use of FTC/TDF in this setting are two Phase III studies conducted in men who have sex with men (MSMs) and transgender women (TGW):

The 'iPrEx' study (sponsored by the US National Institutes of Health (NIH), with cofunding provided by the Bill and Melinda Gates Foundation). Gilead provided study drugs but was not involved in any aspect of design, conduct or analysis of the study.

- A Phase III study known as the 'Partner's PrEP' study sponsored by the Bill and Melinda Gates Foundation, which funded the study but did not oversee the protocol. The University of Washington assumed sponsor oversight responsibilities for the study. Gilead provided study drugs but was not involved in any aspect of design, conduct or analysis of the study.

It is important to note that one supporting study that was provided for review failed to show benefit of FTC/TDF PrEP. This study known as 'FEM-PrEP' was designed to evaluate the safety and efficacy of once-daily oral FTC/TDF compared with placebo as PrEP among high-risk African women. The study was sponsored by Family Health International and funded by USAID and the Gates Foundation. FEM-PrEP was terminated prematurely with similar numbers of HIV-1 infections in the FTC/TDF and placebo groups after a routine (planned) review of the study data by the study's DSMB concluded that the study would not be able to demonstrate efficacy in the study population. While the reason that FTC/TDF was not effective in the FEM-PrEP study is not definitively established, follow-up assessments communicated to Gilead Sciences (GSI) from the FEM-PrEP study team indicated that seroconversion events were correlated with a lack of detectable drug concentrations. The Delegate notes and Gilead agrees that this study highlights the importance of drug adherence.

In both the iPrEx and Partner's PrEP studies, the general consistency of efficacy across multiple subgroups confirms the efficacy of PrEP in the MSM, TGW and serodiscordant couple populations. Within the iPrEx study, randomisation was stratified by investigational centre, and no effect reversal was observed across investigational centres. In addition, no effect reversal was seen within multiple subsets including age, race or ethnic group, region, male circumcision, level of education, or alcohol use. Within the Partner's PrEP study, similar protective trends for FTC/TDF and TDF compared with placebo were observed in each subgroup including gender, and the treatment differences were consistent within most subgroup analyses. Observed differences were due to the magnitude of the effect, rather than the direction of the effect. As indicated previously, the FEM-PrEP study failed to demonstrate efficacy for PrEP with FTC/TDF in women (possibly

due to very low adherence to study drug), while the CDC TDF¹⁵ study demonstrated the efficacy of PrEP in both women and men, thus confirming the results observed in the Partner's PrEP study.

Finally, the ongoing Anti-viral Pregnancy Registry (APR) (GS-US-276-0101) collects data on women who become pregnant while taking FTC/TDF once daily for PrEP. In the September 2014 interim report provided with the submission, 36 women have been reported to the APR and 35/36 discontinued use of FTC/TDF during pregnancy due to protocol restrictions. No adverse pregnancy outcomes and no adverse neonatal outcomes that were attributable to use of FTC/TDF for PrEP have been reported to date.

Given the demonstrated safety and efficacy in women, it is unreasonable to restrict the indication to at-risk women who are in heterosexual serodiscordant couples only as women are also at risk of sexually acquired HIV in other situations outside of a monogamous couple. Taking the Delegate's comments regarding optimum dosing strategy further '*In practice, no doubt, it will be informed by the evolving clinical guidelines from the relevant bodies and the accumulating clinical experience*' similar consideration regarding evolving clinical guidelines should be applied to assessing the appropriate at-risk females that could be additionally protected from contracting sexually acquired HIV. As such the PrEP indication proposed for registration should be:

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples (see CLINICAL studies).

Discussion of Delegate's comments

ACPM advice being sought by the TGA Delegate on the following questions:

1. *Does the Committee consider the supporting evidence for the use of TDF/FTC (300/200mg once daily) for PrEP in the identified high risk populations appropriately applicable in Australian context to allow approval?*

The main route of HIV transmission in Australia continues to be sexual contact in MSMs, which accounted for 70% of the cases in 2014.¹⁶ The iPrEx study therefore provides safety and efficacy data which are directly applicable to the Australian context. The daily dosing is foreseen to be applicable whilst the patient is at-risk. When and if the patient's personal situation changes to a point where they are no longer considered at-risk the counselling physician should advise the patient that prophylaxis is no longer required.

2. *Does the committee propose any additional recommendations with regard to the proposed indication, Dosage and administration and precautions to further facilitate correct and effective use of the medicine?*

Gilead considers that the proposed PI suitably defines the safety and efficacy profile of Truvada used in the treatment of HIV and the PrEP indication. The PI and indication makes it very clear that Truvada used for PrEP is to be used in combination with safer sex practices and education about harm reduction and not as a replacement for safer sex practices.

3. *Does the committee propose any additional pharmacovigilance or risk minimisation activities in the post market phase?*

¹⁵ Thigpen et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana N Engl J Med 2012. DOI: 10.1056/NEJMoa1110711

¹⁶ The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2015. The Kirby Institute, UNSW Australia, Sydney NSW 2052

Currently there are a number of large demonstration projects supported by State Departments of Health and research organisations investigating the appropriate use of FTC/TDF for PrEP in Australia. Such programs include PRELUDE (Kirby Institute, 400 participants), QPrEP (HIV Foundation Queensland, 150 participants) Vic PrEP (The Alfred Hospital, 200 participants), EPIC PrEP (Kirby Institute, 3700 participants) and WA PrEP (WA AIDS Council, 50 participants). The widespread nature and scale of these projects will provide substantial data on enhanced pharmacovigilance and support ongoing risk minimisation activities post approval as their results and their interpretation become available.

Advisory Committee considerations

The ACPM resolved to recommend to the TGA delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of clinical efficacy and safety, agreed with the Delegate and considered Truvada, containing 300 mg of tenofovir disoproxil fumarate and 200 mg of emtricitabine, to have an overall positive benefit–risk profile for the indication:

Treatment of HIV-1 infection:

Truvada is indicated for the treatment of HIV infected adults over the age of 18 years, in combination with other antiretroviral agents.

Pre-Exposure Prophylaxis:

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples (see CLINICAL TRIALS).

In making this recommendation the ACPM;

- noted adherence is critical to successfully preventing transmission
- noted lack of long term safety data and a need to strengthen cautions about prolonged use
- noted the lack of data on bone safety particularly in females.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- The ACPM advised that the sponsor should be required to commit to contributing to the Kirby Institute surveillance of PrEP, including commitment to monitoring PrEP failures prevalence and particularly resistance.

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

The ACPM agreed with the Delegate's proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the Precautions section of the PI and relevant section of the CMI on the need to determine HBV status before starting preventative therapy because of the risk of flare on discontinuation.
- a statement in the Precautions section of the PI and relevant section of the CMI on the risks to women who are pregnant or who are intending to become pregnant

- information in the PI and relevant sections of the CMI emphasising that treatment of HIV and suppression of HIV virus in infected individuals has been shown to be highly effective (around 96%) in preventing transmission of HIV infection to uninfected individuals.
- a statement that infected partners in the serodiscordant couples study had neither previously received anti-HIV treatment, nor received anti-HIV treatment during the course of PrEP study. Under the currently accepted HIV treatment guidelines, all HIV infected individuals need to be treated.
- a strengthening of statements on concurrent counselling, condom use, regular HIV testing, regular STI testing and treatment
- statements in the PI and relevant sections of the CMI that TDF/FTC does not protect against other STIs
- statements for guidance for prescribers on the assessment and identification in Australia of an individual's risk of being infected with HIV. High risk behaviours should be defined in detail in the PRECAUTIONS section of the PI.

Specific advice

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

1. *Does the committee consider the supporting evidence for the use of TDF/FTC (300/200 mg once daily) for PrEP in the identified high risk populations appropriately applicable in Australian context to allow approval?*

The ACPM advised the risks in high risk groups in Australia –MSM and serodiscordant couples - are comparable to those populations in the pivotal trials, even if the overall population risk is lower. However, the risk of transmission is not applicable to all populations at risk of HIV in relationship networks in Australia. The main issue for clinicians will be to assess level of risk.

2. *Does the Committee propose any additional recommendations with regard to the proposed Indication, Dosage and Administration and Precautions to further facilitate correct and effective use of the medicine?*

The ACPM advised the addition of the risk factors for identifying high risk individuals;

- as enumerated in the US and Canadian Product Information documents: 'When considering Truvada for pre-exposure prophylaxis the following factors may help to identify individuals at high risk' (with removal of items not applicable here such as 'incarceration')
- the addition of criterion 1 to 4 for *MSM PrEP Guidelines* from the NSW Kirby Institute program
- the addition of high risk heterosexual partners from high prevalence countries or their partners from high prevalence countries

Clearly a significant issue is risk reduction behaviours including counselling and safe sex practices which are likely to be poorer outside of a trial situation. Therefore statements in PI and CMI on other preventative measures including information on treatment of HIV positive individuals should be strengthened.

3. *Does the Committee propose any additional pharmacovigilance or risk minimisation activities in the post market phase?*

The ACPM advised that the sponsor should be required to commit to contributing to the Kirby Institute surveillance program for PrEP, including commitment to monitoring PrEP failures prevalence and resistance.

The ASA-RMP should include active surveillance for bone and renal toxicity. Concerns remain about toxicity with prolonged use. It is concerning that small proportion (14%) have >5% fall in spine bone mineral density. Consideration should be given to some warnings about use in females, and use for longer than 1-2 years.

The committee also recommended strengthening of renal Precautions in the context of PrEP including regular monitoring such as with urine dipstick testing.

The ACPM was of the view that there should be some modification to the surveillance of newly acquired HIV infections to capture PrEP.

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 Truvada containing fixed dose combination of (300 mg tenofovir disoproxil fumarate/200 mg emtricitabine) tablets, indicated for:

Pre-Exposure Prophylaxis

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. This indication is based on clinical trials in men who have sex with men (MSM) at high risk for HIV-1 infection and in heterosexual serodiscordant couples (see Clinical Studies)

Specific conditions of registration applying to these goods

The Truvada Risk Management Plan (RMP): EU-RMP for Truvada (Version: 8, dated 27 June 2014) with an Australian Specific Annex (ASA) as Annex 13 (Version: 0.1, dated February 2015), included with submission PM-2015-00411-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Truvada at the time this AusPAR was published 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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