14 December 2017
EMA/10650/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Truvada

International non-proprietary name: emtricitabine / tenofovir disoproxil

Procedure No. EMEA/H/C/000594/II/0135

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

3TC lamivudine
ADR adverse drug reaction
AE adverse event
AIDS acquired immunodeficiency syndrome
ALT alanine aminotransferase
ART antiretroviral therapy
ARV antiretroviral
AST aspartate aminotransferase
AUC area under the plasma/serum concentration versus time curve
BCE bone collagen equivalent
BMD bone mineral density
CBV lamivudine/zidovudine (Combivir)
CDC Centers for Disease Control and Prevention
CD4 cluster determinant 4
CI confidence interval
COSTART Coding Symbols for a Thesaurus of Adverse Reaction Terms
CSR clinical study report
d4T stavudine
DAVG difference between time-weighted average postbaseline and baseline
DAVGXX time-weighted average change from baseline at Week xx
DXA dual-energy x-ray absorptiometry
eCTD electronic common technical document
EFV efavirenz
eGFR estimated glomerular filtration rate
EU European Union
FDA Food and Drug Administration
FTC emtricitabine (Emtriva)
FTC/TDF emtricitabine/tenofovir disoproxil fumarate (Truvada)
FTC-TP emtricitabine 5′-triphosphate
GSS genotypic sensitivity score
HIV, HIV-1 human immunodeficiency virus, type 1
HR hazard ratio
ITT intent-to-treat
LLOQ lower limit of quantitation
LOCF last observation carried forward
MedDRA Medical Dictionary for Regulatory Activities
MITT modified intent-to-treat
m module
mo month(s)
Truvada (Emtricitabine/Tenofovir Disoproxil Fumarate)
MSM men who have sex with men
n/N number of subjects in a population (N) or subset (n)
NA not applicable
NC = F non-completer = failure
NNRTI nonnucleoside reverse transcriptase inhibitor
NRTI nucleoside reverse transcriptase inhibitor
OBR optimised background regimen

PBMC peripheral blood mononuclear cell
PCR polymerase chain reaction
PEP post-exposure prophylaxis
PI protease inhibitor
PK pharmacokinetic(s)
PrEP pre-exposure prophylaxis
PRT proximal renal tubulopathy
PTH parathyroid hormone
Q1, Q3 first quartile, third quartile
RAT randomised and treated
RMP risk management plan
RNA ribonucleic acid
RT reverse transcriptase
SAE serious adverse event
SD standard deviation
SmPC summary of product characteristics
SOC system organ class
STB elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild)
STIs sexually transmitted infections
TAM thymidine analogue mutation
TBLH total body less head
TDF tenofovir disoproxil fumarate (Viread)
TFV tenofovir
TFV-DP tenofovir diphosphate
TLOVR time to loss of virologic response
TVD emtricitabine/tenofovir disoproxil fumarate (Truvada)
URAI unprotected receptive anal intercourse
US United States
UTG unable to genotype
vs versus
y year(s)
ZDV zidovudine

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences International Limited submitted to the European Medicines Agency on 1 February 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include pre-exposure prophylaxis of HIV in adolescents aged 12 to < 18 years at high risk; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on extrapolation of data for emtricitabine, tenofovir disoproxil fumarate, and Truvada in HIV-infected and uninfected subjects.

The Package Leaflet and Risk Management Plan (v.15) are updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor linguistic amendments

The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0294/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0294/2015 was completed.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	1 February 2017
Start of procedure:	18 February 2017
CHMP Rapporteur Assessment Report	27 March 2017
CHMP Co-Rapporteur Assessment Report	27 March 2017
PRAC Rapporteur Assessment Report	21 April 2017
PRAC members comments	26 April 2017
Updated PRAC Rapporteur Assessment Report	27 April 2017
PRAC Outcome	5 May 2017
CHMP members comments	8 May 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 May 2017
Request for supplementary information (RSI)	18 May 2017
Re-start	17 July 2017
CHMP Rapporteur Assessment Report	26 July 2017
PRAC Rapporteur Assessment Report	18 August 2017
PRAC members comments	23 August 2017
Updated PRAC Rapporteur Assessment Report	24 August 2017
PRAC Outcome	1 September 2017
CHMP members comments	4 September 2017
Updated CHMP Rapporteur Assessment Report	7 September 2017
2nd Request for supplementary information (RSI)	14 September 2017
Re-start	16 October 2017
CHMP Rapporteur Assessment Report	17 October 2017
PRAC Rapporteur Assessment Report	16 November 2017
PRAC members comments	22 November 2017
Updated PRAC Rapporteur Assessment Report	23 November 2017
PRAC Outcome	30 November 2017
CHMP members comments	4 December 2017
Updated CHMP Rapporteur Assessment Report	7 December 2017
CHMP opinion:	14 December 2017

2. Scientific discussion

2.1. Introduction

This application rests mainly on the safety and efficacy data relevant to pre-exposure prophylaxis (PrEP) in adults that were submitted and fully assessed under EMEA/H/C/594/II/126. The current application includes very limited new clinical data from two studies of PrEP in the target population that were not sponsored by the MAH:

- ATN-113, which investigated the use of Truvada (TVD) for PrEP in HIV-uninfected male adolescents aged 15 to 17 years with a history of having sex with other males (presented publicly in 2016)
- ATN-110, which investigated the use of TVD for PrEP in HIV-uninfected MSM aged 18-22 years (published in 2017)

HIV-1 seroconversion rates and limited PK data are available from these two studies. Available safety information was provided for studies ATN 110 and ATN-113. Additional PK, safety and efficacy data on treatment of HIV-infected adolescents come from the Stribild (STB) Study GS-US-236-0112.

The dossier contains several Gilead-sponsored studies that were already assessed as part of numerous prior applications and which have supported the use of FTC, TDF and TVD for the treatment of HIV in children and adults. The efficacy data from these studies are not strictly relevant to use of TVD for PrEP. The PK data and safety data pertaining to daily dosing of HIV-1-infected adolescents with FTC, TDF or STB are of some relevance to the current application. However, the PrEP usage will be in the HIV-1 uninfected population and will not involve additional anti-retroviral agents that may have influenced the PK and safety profiles described in the treatment studies.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable by the CHMP since TVD is already approved for the treatment of adolescents from age 12 years using a once daily dose.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The two ATN trials were conducted in accordance with operative FDA regulations and usual GCP requirements.

Table 1. Overview of Gilead-Sponsored Studies Included in the Submission

Study	Study Design	Number of Subjects by Treatment Regimen	Data Presented
Paediatrics			
FTC-202	Multicenter, open-label Phase 2 study in ART-naive or very limited ART exposed male or female pediatric subjects. Subjects had no or very limited prior ART exposure	37 subjects enrolled (ITT population), most ART naive; Age groups (n): 3 months to < 3 years: 0 3 to 12 years: 21a 13 to 21 years: 16	Week 48 efficacy and safety, and PK of FTC
FTC-203	Multicenter, open-label Phase 2 study in ART-naive and ART-experienced male or female pediatric subjects. ART-naive subjects had no or very limited prior ART exposure.	116 subjects enrolled (ITT population); 71 ART-naive and 45 ART experienced Age groups (n): 3-24 months: 16 25 months-6 years: 68 7–12 years: 29 13–17 years: 3	Week 48 efficacy and safety, and PK of FTC
FTC-211	Multicenter, open-label Phase 2 study in ART-naive and ART experienced male or female pediatric subjects. ART-naive subjects had no or very limited prior ART exposure	16 subjects enrolled (ITT population), 15 ART-naive, 1 ART-experienced. Age groups: (n) 3-24 months: 0 7–12 years: 1 13–17 years: 15	Week 48 efficacy and safety, and PK of FTC
GS-US-104-0321	Randomized 1:1, double-blind, placebo controlled, multicenter Phase 3 study in HIV-1 infected pediatric subjects to assess the efficacy of TDF plus a genotype guided OBR compared with placebo plus OBR in HIV-1 infected ARV treatment experienced adolescents with plasma HIV-1 RNA levels ≥ 1000 copies/mL	87 randomized and treated (TDF 45, placebo 42); 85 analyzed for efficacy in the double-blind phase (ITT; TDF 44, placebo 41) 8 analyzed for PK (TDF 1, placebo 7) 79 analyzed for efficacy through the extension phase (All TDF Efficacy Analysis Set); TDF 44, placebo/TDF 35) 81 analyzed for safety through the extension phase (All TDF Safety Analysis Set; TDF 45, placebo/TDF 36)	Up to Week 336 efficacy and safety, and PK of TFV
GS-US-236-0112	Phase 2/3, open-label, multicenter, 2-part, single-group study	Enrolled: 50 Part A: 14 Part B: 36 Safety Analysis Set: 50	Week 48 safety and PK of FTC and TFV
HIV-infected Adults			
FTC-101	Open-label, dose-ranging, 14 days of repeated doses of monotherapy	41 subjects enrolled, 41 completed	PK of FTC
FTC−303	Randomized (2:1) open-label, multi-center equivalence study	6 enrolled, 5 completed study Arm 1: 294 Arm 2: 146	Week 48 efficacy and PK of FTC
GS−97−901	Multicenter Parts A & B: randomized, double-blind, placebo controlled, dose escalation. Part C: single arm, open label Extended Dosing: open label.	TDF = 46 TDF 75 mg = 12 TDF 150 mg = 8 TDF 300 mg = 8 TDF 600 mg = 10 TDF + HU = 8	PK of TFV

Study	Study Design	Number of Subjects by Treatment Regimen	Data Presented
		Placebo = 11 Placebo + HU = 2	
GS-99-907	Randomized, double-blind, placebo-controlled, intensification study. PK examined following single dose and during chronic treatment over 12 to 48 weeks	552 enrolled, 550 subjects received at least 1 dose of study drug Single dose: 14 12-48 weeks: 7 to 14	Week 48 efficacy and PK of TFV
GS-99-903	Randomized, double-blind equivalence study	600 subjects TDF: 299 d4T: 301	Efficacy through Week 144 and 336
GS-01-934	Randomized, open-label, parallel, multicenter, active controlled study	TDF+FTC+EFV: 257 CBV+EFV: 254	Efficacy through Week 48 and Week 144
HIV-uninfected Adults			
FTC-106	Open-label, single dose and 8-day repeated doses of FTC (with a single 14C-FTC dose) in healthy adult volunteers	6 enrolled, 5 completed study	PK of FTC
GS-00-914	Single-center, three-period, randomized, open label, bioequivalence and food effect study.	40 enrolled, 36 completed the study	PK of TFV

a One subject in the 3 to 12 year group had prior ART exposure for 1 week.

Table 2. Overview of non-Gilead Studies Included in the Submission

Study	Study Design	Number of Subjects by Treatment Regimen	Data Presented
Adolescents			
ATN-113 (Hosek 2016)	Open-label PrEP demonstration project and Phase 2 safety study	79 enrolled	Week 48 efficacy and safety, and PK of TFV-DP
Young Adults			
ATN-110 (Hosek 2017)	Open-label PrEP demonstration project and Phase 2 safety study	200 enrolled	Week 48 efficacy and safety, and PK of TFV-DP
HIV-Uninfected Adults			
(Patterson 2011)	Open-label, PK study in healthy HIV-negative female and male volunteers	15 subjects (7 females and 8 males)	PK of FTC and TFV
CO-US-104-0288 (iPrEx) Primary Analysis CSR	Phase 3, multicenter, international, randomized, double-blind, placebo-controlled	Randomized: 2499 (1251 FTC/TDF, 1248 placebo); Randomized and treated: 2451 (1226 FTC/TDF, 1225 placebo); Evaluable for efficacy: 2441 (1224 FTC/TDF, 1217 placebo)	Efficacy
CO-US-104-0380 (Partner's PrEP) Primary Analysis CSR	Phase 3, multicenter, international, randomized, double-blind, placebo-controlled	Randomized: 4758 partner subjects (ie, HIV-1 uninfected subjects), including 1583, 1589, and 1586 subjects in the FTC/TDF, TDF, and placebo groups, respectively	Efficacy up to maximum of 36 months

2.3.2. Pharmacokinetics

Truvada is authorised for the treatment of HIV-1 in adolescents from the age of 12 years and 35 kg (opinion reached in II/131). The pharmacokinetic data to support that usage have been assessed in various assessment reports. Since PrEP uses the same once daily dose of Truvada, all of the relevant data in HIV-1 infected adolescents were already assessed with the exception of full data from the STB study in adolescents GS-US-236-0112 and some data on TFV-DP in dried blood spots in ATN 110 and 113.

The dossier includes a Summary of Pharmacokinetics and an Extrapolation Report which:

- Compares the FTC and TFV exposures achieved in adults and in adolescents 12 to < 18 years of age
- Discusses extrapolation of efficacy data for PrEP in adults to adolescents based on comparable PK

The report presents data for plasma FTC, TDF and STB from HIV-infected and uninfected adults and infected adolescents. Some TFV-DP data in dried blood spots are available from ATN 110 and 113.

Table 3. Overview of Data from Clinical Studies in Adolescents and Young Adults Included in the Extrapolation Report

Product	Data included	Study Number	Population	Total N per study	Total N per product identified as adolescents or young adults	Total N identified as adolescents or young adults
Adolescents						
FTC	Efficacy, safety , PK	FTC-202	HIV-1 infected, ART-naïve or very limited ART-experienced paediatric subjects 3 months to 21 years of age	37 (ART-naïve 36; ART-experienced 1) 3 mo to < 3 y = 0 - 3 to 12 y = 21 13 to 21 y = 16	Eff/safety= 29 PK=27	Eff/safety= 74 PK=49
	Efficacy, safety , PK	FTC-203	HIV-1 infected, ART-naïve or ART-experienced paediatric subjects 3 months to 17 years of age	116 (ART-naive 71; ART experienced 45) 3 to 24 mo = 16 25 mo to 6 y = 68 7 to 12 y = 29 13 to 17 y = 3		
	Efficacy, safety , PK	FTC-211	HIV-1 infected, ART-naïve or ART-experienced paediatric subjects 3 months to 17 years of age	16 (ART-naive 15, ART-experienced 1). 3 to 24 mo = 0 7 to 12 y = 1 13 to 17 y = 15		
TDF	Efficacy, safety ,	GS-US-104-0321	HIV-1 infected, ART-experienced	87 (TDF 45, placebo 42)	Eff/safety = 45	

Product	Data included	Study Number	Population	Total N per study	Total N per product identified as adolescents or young adults	Total N identified as adolescents or young adults
	PK		adolescents 12 to < 18 years of age	TDF PK subset = 8	PK = 8	
FTC and TDF	PK	GS-US-236-01112	HIV-infected, ART-naïve adolescents 12 to < 18 years of age	Part A (PK): 14 Part B: 36 Safety Analysis Set: 50	PK=14	
Young adults						
TVD	Efficacy, safety	ATN 110	HIV-1 uninfected young adults 18 to 22 years of age	200	Eff/safety= 200	Eff/safety= 200

To support a conclusion on similar PK between HIV-infected and uninfected adolescents and adults the following data are summarised:

- FTC and TFV exposures following multiple doses of FTC, TDF or STB in HIV-infected adolescents and HIV-infected adults
- TFV-DP exposures following treatment with TVD in HIV-uninfected young adults
- FTC and TFV exposures in HIV-infected and uninfected adults
- FTC and TFV exposures following treatment with TVD in body fluids and mucosal tissues in HIV-uninfected adults

Pharmacokinetic parameters obtained from the FTC studies in paediatric subjects (FTC-202, FTC-211 and FTC-203) were combined. FTC was given at 6 mg/kg once daily up to 40 kg, after which subjects received a 200 mg capsule or 240 mg oral solution once daily. The mean and CV% values for the principal PK parameters for 27 adolescents aged 13-17 years are shown in Table 4.

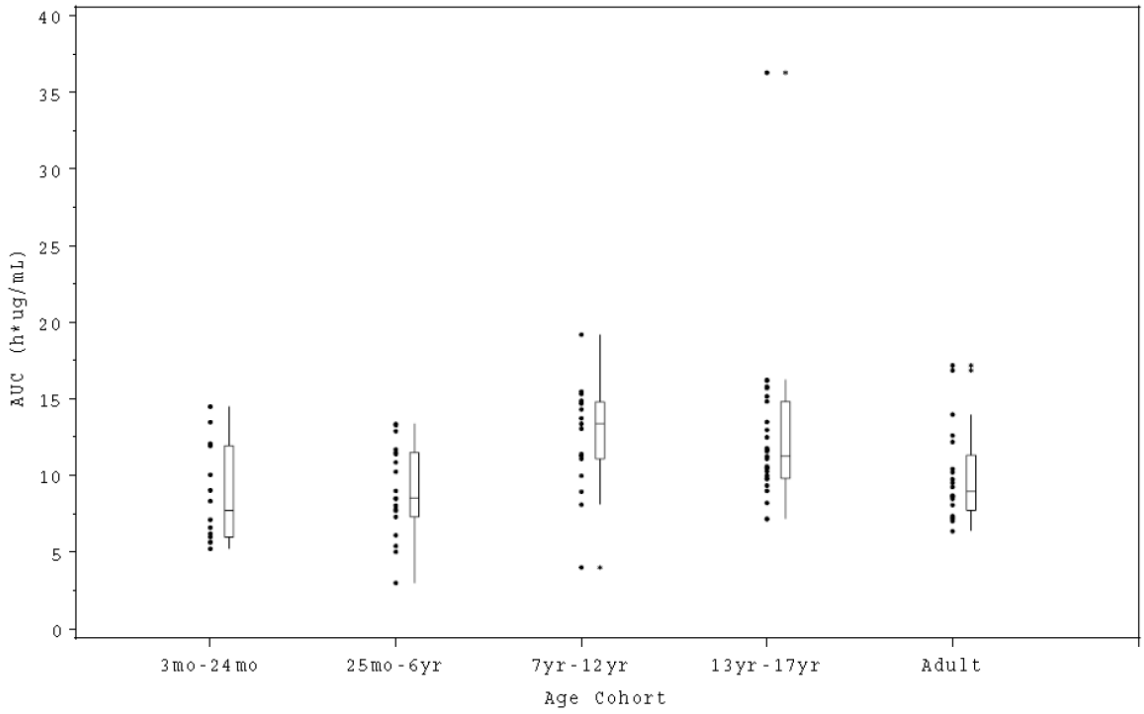
Table 4. FTC-202, FTC-211, and FTC-203 Combined Analysis: Mean (CV%) Values for FTC PK Parameters at Steady-State for Adolescents (All Subjects)

	FTC 202, FTC 211, and FTC 203[a] (13 to 17 years) (N = 27)	
FTC PK Parameter	**Mean**	**CV%**
C_{max} (µg/mL)	2.73	31
C_{min} (µg/mL)	0.064	94
T_{max} (h)	1.7	65
AUC_{tau} (h•µg/mL)	12.55	43
$t_{1/2}$ (h)	8.94	37
CL/F (mL/min/kg)	6.4	45

a One subject (study FTC-203) was excluded from the summary statistics.

The mean AUC_{tau} values in adolescents were in the range seen for HIV-infected adults as shown in Figure 1.

Figure 1. FTC-202, FTC-211, and FTC-203 Combined Analysis: Distribution of AUC (h•µg/mL) by Age Cohort (All Subjects)



One subject was excluded

Plasma TFV levels are available for 8 HIV-1 infected adolescents aged 12-16 years who received TDF (300 mg QD without regard to food) plus a background ARV regimen for at least 4 weeks in Study **GS-US-104-0321**. Serial plasma sampling over a 12-hour period after dosing provided the concentration data for steady state PK analysis. A pre-dose concentration, where available, was used as a surrogate for the 24-hour concentration.

Comparison of the plasma TFV data in adolescents in this study with historical data in HIV-1 infected adults under steady-state conditions revealed slightly higher TFV exposures despite a shorter $t_{1/2}$.

Table 5. GS-US-104-0321: Plasma TFV PK Parameters Following Multiple Doses of TDF (PK Analysis Set) and Comparative Historical Data in Adults

TFV PK Parameter	GS-US-104-0321 300 mg QD (12-16 yr) (N = 8)[a]	Historical Adult Data in HIV-1 Infected Adults					
		GS-97-901 300 mg QD		GS-99-907 300 mg QD			
		8th Dose (N = 8)	28th Dose (N = 8)	12 Weeks (N = 12)	24 Weeks (N = 12)	36 Weeks (N = 7)	48 Weeks (N = 7)
AUC_{tau} (ng•h/mL)[b] Mean (%CV)	3390.6 (36.0)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
C_{max} (ng/mL) Mean (%CV)	377.5 (35.6)	302.9	326.1	348.7 (38.3)	303.9 (36.0)	294.3 (28.0)	326.9 (18.4)
C_{last} (ng/mL) Mean (%CV)	133.4 (42.6)	—	—	—	—	—	—
C_{tau} (ng/mL)[b] Mean (%CV)	64.4 (52.6)	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
T_{max} (h) Median (Q1, Q3)	1.98 (1.46, 2.99)	3.0	2.3	2.3	2.3	1.5	2.5
$t_{1/2}$ (h)[b] Median (Q1, Q3)	10.54 (9.02, 15.30)	13.7	14.4	14.0	14.9	12.4	14.5

a Measured after a minimum of 4 weeks of treatment with TDF; PK samples collected up to 12 hours postdose.

b Parameter was estimated using predose concentration as a surrogate for the concentration at the 24-hour time point.

Pharmacokinetic data for FTC and TFV are available for 14 adolescent subjects who received STB in the PK Analysis Set of Study GS-US-236-0112. Blood samples were collected on Day 10 at pre-dose (0 hours) and at 2, 4, 4.5, 5, 8 and 12 hours post-dose.

FTC exposures were in the range of those observed in adults in historical studies. Cross-study comparison showed that the means were slightly higher in adolescents but the 90% CIs of the GLSM ratios for AUC_{tau}, C_{max} and C_{trough} were contained within 70% to 143%.

Table 6. GS-US-236-0112: Statistical Comparisons of FTC and TFV Plasma PK Parameter Estimates Following Administration of STB to Adolescents in Study GS-US-236-0112 and Adults in Historical Studies (FTC PK Substudy Analysis Set)

PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	Test (Study GS-US-236-0112)	Reference (Historical Control)	
FTC	**N = 14**	**N = 61[a]**	
AUC_{tau} (ng•h/mL)	14,508.95	12,106.32	119.85 (103.27, 139.08)
C_{max} (ng/mL)	2124.40	1813.97[b]	117.11 (100.69, 136.21)
C_{trough} (ng/mL)[c]	98.48	104.44	94.29 (78.77, 112.88)
TFV	**N = 14**	**N = 419[d]**	
AUC_{tau} (ng•h/mL)	4281.03	3114.36	137.46 (121.01, 156.14)
C_{max} (ng/mL)	409.41	313.05	130.78 (110.31, 155.05)
C_{trough} (ng/mL)[c]	83.83	68.21	122.89 (109.33, 138.14)

CI = confidence interval; Ctau = observed drug concentration at the end of the dosing interval; GLSM = geometric least-squares mean

a Combined data from HIV-infected adult subjects who received STB and participated in the PK substudy in historical studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

b N = 62 for Cmax

d Combined data from HIV-infected adult subjects who received STB in historical studies GS-US-236-0103 and GS-US-236-0104, and Study GS-US-236-0102 (PK Substudy).

c The predose trough concentration (Ctrough) represents Ctau.

The mean TFV AUC_{tau} and Cmax in adolescents were higher (approximately 31% to 37%) compared with adults receiving STB in historical studies but they were in the range of those observed in adults taking TDF-containing boosted-protease inhibitor regimens.

For example, among adult subjects taking ATV/r + FTC/TDF the mean (%CV) AUC_{tau} for TFV was 3944.0 (29.7) ng*h/mL (Study GS-US-216-0114), among adults taking LPV/r +TDF the median (range) AUC_{tau} for TFV was 4199 (2031 to 6362) ng*h/mL and among adults taking DRV/r + TDF the mean (%CV) AUC_{tau} for TFV was 4633 (15.9) ng*h/mL.

Regarding PK differences between HIV-1 uninfected and infected adults, FTC PK parameter estimates following oral administration are characterised by relatively low inter-subject variability and consistent PK data regardless of HIV-1 status. The lack of a difference may reflect the oral bioavailability of FTC and the fact that it is primarily excreted unchanged in the urine (~65 to 70% of an oral dose) with only ~13% being metabolised.

Table 7. Summary of Steady-State PK Parameter Estimates for Emtricitabine Following 200 mg Once Daily Dose

	Healthy Subjects	HIV-infected Patients	
Parameter	FTC-106 5 (5M/0F) Healthy volunteers 37 (33–42) yrs	FTC-101 8 (8M/0F) HIV-infected subjects 37 (29–42) yrs	FTC-303 12 (1M/11F) HIV-infected subjects 38 (21–61) yrs
$C_{max,ss}$ (µg/mL)	1.72 (16%)	1.72 (53%)	1.94 (24%)
$T_{max,ss}$ (hr)	1.00 (0%)	2.00 (48%)	1.80 (58%)
$C_{min,ss}$ (µg/mL)	0.07 (28%)	0.05 (24%)	0.11 (71%)
AUC_{tau} (hr•µg/mL)	10.04 (18%)	8.00 (15%)	11.31 (29%)
$T_{½}$ (hr)	10.2 (19%)	8.24 (31%)	8.08 (32%)
CL_{ss}/F (mL/min)	339 (20%)	425 (15%)	317 (27%)

Values are mean (%CV)

There were no significant differences in the PK of TFV between HIV-1 infected patients (n = 17) and uninfected subjects (n = 36) (p = 0.1538) in Studies GS-97-901, GS-99-907 and GS-00-914 with the exception of terminal elimination half-life (p = 0.0001), which was ascribed to a shorter duration of blood sampling post-dose in HIV-1 infected patients vs. healthy subjects (24 hours and 48 hours, respectively).

Table 8. Summary Pharmacokinetics of Tenofovir in HIV-infected Subjects and Healthy Subjects After Oral Administration of Tenofovir DF 300 mg (Studies GS-97-901, GS-99-907, and GS-00-914)

Parameter	Healthy Subjects	HIV-infected Patients
N	36	17
AUC_{inf} (ng•h/mL)	3096	2794
C_{max} (ng/mL)	327.1	316.9
T_{max} (h)	2.0	2.0
$T_{½}$ (h)[a]	16.9	12.0

Median values

a p< 0.0001 (healthy vs HIV infected)

In the publication from Patterson (2011), concerning administration of a single oral dose of TVD to 15 healthy male and female individuals, the concentrations of TFV and FTC and their respective active metabolites TFV-DP and FTC-TP varied according to the mucosal tissue type (see below). The TFV concentration in rectal mucosa was greater and persisted for longer than the FTC concentration. The FTC concentration in vaginal and cervical tissue was greater than the TFV concentration. TFV, TFV-DP and FTC could be quantified in mucosal tissues for 10 to 14 days, whereas FTC-TP was only detected for up to 2 days. The applicant's summary states that the concentrations of ART achieved in female genital tract tissue suggest that standard TDF/FTC oral dosing may not be sufficient to prevent HIV acquisition. It also states that prevention of vaginal acquisition of HIV may require a stronger barrier to infection than that provided by oral dosing with TVD.

Table 9. Pharmacokinetics of TFV, FTC, and their metabolites in body fluids and mucosal tissues

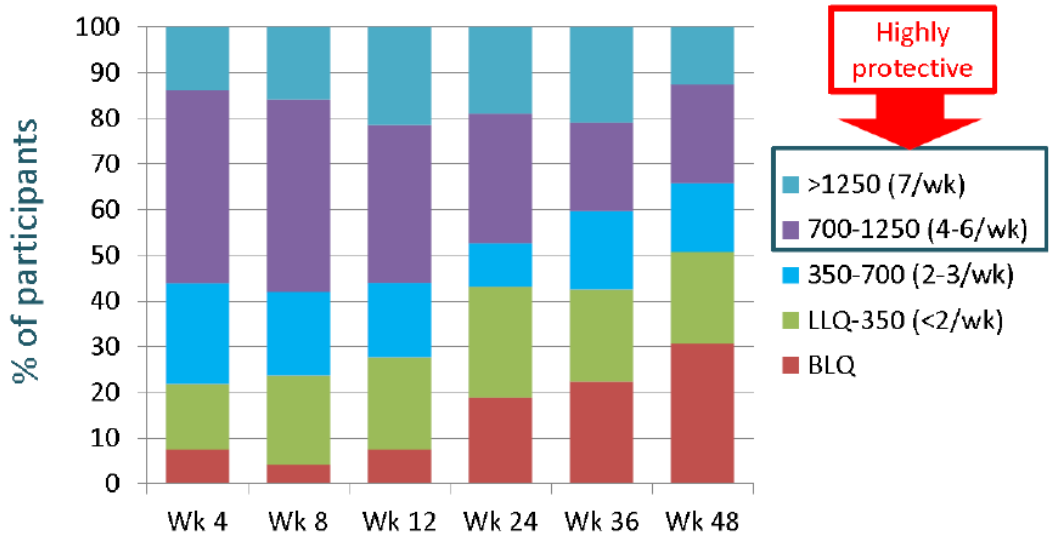
Mucosal tissue type	TFV		TFV-DP		FTC		FTC-CP	
	C_{24h}	AUC_{1-14d}	C_{24h}	AUC_{1-14d}	C_{24h}	AUC_{1-14d}	C_{24h}	AUC_{1-14d}
Blood plasma	41 (34, 47)	91 (82, 98)	_	_	47 (40, 57)	83 (72, 100)	_	_
Seminal plasma	23 (16, 76)	91 (51, 156)	_	_	253 (148, 352)	408 (233, 586)	_	_
Rectal tissue	1,877	2,989	206,950	649,502	124	266	8,450	20,111
Cervicovaginal fluid	69 (57, 586)	251 (151, 1257)	_	_	1183 (638, 2277)	2445 (2309, 3631)	_	_
Vaginal tissue	6.8	50	1645	2939	63.4	4197	63,469	_
Cervical tissue	50	510	BLQ	441	170	2496	11,090	_

BLQ=below limit of quantification

Median values

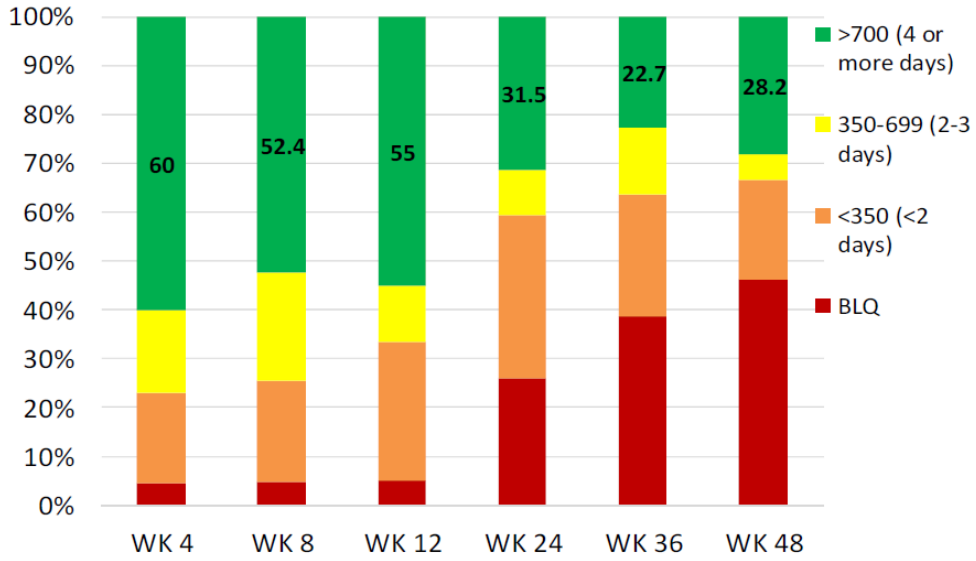
Pharmacokinetic data are available for TFV-DP in HIV-uninfected young adults 18 to 22 years of age in Study **ATN 110** who received TVD QD for PrEP. The study enrolled 200 subjects and 135 completed 48 weeks of treatment. Pharmacokinetic data for plasma TFV and FTC are not reported. Levels of TFV-DP in dried blood spots (DBS) that were ≥ 700 fmol/punch were reported for between 50% and 60% of subjects through Week 12. Only 35% of subjects had this TFV-DP level by Week 48. Participants who reported unprotected intercourse had higher levels of TFV-DP.

Figure 2. ATN 110: TFV-DP Concentrations (fmol/punch) Over Time



Pharmacokinetic data are available for TFV-DP in HIV-uninfected adolescents 15 to 17 years of age in Study **ATN-113** in which subjects received open-label TVD for up to 48 weeks. Of 79 enrolled subjects, 47 completed 48 weeks of treatment. Plasma TFV and FTC data are not available. TFV-DP levels in DBS were ≥ 700 fmol/punch (indicator of dosing for ≥ 4/7 days/week) for 52% to 60% of subjects through Week 12 but in only ~23-31% from Weeks 24-48, indicating a marked drop in treatment adherence.

Figure 3. ATN 113: TFV-DP Concentrations (fmol/punch) Over Time



2.3.3. Discussion on clinical pharmacology

The exposure to FTC at steady state in 27 HIV-infected adolescents (aged 13 to 17 years) dosed with 6 mg/kg or the adult dose (or equivalent) was similar to that seen in HIV-infected adults receiving a dose of 200 mg once daily.

The exposure to TFV after dosing with 300 mg TDF QD to steady state in 8 HIV-infected adolescents (aged 12 to 16 years) was higher than that seen in similarly dosed HIV-infected adults.

In 14 HIV-infected adolescents (aged 12 to 17 years) receiving STB once daily, the exposure to FTC was ~20% higher and the exposure to TFV was ~40% higher than that in HIV-infected adults treated with STB. The exposures to TFV in the adolescents were within the range described for adults who received TDF with various ritonavir-boosted PIs in prior studies.

Plasma exposures to FTC and TFV are similar in HIV-infected and uninfected adults.

Plasma exposures to FTC and TFV were not determined in uninfected adolescents who received 200 mg FTC and 300 mg TDF QD. Based on the comparisons made above, it is reasonably expected that plasma exposures to FTC and TFV in HIV-uninfected adolescents will be slightly higher than those in uninfected adults at the same level of adherence to TVD for PrEP. This observation underlines the potential safety concerns regarding TFV effects on renal function and bone formation and maintenance, especially in adolescents who are pre-pubertal (noting that the applicant proposes use for PrEP from the age of 12 years) and in those who have not completed their growth spurt. In this regard, it should be noted that the MAH has not addressed the potential that plasma exposures may differ between genders, possibly being even greater in post-pubertal females compared to post-pubertal males. There are inadequate PK data in male and female adolescents to assess this matter. The safety implications of the higher exposures to FTC and TFV in adolescents vs. adults are discussed in the safety section.

Although plasma exposures to TFV and FTC are expected to be higher in adolescents than adults at the same level of adherence, the few published data that are available strongly suggest that adherence to TVD QD for PrEP will very likely be even less in adolescents than in adults, even when the comparison is made between 15-17 year-olds and 18-22 year-olds in two studies conducted by the same group of investigators in the US. This matter is discussed further in the clinical efficacy section.

The published data on penetration of FTC and TFV to the genital tract and rectum on dosing 15 adults with TVD QD for 14 days were discussed in II/126. Also considered at that time was a publication by Cottrell et al. (2016) describing a PK/PD model based on mucosal tissue concentrations in 47 healthy women. Overall, there is a suggestion from publications that adherence may be even more critical for women at risk of HIV-1 acquisition via the genital tract compared to men at risk from rectal transmission. The two published studies ATN 100 and 113 did not enrol any females. Data reported to the MAH indicate that there was no gender difference in poor adherence observed in the CHAMPS study conducted in 148 teenagers, including 98 females.

2.3.4. Conclusions on clinical pharmacology

The plasma exposures to FTC and especially to TFV are expected to be higher in adolescents than in adults at the same level of adherence. It is possible that exposures could be even higher in female adolescents than male adolescents after completion of the growth spurt. However, the actual plasma exposures in adolescents who are prescribed TVD for PrEP may be lower than in adults due to poor adherence.

2.4. Clinical efficacy

Since the PrEP data in adults were fully assessed in EMEA/H/C/594/II/126 this section will focus on the efficacy data available on FTC, TDF and STB for the treatment of HIV-1-infected adolescents and the very limited data available on use of TVD for PrEP in males aged 15-17 years and aged 18-22 years.

Treatment of HIV-1 in adolescents

FTC in ART-Naive and ART-Experienced HIV-Infected Adolescents

Analysis by age group across the study populations of FTC-203 and FTC-211 showed similar antiviral response rates in the different age groups. In the 13-17 years age group 17/18 (94%) achieved and maintained suppression at ≤ 400 copies/mL at Week 48 and 14/18 (78%) had < 50 copies/mL.

Table 10. Summary of Primary Efficacy Endpoint at Week 48 by Age Group: Studies FTC-203 and FTC-211 (ITT Population)

Endpoint (NC = F)	Age Group (1-4) [a]				Overall
	3 mo – 24 mo	25 mo – 6 y	7 y – 12 y	13 y – 17 y	
FTC-203, n/N (%)	**N = 16**	**N = 68**	**N = 29**	**N = 3**	**N = 116**
≤ 400 copies/mL	13/15 (86.7)	62/66 (93.9)	24/29 (82.8)	3/3 (100.0)	102/113 (90.3)
≤ 50 copies/mL	11/15 (73.3)	52/66 (78.8)	23/29 (79.3)	2/3 (66.7)	88/113 (77.9)
FTC-211, n/N (%)	**N = 0**	**NA**	**N = 1**	**N = 15**	**N = 16**
≤ 400 copies/mL	NA	NA	1/1 (100.0)	14/15 (93.3)	15/16 (93.8)
≤ 50 copies/mL	NA	NA	1/1 (100.0)	12/15 (80.0)	12/16 (75.0)
Combined, n/N (%)	**N = 16**	**N = 68**	**N = 30**	**N = 18**	**N = 132**
≤ 400 copies/mL	13/15 (86.7)	62/66 (93.9)	25/30 (83.3)	17/18 (94.4)	117/129 (90.7)
≤ 50 copies/mL	11/15 (73.3)	52/66 (78.8)	24/30 (80.0)	14/18 (77.7)	100/129 (77.5)

a Two subjects are censored, because they had no Week 48 data and were below the LLOQ (≤ 50 copies/mL) at the visits immediately prior to and after Week 48.

The mean absolute CD4 cell count increase from baseline to Week 48 ranged from 165 to 273 cells/mm^3 across the paediatric studies.

Table 11. Summary of Change in Absolute and Percent CD4 Cell Counts from Baseline to Week 48 by FTC Studies and ART Experience

Study/Endpoint Change from Baseline Mean (range)	ART Stratum		Overall
	ART-naive	ART-experienced	
Study FTC-202			
Absolute CD4 (cells/mm^3)	273 (-612, 1308)		273 (-612, 1308)
Percent CD4 (%)	13.1 (-16.0, 27.0)		13.1 (-16.0, 27.0)
Study FTC-203			
Absolute CD4 (cells/mm^3)	326 (-512, 1521)	-18 (-945, 712)	197 (-945, 1521)
Percent CD4 (%)	11.6 (-4.6, 33.8)	3.4 (–10.8, 12.6)	8.5 (-10.8, 33.8)
Study FTC-211[a]			
Absolute CD4 (cells/mm^3)	165 (-107, 366)		165 (-107, 366)
Percent CD4 (%)	10.7 (3.0, 29.0)		10.7 (3.0, 29.0)

These data were not analyzed by ART stratum. Because all but one patient was ART-naive, overall data are presented in the ART-naive column.

After a median duration of follow up of 96 weeks virologic failure had occurred in 16/132 patients (12.1%), of which 3 were adolescents (aged 12 – 17 years). Genotypic testing of TLOVR-defined virologic failures confirmed the emergence of the M184V mutation in 4/16, all of whom were < 12 years of age.

TDF in ART-Experienced HIV-Infected Adolescents

Study **GS-US-104-0321** involved randomisation of treatment experienced adolescents with plasma HIV-1 RNA ≥ 1000 copies/mL (i.e. failing their prior regimen) to TDF or placebo, each given with a genotype-guided OBR. After week 48 a switch from placebo to TDF was allowed. The TDF and placebo groups exhibited decreases from baseline in plasma HIV-1 RNA with median time-weighted average changes from baseline through Week 24 ($DAVG_{24}$) of −1.580 log_{10} copies/mL in the TDF group and −1.549 log_{10} copies in the placebo group. According to Della Negra *et al*. (2015) at week 144 the proportions with HIV-1 RNA <50 copies/mL were 30.4% (7/23) for those initially randomised to TDF and 41.7% (5/12) for those who switched from PBO to TDF.

There were no statistically significant differences between treatment groups in HIV-1 RNA $DAVG_{24}$ or for any of the secondary efficacy endpoints at any of the time points analysed as follows:

- The median $DAVG_{48}$ in plasma HIV-1 RNA was −1.423 log_{10} copies/mL in the TDF group and −1.352 log_{10} copies/mL in the placebo group (p = 0.40).
- The median change from baseline in HIV-1 RNA levels at Week 48 (LOCF) was −0.97 log_{10} copies/mL in the TDF group and −1.53 log_{10} copies/mL in the placebo group (p = 0.37).
- Nine of 45 TDF subjects compared to 2/42 placebo subjects developed NRTI-associated resistance mutations at Week 48. This difference was due to more subjects developing K65R (n = 1), M184V (n = 4) and thymidine-analogue associated mutations (TAMs; n = 4) in the TDF group as compared to the placebo group (n = 0, 2 and 1, respectively).

- The mean CD4 cell count increase from baseline to Week 48 was 155 cells/mm^3 for TDF and 182 cells/mm^3 for placebo. There was no significant difference between treatment groups in CD4 percentage or change from baseline at any post-baseline time point up to Week 48.

Study **GS-US-236-0112** evaluated the pharmacokinetics, safety, tolerability, and antiviral activity of the elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Stribild) in HIV-1 infected, antiretroviral treatment (ART)-naive adolescents. Fifty subjects aged 12-<18 years and at least 35 kg in the US, South Africa and Thailand. Subjects had plasma HIV-1 RNA levels ≥ 1,000 copies/mL, CD4 cell counts > 100 cells/μL and eGFR ≥ 90 mL/min/1.73m^2 (as calculated using the Schwartz formula) at screening. At the data cut for the interim Week 48 analysis, 48 had completed main study treatment and 40 had entered into the extension phase, with 35 still receiving study treatment.

The virologic success rate achieved with STB was 88.0% (44/50) at Weeks 24 and 48 using the FDA-defined snapshot algorithm with a cut-off of HIV-1 RNA < 50 copies/mL. Rates were 94.0% at Week 24 and 92.0% at Week 48 at the < 400 copies/mL cut-off. Using both the M = F and M = E analyses, the percentage of subjects with HIV-1 RNA < 20 copies/mL was 80.0% and 86.0% at Weeks 24 and 48, respectively. The percentage of subjects who were pure virologic responders at Week 48 was 84.0% (42/50). Through Week 48, 2 subjects experienced pure virologic failure (PVF) and study drug discontinuation (1 who had PVF before study drug discontinuation due to non-adherence and 1 who discontinued due to pregnancy before PVF).

At Weeks 24 and 48, the mean (SD) change from baseline in HIV-1 RNA was −3.08 (0.922) $\log_{10}$ copies/mL and −3.16 (0.705) $\log_{10}$ copies/mL, respectively. At Weeks 24 and 48, the mean (SD) increase from baseline in CD4 cell count was 178 (165.4) cells/μL and 229 (245.3) cells/μL, respectively, and the mean (SD) increase from baseline in CD4% was 7.4% (4.70%) and 8.1% (5.34%), respectively.

Of the 50 subjects, 3 (6%) met the criteria for inclusion in the resistance analysis population. No subjects developed resistance to study drugs.

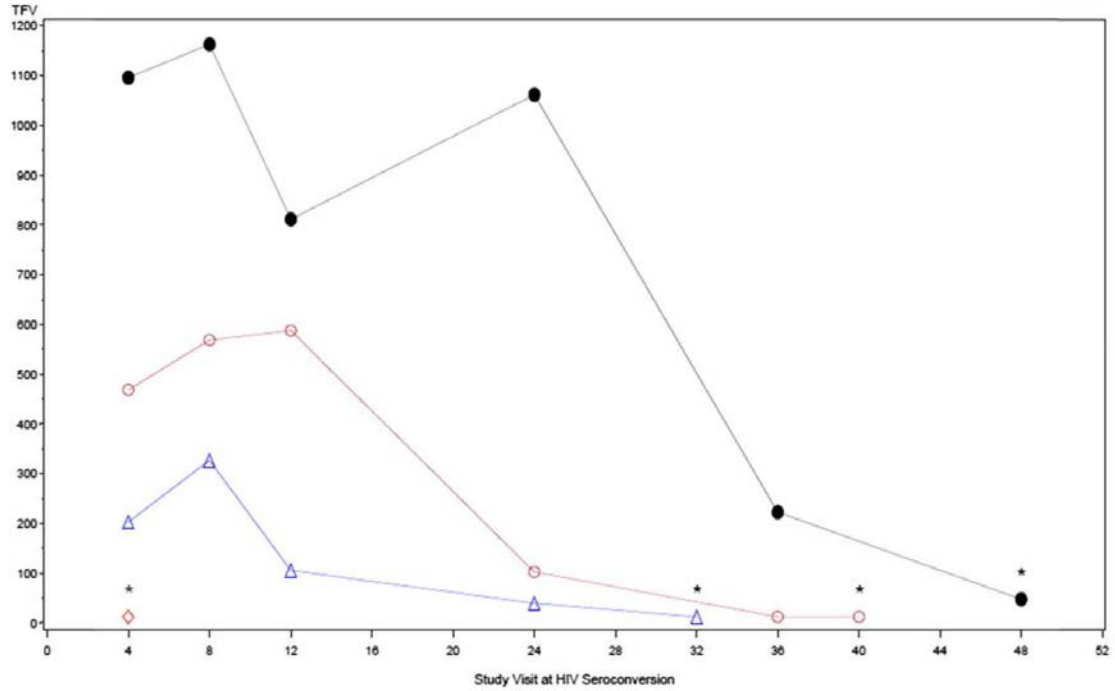
PrEP in young adults (MSM aged 18-22 years)

Study **ATN 110** was an open-label study of once daily TVD in 200 MSM (77.8% homosexual; rest bisexual) aged 18-22 years. They were also offered one of two types of counselling in addition to that supplied at each visit under the protocol routine measures. The median age of subjects enrolled was 20 years. The most common races were black/African American (46.5%), white/non-Hispanic (21.0%) and other/mixed race (21.0%). Overall, 81% reported unprotected (no condom) rectal intercourse in the past month, 58% reported unprotected rectal intercourse with their last partner and 28.6% reported exchanging sex for money. At baseline, 22% had a positive STI test result.

Of the 200 enrolled, 58 prematurely discontinued from the study including 34 LTFU and two because of a diagnosis of acute HIV infection identified by HIV RNA assay at the baseline visit. Overall, study retention was 71% but for those that remained on study the visit retention was 91.8% of all expected visits.

Through 48 weeks 4 subjects experienced seroconversion events (HIV incidence = 3.29 per 100 person-years; 95% CI 0.07 to 6.52) with one event each at Week 4, 32, 40 and 48. None of the subjects who seroconverted had detectable levels of TFV-DP in the sample that was drawn closest to the seroconversion date (see Figure 4). All subjects who seroconverted were immediately linked to medical care and no ARV drug resistance was detected.

Figure 4. TFV-DP levels among seroconverters by study week until seroconversion (*)



Adherence decreased over the 48-week treatment period. The most common reasons reported by subjects for missing study pills were forgot (28.5%), away from home (27.3%) and too busy with other things (26.7%). Subjects also reported missing their medication due to wanting to avoid side effects (4.48%), because they did not want others to see them taking the medication (2.47%) and because they believed the pill was harmful (1.9%).

Based on categorisation of subjects as adherent (≥ 4 pills/week) or non-adherent (< 4 pills/week) the adherent subjects worried less about getting HIV (p = 0.01), felt more comfortable having sex with a HIV-positive partner (p = 0.01) and feared developing medication resistance if they contracted HIV (p = 0.004) compared with non-adherent subjects. Significantly more non-adherent subjects reported not liking taking pills than adherent subjects (p = 0.02). One-third of subjects did not like the size of the pill and over half (52.2%) did not like the taste of the pill. However, most subjects (60.3%) found that it was acceptable taking a pill every day.

The overall STI incidence rate on study was 66.44 (95% CI: 50.53 – 82.35), with greater STI incidence in the first 24 weeks of study (76.48/100 person-years) than the latter half of the study (60.99/100 person-years). An additional indicator of HIV exposure – post-exposure prophylaxis (PEP) prescriptions – remained stable with 1 or 0 subjects requesting PEP at each study visit week.

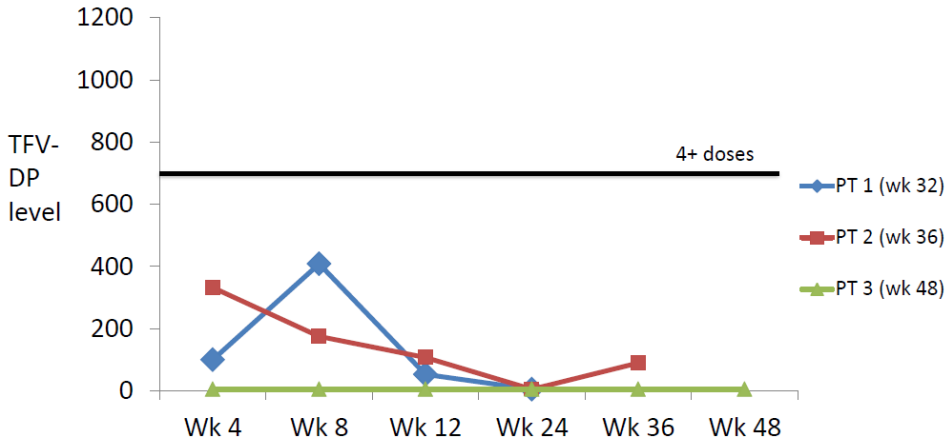
PrEP in adolescents

Study **ATN 113** was an open-label study of once daily TVD in 15 to 17-year-old HIV uninfected MSM (homosexual [58%] or bisexual) who reported HIV transmission risk behaviour in the previous 6 months. Study visits occurred at baseline, monthly through week 12 and then quarterly through week 48. Dried blood spots were serially collected for the quantification of TFV-DP.

There were 79 subjects enrolled and 32 discontinued early, including 19 who were LTFU. The mean age of subjects was 16.5 years. Subjects reported a mean of 2 male partners in the past month, 60% reported unprotected receptive anal intercourse with their last partner and 17% had been previously been paid for sex. At baseline, 15.4% of subjects had a positive sexually transmitted infection (STI) test result.

The 3 subjects with seroconversion through 48 weeks (HIV incidence = 6.4 per 100 person-years; 95% CI: 0.0 to 13.7) had TFV-DP levels consistent with < 2 doses per week.

Figure 5. ATN-113: TDF-DP levels among seroconverts



Adherence decreased over the 48-week treatment period, as demonstrated by the levels of TFV-DP in DBS (see the previous section). The most common overall non-adherence reasons were away from home (31.7%), too busy (27.6%), forgot to take medication (25.8%) and change in routine (18.5%). Non-adherent subjects were more likely to worry about others observing them taking pills and thinking they were HIV positive and/or that they were having sex with other men. At Weeks 12 and 48 over 70% and over 60% found Truvada pills acceptable and about 40% found the taste to be acceptable.

2.4.1. Discussion on clinical efficacy

Once daily dosing with FTC 200 mg and TDF 300 mg when used as part of appropriate regimens, is effective for the treatment of HIV-1 in adolescents who are adherent.

The efficacy of daily TVD for PrEP in male adolescents who have sex with other males can be expected to be the same as that previously described in MSM at the same level of treatment adherence. However, the few available data in adolescent males aged 15-17 years and in 18-22 year-old adult males who had a history of unprotected rectal intercourse indicate a marked drop off in study participation and in adherence to treatment over time.

Through 48 weeks of treatment with TVD for PrEP in adult males aged 18-22 in ATN 110 the HIV incidence was 3.29 per 100 person-years. In the adolescents in ATN 113 the HIV seroconversion rate was double this at 6.4 per 100 person-years. In reality, PrEP may be far less successful in subjects aged < 18 years or 18-22 years compared to older adult men simply due to poor adherence.

For example, although cross-study comparisons must be made with caution, ATN 100 and 113 gave HIV seroconversion rates similar to or higher than observed in the placebo group in the randomised phase of iPrEX. In the open label extension phase of iPrEX 1526/1678 eligible subjects were MSM who had previously been enrolled in iPrEx and avoided acquisition of HIV-1. Other subjects came from two other studies in men and transgender women who have sex with men. Of those receiving PrEP, the HIV incidence was 1.8 infections per 100 p-y, compared with 2.6 infections per 100 p-y in those who concurrently did not choose PrEP (HR 0.51, 95% CI 0.26–1.01, adjusted for sexual behaviours). These rates compare with 3.9 infections per 100 p-y in the placebo group of the previous randomised phase in iPrEx (HR 0.49, 95% CI 0.31–0.77). Considering only participants from iPrEx, the HIV incidence on PrEP was 53% (95% CI 26 to 70) lower than in the placebo group of the randomised phase (3.93 infections

per 100 p-y) and 51% (95% CI 23 to 69) lower than during the gap between the randomised phase and the OLE (3.81 infections per 100 p-y).

There is also an issue surrounding gender. Effectiveness data from the Partners PrEP study showed that women had a numerically higher seroconversion rate than their male counterparts across all 3 treatment groups (including placebo). When efficacy was assessed by sex, the 95% confidence intervals (CIs) for the hazard ratios (HRs) for reduction in HIV-1 infection risk were overlapping between males and females for the Truvada or Viread groups relative to placebo. Poor adherence (< 80% pill count) was less prevalent among women than men in the sub-study. Overall, the Partners PrEP results supported an association between high rates of adherence and high rates of efficacy among study participants of both sexes. However, there are no data on TVD PrEP in female adolescents. No assumptions can be made regarding adherence in female adolescents, especially when women in Partners' PrEP were highly motivated to protect themselves within the setting of stable serodiscordant couples, which is not a setting likely to apply to adolescents. This is a concern in female adolescent sex workers who request PrEP as they could have multiple risk exposures per day or per week.

2.4.2. Conclusions on the clinical efficacy

Use of TVD from the age of 12 years is supported by efficacy data. If adherence were to be similar in adolescents as in the older subjects enrolled into iPrEX and Partners' PrEP then there is no reason to think that protection would be any different. Study ATN 113 indicate that adherence to Truvada for PrEP in male adolescents (15 to 18 years of age) was good in the first three months but then declined over time, a result that was partially confounded by the decreased frequency of scheduled clinic visits over the course of the study. To address this concern the CHMP requested to reinforce the importance of maintaining adherence at frequent intervals for the duration of the PrEP intervention with Truvada.

Subjects aged 12-15 years are likely to be even more vulnerable to the considerations that led to poor adherence in subjects aged 15-22 years. Setting a minimum age of 12 years or simply referring to adolescents in the indication rather than mentioning a lower age cut-off would require very careful consideration of the position and level of understanding of the individual patient. It is not just the subjects' ability to understand the importance of adherence but also to appreciate the potential risks of taking Truvada in terms of the possible long term effects on bone and renal function. These concerns are adequately reflected in SmPC section 4.4.

2.5. Clinical safety

Exposure of adolescents to FTC, TDF and TVD

In **FTC-202, FTC-203 and FTC-211** there were 34 subjects aged 13 to 21 years (29 aged < 18 years). Collectively, across the three clinical studies, 152 subjects aged < 18 years received FTC for at least 48 weeks and 88 were treated for at least 96 weeks.

The long-term paediatric and adolescent study **GS-US-104-0321** included 45 adolescents initially randomised to TDF + OBR in whom median (Q1, Q3) exposure to TDF in the double-blind phase was 47.71 (37.7, 48.0) weeks. In the open label phase, including those who switched to TDF, 81 subjects received TDF. Up to Week 336, the median duration of exposure was 72.0 weeks (Q1, Q3: 37.7, 144.0) with a maximum of 294 weeks.

In **GS-US-236-0112** as of the cut-off for the Week 48 CSR, the median (Q1, Q3) duration of exposure to study drug was 61.6 weeks (52.1, 96.3) and 30.0% had received STB for ≥ 96 weeks.

Exposure data are not available for **ATN 110** but 135/200 completed a Week 48 visit. Similarly, exposure data are not available for **ATN 113** but 32/79 discontinued prematurely. Also, exposure is unknown since there was marked waning in adherence over 48 weeks (see previous section).

Adverse Events

Over 48 weeks and across the age groups 113/116 subjects (97.4%) had at least 1 AE in Study **FTC-203** as did 10/16 subjects (62.5%) in Study **FTC-211**. Also, 11/37 subjects (29.7%) in Study **FTC-202** had AEs of Grade 3 or Grade 4 severity, most of which were SAEs (see below) but including non-serious rash (n = 1), low glucose (n = 1) and ear pain (n = 1), all considered unrelated to study treatment. The most frequent (≥ 10%) AEs reported through the 48-week cut-off date in Study FTC-203 are shown below. A number of events (e.g. rash, eczema, diarrhoea and otitis media) were reported with decreasing frequency according to increasing age. All except one subject in Study FTC-211 were aged 13 to 17 years and the AE profile was similar to that in this same age range in Study FTC-203.

Table 12. Most Frequent (≥ 10%) Adverse Events Through the Data Cut-off Date by Age Group: Study FTC-203 (ITT Population)

Body System Preferred Term Number (%) of Subjects	Age Group[a] 3 mo–24 mo N = 16	 25 mo–6 y N = 68	 7 –12 y N = 29	 13–17 y N = 3	 Overall N = 116
At Least One Adverse Event	16 (100)	66 (97.1)	29 (100.0)	2 (66.7)	113 (97.4)
Body as a Whole					
Any Body as a Whole	15 (93.8)	58 (85.3)	25 (86.2)	2 (66.7)	100 (86.2)
Infection	14 (87.5)	48 (70.6)	17 (58.6)	0	79 (68.1)
Fever	5 (31.3)	17 (25.0)	6 (20.7)	1 (33.3)	29 (25.0)
Infection Parasitic	6 (37.5)	17 (25.0)	4 (13.8)	0	27 (23.3)
Viral Infection	3 (18.8)	13 (19.1)	9 (31.0)	0	25 (21.6)
Accidental Injury	4 (25.0)	14 (20.6)	5 (17.2)	1 (33.3)	24 (20.7)
Abdominal Pain	0	12 (17.6)	7 (24.1)	0	19 (16.4)
Respiratory					
Any Respiratory	12 (75.0)	55 (80.9)	23 (79.3)	2 (66.7)	92 (79.3)
Cough Increased	8 (50.0)	30 (44.1)	10 (34.5)	1 (33.3)	49 (42.2)
Rhinitis	2 (12.5)	28 (41.2)	7 (24.1)	1 (33.3)	38 (32.8)
Pharyngitis	5 (31.3)	18 (26.5)	10 (34.5)	1 (33.3)	34 (29.3)
Pneumonia	5 (31.3)	15 (22.1)	2 (6.9)	0	22 (19.0)
Lung Disorder	3 (18.8)	13 (19.1)	3 (10.3)	0	19 (16.4)
Asthma	2 (12.5)	9 (13.2)	4 (13.8)	0	15 (12.9)
Digestive					
Any Digestive	14 (87.5)	46 (67.6)	20 (69.0)	2 (66.7)	82 (70.7)
Vomiting	7 (43.8)	20 (29.4)	11 (37.9)	0	38 (32.8)
Diarrhea	10 (62.5)	17 (25.0)	6 (20.7)	0	33 (28.4)
Gastroenteritis	4 (25.0)	14 (20.6)	3 (10.3)	1 (33.3)	22 (19.0)
Anorexia	3 (18.8)	15 (22.1)	1 (3.4)	0	19 (16.4)
Tooth Caries	1 (6.3)	9 (13.2)	3 (10.3)	0	13 (11.2)
Skin and Appendages					
Any Skin and Appendages	13 (81.3)	46 (67.6)	19 (65.5)	2 (66.7)	80 (69.0)
Skin Discoloration	5 (31.3)	28 (41.2)	12 (41.4)	0	45 (38.8)
Hyperpigmentation[b]	5 (31.3)	27 (39.7)	10 (34.5)	0	42 (36.2)
Rash	8 (50.0)	17 (25.0)	5 (17.2)	0	30 (25.9)
Fungal Dermatitis	4 (25.0)	15 (22.1)	2 (6.9)	0	21 (18.1)
Eczema	5 (31.3)	15 (22.1)	0	0	20 (17.2)
Pustular Rash	3 (18.8)	8 (11.8)	4 (13.8)	1 (33.3)	16 (13.8)
Special Senses					
Any Special Senses	12 (7.5)	31 (45.6)	11 (37.9)	2 (66.7)	56 (48.3)
Otitis Media	8 (50.0)	22 (32.4)	5 (17.2)	2 (66.7)	37 (31.9)
Conjunctivitis	4 (25.0)	12 (7.6)	5 (17.2)	1 (33.3)	22 (19.0)
Hemic and Lymphatic					
Any Hemic and Lymphatic	10 (62.5)	18 (26.5)	7 (24.1)	0	35 (30.2)
Lymphadenopathy	5 (31.3)	7 (10.3)	3 (10.3)	0	15 (12.9)
Anemia	1 (6.3)	7 (10.3)	4 (13.8)	0	12 (10.3)

a Adverse events with ≥ 10% incidence overall. Adverse events are sorted by decreasing overall incidence by body system and presented by body system and preferred term within body system.

b A subset of skin discoloration events, identified by medical review of adverse events that coded to COSTART term "skin discoloration."

In **GS-US-104-0321** in the double-blind treatment period up to Week 48, all 45 TDF and 40 (95%) placebo patients reported at least 1 AE. In the TDF group, the most commonly reported AEs were vomiting, sinusitis, nausea and cough. By Week 336, AEs were reported for 77 subjects (95.1%) in the All TDF group. The most common AEs in the All TDF group were sinusitis, cough and vomiting.

Table 13. GS-US-104-0321: Treatment-Emergent Adverse Events Reported for at Least 10% of Subjects Through Week 336 in Any Subject Group (All TDF Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b,c,d]	TDF (N=45)	Placebo/TDF (N=36)	All TDF (N=81)
Subjects Experiencing Any Treatment-Emergent Adverse Event	45 (100.0%)	32 (88.9%)	77 (95.1%)
Blood and Lymphatic System Disorders	8 (17.8%)	5 (13.9%)	13 (16.0%)
Neutropenia	5 (11.1%)	2 (5.6%)	7 (8.6%)
Gastrointestinal Disorders	35 (77.8%)	15 (41.7%)	50 (61.7%)
Vomiting	16 (35.6%)	5 (13.9%)	21 (25.9%)
Diarrhea	10 (22.2%)	7 (19.4%)	17 (21.0%)
Nausea	11 (24.4%)	4 (11.1%)	15 (18.5%)
Abdominal Pain	8 (17.8%)	1 (2.8%)	9 (11.1%)
Gastritis	5 (11.1%)	2 (5.6%)	7 (8.6%)
Infections and Infestations	42 (93.3%)	29 (80.6%)	71 (87.7%)
Sinusitis	17 (37.8%)	9 (25.0%)	26 (32.1%)
Nasopharyngitis	10 (22.2%)	8 (22.2%)	18 (22.2%)
Upper Respiratory Tract Infection	9 (20.0%)	8 (22.2%)	17 (21.0%)
Tonsillitis	11 (24.4%)	1 (2.8%)	12 (14.8%)
Pneumonia	7 (15.6%)	3 (8.3%)	10 (12.3%)
Oral Herpes	6 (13.3%)	3 (8.3%)	9 (11.1%)
Tracheobronchitis	7 (15.6%)	2 (5.6%)	9 (11.1%)
Rhinitis	5 (11.1%)	2 (5.6%)	7 (8.6%)
Herpes Zoster	1 (2.2%)	4 (11.1%)	5 (6.2%)
Metabolism and Nutrition Disorders	10 (22.2%)	4 (11.1%)	14 (17.3%)
Hypertriglyceridemia	5 (11.1%)	1 (2.8%)	6 (7.4%)
Nervous System Disorders	17 (37.8%)	9 (25.0%)	26 (32.1%)
Headache	9 (20.0%)	7 (19.4%)	16 (19.8%)
Dizziness	9 (20.0%)	2 (5.6%)	11 (13.6%)
Respiratory, Thoracic and Mediastinal Disorders	22 (48.9%)	18 (50.0%)	40 (49.4%)
Cough	12 (26.7%)	12 (33.3%)	24 (29.6%)
Skin and Subcutaneous Tissue Disorders	13 (28.9%)	11 (30.6%)	24 (29.6%)
Acne	5 (11.1%)	2 (5.6%)	7 (8.6%)

a.Denominator (for %) is the number of All TDF Safety subjects within the treatment group.

b.Adverse events are mapped according to the MedDRA thesaurus Version 16.1.

c.System organ class is sorted alphabetically; preferred terms in descending order of frequency within SOC.

d.AEs with onset after last TDF dose date (if terminated) + 30 days are excluded from analysis

AEs considered to be related to study drug by the investigator were reported for 18 subjects (22.2%) in the All TDF group, including 14 subjects (31.1%) in the TDF subgroup and 4 subjects (11.1%) in the placebo/TDF subgroup. The study drug-related AEs reported for more than 1 subject in the All TDF group were vomiting (4), osteopenia (5 [6.2%]) and gastritis (2).

The majority of AEs reported in the study were Grade 1 or 2. Grade 3 or 4 AEs were reported for 7 subjects (8.6%) in the All TDF group, including 5 subjects (11.1%) in the TDF subgroup and 2 (5.6%) in the placebo/TDF subgroup. No Grade 3 or 4 AE was reported for more than 1 subject. One subject (2.2%) in the TDF subgroup experienced Grade 3 hyperamylasaemia considered by the investigator to be related to study drug with onset on Day 1341. No action was taken and the event resolved on Day 1352.

Through 48 weeks of STB treatment in **GS-US-236-0112** 45/50 (90.0%) of subjects had at least 1 AE.

Table 14. GS-US-236-0112: Adverse Events Occurring in at Least 5% of Subjects (Safety Analysis Set)

Adverse Event by System Organ Class and Preferred Term[a,b]	STB (N=50)
Subjects Experiencing Any Treatment-Emergent Adverse Event	45 (90.0%)
Gastrointestinal disorders	24 (48.0%)
Vomiting	9 (18.0%)
Diarrhea	7 (14.0%)
Nausea	7 (14.0%)
Hemorrhoids	3 (6.0%)
Toothache	3 (6.0%)
General disorders and administration site conditions	5 (10.0%)
Pyrexia	3 (6.0%)
Infections and infestations	38 (76.0%)
Upper respiratory tract infection	14 (28.0%)
Pharyngitis	5 (10.0%)
Bronchitis	4 (8.0%)
Nasopharyngitis	4 (8.0%)
Oropharyngeal gonococcal infection	3 (6.0%)
Proctitis gonococcal	3 (6.0%)
Secondary syphilis	3 (6.0%)
Injury, poisoning and procedural complications	5 (10.0%)
Skin abrasion	3 (6.0%)
Investigations	9 (18.0%)
Weight decreased	4 (8.0%)
Metabolism and nutrition disorders	11 (22.0%)
Vitamin D deficiency	6 (12.0%)
Musculoskeletal and connective tissue disorders	7 (14.0%)
Myalgia	3 (6.0%)
Nervous system disorders	18 (36.0%)
Headache	12 (24.0%)
Dizziness	4 (8.0%)
Skin and subcutaneous tissue disorders	16 (32.0%)
Acne	6 (12.0%)
Rash	4 (8.0%)
Dermatitis	3 (6.0%)
Dermatitis contact	3 (6.0%)

a Adverse events were coded using MedDRA 18.1.

b Multiple AEs were counted only once per subject for each system organ class and preferred term, respectively. System organ class was presented alphabetically and preferred term was presented by descending order of the total frequencies.

Adverse events related to study drug were reported for 10 subjects (20.0%). Headache (8.0%, 4 subjects) and nausea (6.0%, 3 subjects) were the only study drug-related AEs reported for more than 2 subjects. Most AEs reported were Grade 1 or Grade 2 in severity. No Grade 4 AEs were reported. Grade 3

AEs were reported for 2 subjects (4.0%) including *Shigella* gastroenteritis and suicidal behaviour in one subject and weight decreased in the other subject.

Three subjects in Study **ATN 110** had AEs deemed related to study drug: nausea, weight loss and headache. All were Grade 3 (ATN Grading Severity of Adolescent Adverse Events) and resolved when medication was discontinued. An additional 21 Grade 3 or higher AEs deemed unrelated to study drug were reported for 15 subjects; no further information regarding these events is available.

In **ATN-113** three Grade 3 AEs were reported for 2 subjects that were considered related to study drug by the investigator.

SAEs and deaths

In Study FTC-203 one child aged 2 years died with acute myeloid leukaemia. No other deaths were reported in the studies of interest.

In Study **FTC-203**, 24 subjects (20.7%) experienced at least one SAE but no SAEs occurred in the 13-17 years age group. SAEs that occurred in more than 1 subject were pneumonia (7), hepatitis A (4), pharyngitis and accidental injury (3 for each) and pancreatitis (2). Three SAEs were assessed by the reporting investigator as possibly or probably related to study drug, including one subject with Grade 3 anaemia and 2 subjects with pancreatitis assessed as related to the use of FTC and d4T who discontinued from the study.

In **FTC-202** 12 subjects developed SAEs, including 6 who were hospitalised. Four of these SAEs occurred in adolescents aged 12 to 17 years. No SAE occurred in more than two subjects. SAEs included elevated creatine kinase (2) and single reports of LFTs increased, decreased glucose, nausea with asthenia and dizziness, abdominal pain with headache (subject was also hospitalised for lymphadenitis), mild cervical dysplasia with human papilloma virus, rash with diarrhoea, rectal pain, herpes zoster, otitis media and major depression.

In Study **FTC-211**, a 15-year-old subject had 2 SAEs of mumps and orchitis not related to FTC.

During the double-blind treatment period up to Week 48 of Study **GS-US-104-0321**, SAEs were reported for 10 TDF subjects [22.2%] and 3 placebo subjects [7.1%]. SAEs reported for more than 1 subject were pneumonia (TDF 3; placebo 1) and *Pneumocystis jiroveci* pneumonia and sinusitis (TDF 2; placebo 0).

By the end of the study at Week 336, SAEs were reported for 20 subjects (24.7%) in the All TDF group, including 12 subjects (26.7%) in the TDF subgroup and 8 subjects (22.2%) in the placebo/TDF subgroup. SAEs reported for > 1 subject in the All TDF group were pneumonia (5), herpes zoster (3), *Pneumocystis jiroveci* pneumonia (2) and sinusitis (2). No SAE was considered related to study drug by the investigator.

Through 48 weeks of STB treatment in **GS-US-236-0112** four subjects (8.0%) had an SAE. Acute kidney injury in 1 subject was noted as a clinically significant renal event (see details below). Disseminated tuberculosis in another subject was noted as a CDC Class C AIDS-defining event. No SAE occurred in more than 1 subject, and none was considered related to study drug by the investigator.

Information on SAEs for Studies **ATN 110 and ATN 113** is not available.

AEs leading to discontinuation

Three 3 subjects in Study **FTC-203** (none was adolescent) discontinued due to AEs. Two subjects in Study **FTC-202** had an AE of rash (one adolescent) that led to study drug discontinuation and both resolved within 3 weeks of the last dose. No instances occurred in **FTC-211** or in **GS-US-236-0112**.

In Study **GS-US-104-0321** through Week 336 one subject had an AE of vomiting that led to study drug discontinuation. The event resolved the same day.

In Study **ATN 110**, the most common reasons for discontinuation were personal choice/decision and AEs (predominantly GI symptoms). In the publication details are available for 3 subjects who discontinued due to nausea, weight loss or headache. One participant in **ATN 113**permanently discontinued TDF/FTC due to possibly related Grade 3 weight loss.

Adverse Events of Interest or Important Adverse Events

From preclinical studies, the target organs of toxicity associated with FTC were confined to high dose groups and consisted of changes in erythrocyte parameters. Mild reversible anaemia was observed in mice at more than 150 times the AUC exposure in humans dosed with 200 mg/day. In the FTC SmPC the ADRs that were reported more frequently in paediatric subjects vs. adults in clinical studies and post-marketing experience were anaemia (common) and increased skin pigmentation (very common).

Gastrointestinal disorders including diarrhoea and nausea were reported as very common ADRs with both FTC and TDF components of TVD. Renal and bone ADRs are considered to be of special interest for TDF because of nonclinical toxicity findings and post-marketing safety surveillance data.

Hyperpigmentation

The overall incidence of hyperpigmentation was 42/132 subjects (31.8%) across Studies FTC-203 and FTC-211 but all reported cases occurred in study FTC-203 and there were no events in Study FTC-202. None of the cases of hyperpigmentation occurred in adolescents.

Haematologic toxicities

The overall incidence of anaemia and iron deficiency anaemia in studies FTC-203, FTC-202 and FTC-211 was 9.5% (16/169). In Study FTC-203 there were no cases in the 13 to 17 years age group.

Renal Events

During the double-blind treatment period of Study **GS-US-104-0321**, 6 TDF (13.3%) and 4 placebo subjects (9.5%) reported at least one AE in the renal and urinary disorders SOC. The only renal event reported for > 1 subject in either group was haematuria, which was reported for 2 in each treatment group. No renal and urinary AEs in the TDF group were considered related to study drug by the investigator. In the placebo group, AEs of nephrolithiasis and haematuria (each reported for 1 subject [2.4%]) were considered related to study drug by the investigator.

By the end of the study at Week 336, no AEs of Fanconi syndrome or tubulopathy were reported. The only renal AE reported for > 1 subject in the All TDF group was proteinuria in 2 subjects (2.5%). Two subjects met the algorithm-specified criteria for potential PRT, of which one was not considered to have PRT because of intermittent laboratory abnormalities that were not confirmed and generally were not concurrent. The other subject had findings consistent with PRT, some of which resolved during continued therapy with TDF. Neither subject discontinued TDF prematurely.

During the double-blind treatment period up to Week 48 the median serum creatinine concentrations were below the normal range at baseline and did not change markedly to Week 48 in either group. No graded serum creatinine abnormalities were reported. After the double-blind treatment period at Weeks 144 and 336 there were small increases from baseline in serum creatinine in the All TDF group (median change from baseline at Week 144 was 0.16 mg/dL [n = 25] and at Week 192 was 0.24 mg/dL [n = 16]). No graded serum creatinine abnormalities were reported.

Median serum phosphate concentrations were within the normal range at baseline and did not change markedly to Week 48 in either group. By the end of the study at Week 336, no clinically relevant changes from baseline were seen in the All TDF group.

Reductions from baseline to Week 48 in estimated creatinine clearance were observed with median changes from baseline to Week 48 of −11.00 mL/min/1.73 m^2 in the TDF group and −5.35 mL/min/1.73 m^2 in the placebo group. The median absolute values remained within normal ranges. At Week 144, the median change from baseline was –38.1 mL/min/1.73 m^2 in the All TDF group ($n = 25$, $p < 0.001$, Wilcoxon signed rank test). Median changes from baseline at Week 144 were −36.1 mL/min/1.73 m^2 ($n = 12$, $p < 0.001$) in the TDF subgroup and −43.8 mL/min/1.73 m^2 ($n = 13$, $p < 0.001$) in the placebo/TDF subgroup. The changes were considered to be consistent with normal changes in renal function in an adolescent population progressing towards adulthood.

No case of Grade 3/4 proteinuria was reported in either treatment group up to Week 48. Proteinuria was reported as an SAE for 1 subject in the TDF group but it was not considered related to study drug by the investigator. By Week 336, Grade 3 proteinuria was reported for 1 subject in the TDF subgroup.

No graded urine glucose abnormalities were reported in the double-blind period. By Week 336, Grade 1 glycosuria was reported for 3 subjects (3.7%) in the All TDF group, including 2 subjects (4.4%) in the TDF subgroup and 1 subject (2.8%) in the placebo/TDF subgroup.

In **GS-US-236-0112**, with cobicistat in the STB, increases in serum creatinine were noted as early as Week 2, after which they generally stabilised through Week 48. The median change from baseline at Weeks 2 and 24 was 0.08 mg/dL and at Week 48 it was 0.11 mg/dL.

Median serum phosphorus values were within normal ranges throughout the study.

Decreases in eGFR using the Schwartz formula followed the pattern of serum creatinine changes. The median change from baseline at Week 2 and Week 48 was −15.0 mL/min/1.73 m^2. Using the modified Schwartz formula, the median changes from baseline at Weeks 2, 24 and 48 were −7.4, −4.2 and −3.6 mL/min/1.73 m^2, respectively.

The only urine glucose abnormality reported was Grade 2 urine glucose in 1 subject. The subject had Grade 1 urine glucose on Day 225, which increased to Grade 2 on Day 421 and was ongoing at Day 684 (trace), but was normoglycaemic throughout. The subject also had concurrent Grade 1 to 2 proteinuria.

At baseline, 4/50 (8.0%) had proteinuria as assessed by dipstick analysis (all Grade 1). Post-baseline, Grade 1 or 2 proteinuria, generally isolated and transient, was reported for 22 subjects (44%; 15 Grade 1, 7 Grade 2). There was an increase in proteinuria as assessed by urine protein to creatinine ratio for which the median [Q1, Q3] percentage change from baseline to Week 48 was 8.70% [−20.64%, 52.06%]. There was an increase in urine retinol binding protein to creatinine ratio with a median percentage change from baseline to Week 48 of 14.21% [−15.12%, 61.13%]). The urine beta-2-microglobulin to creatinine ratio decreased with a median percentage change from baseline to Week 48 of −23.7% [−38.7%, 51.3%]). Other renal laboratory parameters (renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate, fractional excretion of phosphate and fractional excretion of uric acid using serum creatinine standard or adjusted values) remained relatively stable from baseline through Week 48.

There were no reported cases of PRT or Fanconi syndrome. One clinically significant renal SAE involved acute kidney injury secondary to dehydration from *Shigella* dysentery, with onset on Day 275 and duration of 6 days. The event was considered unrelated to study drug by the investigator and study drug was continued. Serum creatinine at baseline was 0.90 mg/dL and values on Days 282, 337 and 366 were 1.19, 1.23 and 0.92 mg/dL, respectively. Estimated GFR (Schwartz) at baseline was 121 mL/min/1.73 m^2 and values at Days 282, 337 and 366 were 92, 89 and 119 mL/min/1.73 m^2, respectively. No graded abnormality of serum creatinine was reported. Intermittent Grade 1 proteinuria was noted at Days 113, 144, 170, 282, 337 (Week 48) and 366. Serum phosphate and urine glucose were within normal reference ranges at all visits. The absence of persistent renal abnormalities suggested no PRT.

Bone Safety

Fracture AEs were reported for 2 subjects in the TDF group (clavicle fracture and right malleolar fracture) during the double-blind treatment period of Study **GS-US-104-0321**. These were non-serious and were not considered related to study drug by the investigator. Osteopenia was reported as a non-serious AE for 3 subjects (6.7%) in the TDF group and 2 subjects (4.8%) in the placebo group in the double-blind treatment period and all were considered related to study drug. After the double-blind treatment period, up to Week 336 no further fracture AEs or AEs of osteopenia were reported.

In Study **GS-US-236-0112**, no fracture events were reported. In Study **ATN-110**, 5/200 reported fracture events that all appear to have been trauma-related.

Different methodologies were used for the analyses of BMD between TDF in HIV-infected adolescents, FTC and TDF in HIV-infected adolescents and TVD in HIV-uninfected young adults. Therefore, no direct comparisons can be made. The following describes BMD and bone biomarker data by study.

During the double-blind treatment period of **GS-US-104-0321**, differences between the TDF and placebo groups in the percentage change from baseline in spine BMD were not statistically significant.

As expected for this adolescent population, increases from baseline in lumbar spine BMD were seen for both treatment groups at Weeks 24 and 48 with mean [SD] changes from baseline at Week 48 of 3.148% [7.2936%] for TDF and 3.807% [4.9797%] for placebo (p = 0.54). After the double-blind treatment period, the median percentage changes for the All TDF group in spine BMD from baseline (baseline median 0.964 g/cm^2) to Week 144 were 12.702% (n = 26) and at Weeks 192 and 240 the changes were 16.920% (n = 18) and 19.137% (n = 11), respectively.

There were no clinically relevant changes in spine BMD Z-scores in either TDF or placebo group at Weeks 24 or 48. In the TDF group, no clinically relevant changes were seen at any time point. After the double-blind treatment period, among the 28 subjects who received TDF for 96 weeks, a decrease in the spine BMD Z-score was observed (−0.341). After Week 96, the median changes from baseline in unadjusted spine BMD Z-scores were not significant.

Table 15. GS US 104 0321: Percentage Change from Baseline in Spine BMD and BMD Z-Scores at Weeks 24 and 48 (RAT Analysis Set)

	TDF N = 45			Placebo N = 42			p-value[a]: TDF vs Placebo
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)	
Percentage Change in Spine BMD							
Baseline (g/cm^2)	45	0.944 (0.1520)	0.942 (0.83, 1.03)	42	0.945 (0.1428)	0.964 (0.85, 1.04)	0.78
% Change at Week 24	44	1.199 (4.9620)	1.248 (–2.69, 5.17)	42	1.932 (4.5227)	2.533 (–1.53, 5.11)	0.59
% Change at Week 48	33	3.148 (7.2936)	2.593 (–2.94, 8.28)	33	3.807 (4.9797)	3.723 (0.13, 6.59)	0.54
Change in Spine BMD Z-Score							
Baseline	45	−1.004 (1.2102)	−0.900 (−1.72, −0.41)	42	–0.809 (1.4088)	–0.862 (–1.79, 0.21)	–
Change at Week 24	44	−0.170 (0.4901)	−0.175 (−0.39, 0.15)	42	–0.120 (0.3181)	–0.144 (–0.32, 0.11)	–
Change at Week 48	33	−0.215 (0.6209)	−0.188 (−0.59, 0.09)	33	–0.165 (0.3739)	–0.156 (–0.37, 0.10)	–

a The p-value comparing randomized treatment groups is from the Wilcoxon rank sum test

During the double-blind treatment period at Week 48, differences between groups in the percentage change from baseline in total body BMD were not statistically significant. As expected for this adolescent population, increases from baseline in total body BMD were seen in both groups at Weeks 24 and 48 with mean [SD] changes from baseline to Week 48 of 1.495% [3.1138%] for TDF and 1.518% [3.8072%] for placebo (p = 0.96). The median percentage change in total body BMD from baseline to Week 144 was 4.322% (n = 26), to Week 192 was 5.869% (n = 18) and to Week 240 was 6.951% (n = 11).

The mean (SD) total body BMD Z-score at baseline was −0.866 (1.2293) for subjects in the TDF group and −0.584 (1.2245) for subjects in the placebo group, suggesting that these children were below average height and weight for their sex and age There were no clinically relevant changes in total body BMD Z-scores in either group at Weeks 24 or 48. At Week 48, the mean (SD) change in total bone BMD Z-score was −0.254 (0.3918) for subjects in the TDF group and −0.179 (0.3453) for subjects in the

placebo group. Among the 15 subjects who received TDF for 96 weeks, the mean (SD) total body BMD Z-score had decreased −0.403 [0.6647]). By Week 336, 13/81 (16.05%) in the All TDF group had decreases from baseline of > 4% in spine and/or total body BMD at ≥1 time points (11 subjects in the TDF subgroup and 2 in the placebo/TDF subgroup). Of these 13, 11 had decreases > 4% in spine BMD only, 1 had decreases > 4% in total body BMD only and 1 had decreases > 4% in spine and total body BMD.

Decreases > 4% were persistent (occurring at more than 1 consecutive visit) in 5/13 subjects. Also, 3/13 had low BMD at any visit (spine or total body unadjusted Z-score ≤ −2.0).

Table 16. GS US 104 0321: Percentage Change from Baseline in Total Body BMD and BMD Z-Scores at Weeks 24 and 48 (RAT Analysis Set)

	TDF N = 45			Placebo N = 42			p-value[a]: TDF vs Placebo
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)	
Percentage Change in Total Body BMD							
Baseline (g/cm^2)	45	1.002 (0.0952)	1.000 (0.94, 1.07)	42	1.016 (0.0857)	1.031 (0.94, 1.07)	0.63
% Change at Week 24	44	0.501 (2.2374)	0.107 (–1.11, 2.75)	42	0.826 (2.6984)	0.803 (0.10, 2.58)	0.28
% Change at Week 48	33	1.495 (3.1138)	1.318 (–0.82, 3.33)	33	1.518 (3.8072)	0.969 (–0.28, 3.60)	0.96
Change in Total Body BMD Z-Score							
Baseline	45	−0.866 (1.2293)	−0.758 (−1.74, 0.00)	42	-0.584 (1.2245)	-0.693 (-1.46, 0.46)	–
Change at Week 24	44	−0.178 (0.3484)	−0.205 (−0.31, 0.11)	42	-0.115 (0.2094)	-0.121 (-0.23, 0.00)	–
Change at Week 48	33	−0.254 (0.3918)	−0.237 (−0.53, 0.08)	33	-0.179 (0.3453)	-0.147 (-0.41, 0.07)	–

a The p-value comparing randomized treatment groups is from the Wilcoxon rank sum test

During the double-blind treatment period at Week 48 there were no significant differences between treatment groups in the change from baseline in markers of bone formation (serum osteocalcin and bone-specific alkaline phosphatase) at any time point. By Week 336, decreases from baseline were observed with long-term treatment in the All TDF group:

- The median changes from baseline in serum osteocalcin were −16.6 ng/mL at Week 144 (n = 22), −42.3 ng/mL at Week 192 (n = 14) and −73.0 ng/mL at Week 240 (n = 6).
- The median changes from baseline in bone specific alkaline phosphatase were −24.6 U/L at Week 144 (n = 24), −51.8 U/L at Week 192 (n = 15) and −38.6 U/L at Week 240 (n = 5).

During the double-blind treatment period at Week 48, there were no statistically significant differences between groups in the change from baseline in markers of bone resorption (N- and C-telopeptides) at any time point. There were decreases from baseline in C-telopeptides after Week 48 in the All TDF group with median changes from baseline of −0.434 ng/mL at Week 144 (n = 21), −0.406 ng/mL at Week 168 (n = 15), −0.512 ng/mL at Week 192 (n = 14) and −0.580 ng/mL at Week 240 (n = 5). There were also decreases from baseline in N-telopeptides at Weeks 72 to 168, but from Week 192 there were increases in N-telopeptides for the small numbers of subjects with available data.

The median change from baseline for bone collagen equivalent [BCE] N-telopeptides was −3.9 nM BCE at Week 144 (n = 18), −20.3 nM BCE at Week 168 (n = 13), 24.2 nM BCE at Week 192 (n = 10) and 113.6 nM BCE at Week 240 (n = 3).

The baseline values for PTH were significantly lower in the TDF group (median 38 pg/mL vs. 47 pg/mL, p = 0.033). Differences between groups in the change from baseline in PTH were statistically significant at

Weeks 4, 16, and 24, but not at Weeks 32 and 48. There were small increases in PTH in the TDF group compared to small decreases in the placebo group but the median values remained in the normal range in both groups. By Week 336, there were generally small increases from baseline in PTH in the All TDF group. The median changes were 8.0 pg/mL (n = 23, p = 0.010) at Week 144, 8.0 pg/mL (n = 13, p = 0.37) at Week 192 and −1.4 pg/mL (n = 6, p = 0.69) at Week 240 and values were in the normal range.

During the double-blind treatment period, there were no statistically significant differences between TDF and placebo groups in the change from baseline in 25-OH Vitamin D at any time. There were statistically significant median increases from baseline through Week 144 in the All TDF group. The median decreases in 25-OH vitamin D observed at some of the later time points in the study were in small numbers of subjects and were not sustained.

In **GS-US-236-0112** the percentages of subjects with ≥ 4% decrease from baseline in spine and TBLH BMD at Weeks 24 and 48 were as follows:

- Spine: 10/47 (21.3%) at Week 24 and 7/46 (15.2%) at Week 48 (6 had ≥ 4% decrease at both Weeks 24 and 48)
- TBLH: 1/49 (2.0%) at Week 24 and 2/48 (4.2%) at Week 48 (1 had ≥ 4% decrease at both Weeks 24 and 48).

Table 17. GS-US-236-0112: Percentage Changes from Baseline in Spine and TBLH BMD (Spine and TBLH DXA Analysis Sets)

	Spine			TBLH		
Time Point	**N**	**Mean (SD)**	**Median (Q1, Q3)**	**N**	**Mean (SD)**	**Median (Q1, Q3)**
Week 24	47	−0.964 (3.6551)	−0.985 (−3.571, 0.945)	49	−0.141 (2.1251)	−0.488 (−1.448, 0.852)
Week 48	46	0.676 (4.5255)	1.067 (−2.284, 3.341)	48	0.771 (2.6462)	0.431 (−0.817, 2.175)

Five subjects showed a worsening from baseline (change from > −2 to ≤ −2) in their spine and/or TBLH height-age BMD Z-scores at Week 24 and/or Week 48, as follows:

- Height-age TBLH BMD Z-score: 2 subjects at Week 24 and 3 subjects at Week 48 (1 subject had a worsening from baseline at both Weeks 24 and 48)
- Height-age spine BMD Z-score: 1 subject at both Weeks 24 and 48

Table 18. GS-US-236-0112: Spine and TBLH Height-age BMD Z-Scores at Baseline, and Change from Baseline at Weeks 24 and 48 (Spine and TBLH DXA Analysis Sets)

	Spine BMD Z-Score (Height-age[a])			TBLH BMD Z-Score (Height-age[a])		
	N	**Mean (SD)**	**Median (Q1, Q3)**	**N**	**Mean (SD)**	**Median (Q1, Q3)**
Baseline	38	0.00 (1.240)	0.09 (−0.97, 0.98)	39	−0.52 (1.027)	−0.67 (−1.36, 0.29)
Change from Baseline at:						
Week 24	38	−0.15 (0.290)	−0.14 (−0.31, −0.02)	39	−0.11 (0.139)	−0.10 (−0.21, 0.00)
Week 48	37	−0.09 (0.384)	−0.02 (−0.28, 0.14)	38	−0.12 (0.291)	−0.10 (−0.37, 0.07)

a.Some subjects had missing height-age Z-scores because their heights were outside the median height in the CDC growth chart, or the height-ages were outside the BMD reference data for Z-scores.

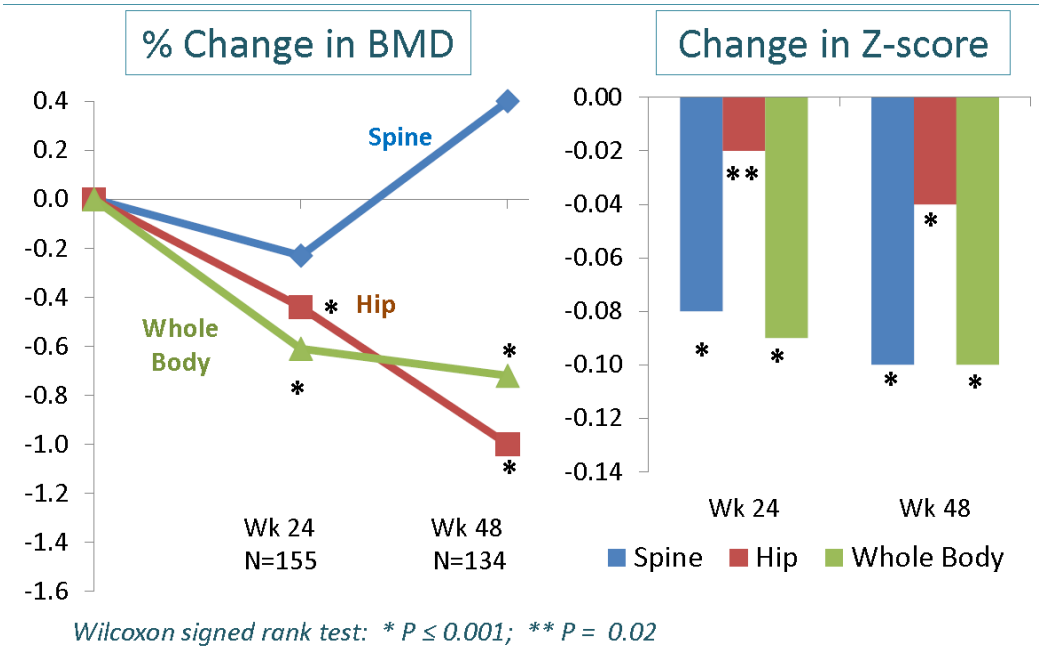
There were median percentage increases (> 10%) from baseline at Weeks 24 and 48 in N-telopeptide (15.9% and 19.2%), osteocalcin (31.74% and 25.53%), bone specific alkaline phosphatase (13.22% and 15.59%) and PTH (14.6% and 40.8%).

Table 19. GS-US-236-0112: Change from Baseline in Serum Bone Biomarkers (Safety Analysis Set)

	STB		
	N	Median	Q1, Q3
N-telopeptide (nmol BCE/L)			
Baseline	49	27.7	20.5, 46.2
% Change at Week 24	46	15.9	-7.8, 36.4
% Change at Week 48	46	19.2	-14.8, 37.9
C-telopeptide (µg/L)			
Baseline	49	9.3	7.3, 11.1
% Change at Week 24	48	6.4	-13.1, 22.0
% Change at Week 48	46	-2.6	-17.3, 19.7
Osteocalcin (ng/mL)			
Baseline	50	45.89	32.06, 78.58
% Change at Week 24	48	31.74	9.17, 58.46
% Change at Week 48	47	25.53	-0.56, 45.05
Bone-Specific Alkaline Phosphatase (µg/L)			
Baseline	50	29.16	19.74, 44.75
% Change at Week 24	49	13.22	1.92, 41.17
% Change at Week 48	47	15.59	-9.74, 44.17
PTH (pg/mL)			
Baseline	48	32.0	24.0, 42.6
% Change at Week 24	46	14.6	-5.5, 66.9
% Change at Week 48	46	40.8	-4.7, 98.7
25-OH Vitamin D (ng/mL)			
Baseline	50	23.3	21.1, 28.4
% Change at Week 24	49	5.0	-13.1, 34.5
% Change at Week 48	47	0.0	-11.1, 18.6

In Study **ATN 110**, the median BMD Z-Scores at baseline (spine −0.50, hip −0.45, whole body −0.40) were consistent with other PrEP studies in HIV-negative at-risk men.

Figure 6. ATN 110: Percentage Changes from Baseline in BMD and Z Scores at Weeks 24 and 48



*Wilcoxon signed rank test: * P ≤ 0.001; ** P = 0.02*

Bone results in seroconverters (n = 4) were censored beginning with date of seroconversion.

Hip results in 1 participant were censored due to interference from implants.

Between baseline and Week 24, median BMD decreased in the hip (−0.44%), spine (−0.23%) and whole body (−0.61%). The decreases were statistically significant in the hip and whole body ($p < 0.001$). Median BMD decreased from baseline at Week 48 in the hip and whole body (approximately −1.0% and

−0.7%, respectively; p < 0.001 for the change from baseline), but increased in the spine (approximately 0.4%).

Decreases from baseline in all Z-scores were small but statistically significant at Weeks 24 and 48 (median absolute change from baseline at Week 24: spine approximately −0.08, hip approximately −0.02 [p = 0.02], whole body approximately −0.09; at Week 48: spine approximately −0.10, hip approximately −0.04, whole body approximately −0.10; p < 0.001 for all other parameters at both time points).

After 48 weeks, changes in hip and spine BMD were negatively correlated with the magnitude of TFV exposure. That is, bone loss in participants with TFV-DP in the range considered to be highly protective in adults (> 700 fmol/punch) was significantly greater than in those with drug levels below the limit of quantitation.

Laboratory abnormalities

Through Week 48 in study **FTC-203**, treatment-emergent grade 3/4 laboratory abnormalities occurred in 6/116 subjects (5%). The overall incidence of Grade 3/4 laboratory abnormalities through a median follow up of 96 weeks was 8.6% (10 subjects). These included elevated ALT (3), neutropenia, hyperbilirubinaemia, and elevated amylase [normal lipase] (each in 2) and elevated AST, low haemoglobin, elevated lipase and low platelets (each in 1 subject). The overall incidence of Grade 3 and 4 laboratory abnormalities was consistently low in **FTC-211 and FTC-202**.

In **GS-US-104-0321** up to Week 48, Grade 3 or 4 abnormalities were reported for 10 in the TDF group and 9 in the placebo group. The most frequently reported were abnormalities of neutrophil counts (7 TDF and 2 placebo) and total bilirubin (4 in each group). By Week 336, Grade 3 or 4 abnormalities were reported for 25 subjects in the All TDF group, including 12 in the TDF subgroup and 13 in the placebo/TDF subgroup. The most commonly reported were abnormalities in neutrophil counts (15) and total bilirubin (7).

In Study **GS-US-236-0112**, transient Grade 3 increased AST and Grade 4 increased creatine kinase at Week 40 were reported for 1 subject, who had a tendency toward increased creatine kinase values from screening onward. Grade 3 increased creatine kinase at Weeks 16 and 40 were reported for 1 subject, who also had Grade 1 increased AST at the same time points.

Clinical laboratory data were not available for Study ATN 110 or ATN 113.

2.5.1. Discussion on clinical safety

Effectively, the safety data on use of FTC and TDF in adolescents come from studies in HIV-infected subjects. The safety profiles of each of FTC and TDF are well known for HIV-infected adults. Although there are relatively few safety data obtained in clinical trials with these agents in adolescents the overall safety profile appears to be similar to that in adults.

Whilst FTC is not without its safety issues, the main concerns with regard to the use of TVD in uninfected adolescents relate to the effects of TFV on renal function and normal bone formation and turnover.

Renal effects

During the double-blind treatment period of Study GS-US-104-0321, 6 TDF (13.3%) and 4 placebo subjects (9.5%) reported at least one AE in the renal and urinary disorders SOC but none in the TDF group was considered related to study drug by the investigator. By the end of the study at Week 336, no

AEs of Fanconi syndrome or tubulopathy were reported. The only renal AE reported for > 1 subject in the All TDF group was proteinuria in 2 subjects (2.5%).

Two subjects met the algorithm-specified criteria for potential PRT, one of which had findings consistent with PRT although some of these resolved during continued therapy with TDF. Neither subject discontinued TDF prematurely.

Reductions from baseline to Week 48 in eGFR were −11.00 mL/min/1.73 m2 in the TDF group and −5.35 mL/min/1.73 m2 in the placebo group and at Week 144 the median change from baseline was –38.1 mL/min/1.73 m2 in the All TDF group. The changes were considered to be consistent with normal changes in renal function in an adolescent population progressing towards adulthood but there was no control group after Week 48 to put the changes into context.

In GS-US-236-0112, with cobicistat in the STB, there were expected initial increases in serum creatinine and decreases in eGFR that stabilised through Week 48. At baseline, 4/50 (8.0%) had proteinuria as assessed by dipstick analysis (all Grade 1). Post-baseline, Grade 1 or 2 proteinuria, generally isolated and transient, was reported for 22 subjects (44%; 15 Grade 1, 7 Grade 2). There was an increase in proteinuria as assessed by urine protein to creatinine ratio, an increase in urine retinol binding protein to creatinine ratio and a decrease in the urine beta-2-microglobulin to creatinine ratio. There were no reported cases of PRT or Fanconi syndrome.

Bone effects

Cross-study comparisons cannot be made due to the differences in methodologies and the different age ranges enrolled. In this regard, peak bone mass is generally achieved by 30 years of age, and 80% of peak bone mass is attained by age 18 years. The greatest gains in bone mass at the spine and the hip occur between 11 and 14 years of age in girls and 13 and 17 years of age in boys.

Adolescent subjects in Study GS-US-104-0321 were within the period of greatest gain and BMD increased. Over 48 weeks the differences between the TDF and placebo groups in the percentage change from baseline in spine or total body BMD were not statistically significant. Increases from baseline in lumbar spine BMD at Week 48 were 3.148% for TDF and 3.807% for placebo (p = 0.54). After the double-blind treatment period, the median percentage change for the All TDF group in spine BMD from baseline to Week 144 was 12.702% (n = 26). There were no clinically relevant changes in spine BMD Z-scores in either TDF or placebo group at Weeks 24 or 48. After the double-blind treatment period, among the 28 subjects who received TDF for 96 weeks, a decrease in the spine BMD Z-score was observed (−0.341).

Increases from baseline in total body BMD to Week 48 were 1.495% for TDF and 1.518% for placebo (p = 0.96). The median percentage change in total body BMD from baseline to Week 144 was 4.322%. At Week 48, the mean change in total bone BMD Z-score was −0.254 in the TDF group and −0.179 in the placebo group. Among the 15 subjects who received TDF for 96 weeks, the mean (SD) total body BMD Z-score had decreased by −0.403.

By Week 336, 13/81 (16.05%) in the All TDF group had decreases from baseline of > 4% in spine and/or total body BMD at ≥ 1 time points. Decreases > 4% were persistent in 5/13 subjects. Also, 3/13 had low BMD at any visit (spine or total body unadjusted Z-score ≤ −2.0).

The overall picture in these HIV-infected adolescents points to a slightly greater effect of TDF over 48 weeks and a negative effect over time that cannot be put into context due to lack of a longstanding control group.

In GS-US-236-0112, with no control group, the percentages of subjects with ≥ 4% decrease from baseline in spine BMD were 10/47 (21.3%) at Week 24 and 7/46 (15.2%) at Week 48 (6 had ≥ 4% decrease at both Weeks 24 and 48). Similar decreases on TBLH were observed in 1/49 (2.0%) at Week 24 and 2/48 (4.2%) at Week 48 (1 had ≥ 4% decrease at both Weeks 24 and 48). Five of the 50 subjects showed a worsening from baseline (change from > −2 to ≤ −2) in their spine and/or TBLH height-age BMD Z-scores at Week 24 and/or Week 48. The picture is compatible with the conclusion above but there is no control group.

In Study ATN 110, in male subjects aged 18-22 years, the median BMD decreased over 24 weeks in the hip (−0.44%), spine (−0.23%) and whole body (−0.61%). Median BMD also decreased from baseline at Week 48 in the hip and whole body (approximately −1.0% and −0.7%, respectively; $p < 0.001$ for the change from baseline), but increased in the spine (approximately 0.4%). Decreases from baseline in all Z-scores were small but statistically significant at Weeks 24 and 48 (median absolute change from baseline at Week 24: spine approximately −0.08, hip approximately −0.02 [$p = 0.02$], whole body approximately −0.09; at Week 48: spine approximately −0.10, hip approximately −0.04, whole body approximately −0.10; $p < 0.001$ for all other parameters at both time points). Bone loss in participants with TFV-DP in the range considered to be highly protective in adults (> 700 fmol/punch) was significantly greater than in those with drug levels below the limit of quantitation.

Within the limitation of the ATN 113 study there are no new safety concerns raised.

The MAH has concluded that the impact of TDF on BMD is less in uninfected adults and young adults compared with infected adults and proposes that by extrapolation there will be a lesser effect in HIV-uninfected adolescents vs. infected adolescents and adults. However the CHMP considered that this supposition cannot be concluded from available data.

2.5.2. Conclusions on clinical safety

As was the case in the adult PrEP studies, there were no confirmed and clear cases of PT or Fanconi's syndrome in the small number of adolescents exposed to TDF in clinical trials for treatment or for PrEP. In uninfected adolescents total TDF consumption was limited to 48 weeks and adherence was poor, so that exposure was lower than likely occurred in HIV-infected adolescents.

The available data in infected adolescents and uninfected adult males do suggest some negative effects of TDF on bone. It is not possible to compare the data with those previously described for adult HIV-1 infected males and therefore the MAH's conclusion that the effects are lesser in adolescents vs. adults cannot be supported. Furthermore, some adolescents who commence PrEP may choose to persist with intermittent usage into adulthood with unknown implications for long-term effects.

The TVD SmPC already warns about the renal and bone effects of TFV but this is in the context of the considerable efficacy that has been demonstrated for TVD-containing regimens in HIV-1 infected persons. The risk in uninfected adolescents cannot be quantified from the available data.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 15.4 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this assessment without changes.

The CHMP endorsed the Risk Management Plan version 15.4 with the following content:

Safety concerns

The list of safety concerns were not changed within the extension in adolescents.

Important Identified Risks	FTC, TDF	Post-treatment hepatic flares in HBV infected patients
	TVD	HIV-1 acquisition, including infection resulting from non-adherence (PrEP indication)
	TVD	Development of resistance in patients with unrecognized or acute HIV-1 infection (PrEP indication)
	TDF	Renal toxicity
	TDF	Bone events due to proximal renal tubulopathy/loss of BMD
	TDF	Interaction with didanosine
	TDF	Pancreatitis
Missing Information	TDF	Safety in children (including long-term safety)
	FTC, TDF	Safety in elderly patients
	FTC, TDF	Safety in pregnancy
	FTC, TDF	Safety in lactation
	TDF	Safety in patients with renal impairment

Pharmacovigilance plan

The proposition of a Drug Utilization Study of Truvada for Pre-Exposure Prophylaxis in the European Union was replaced by a Post-Authorization Safety Study to Assess Healthcare Provider's Level of Awareness of Risk Minimisation Materials for Truvada for Pre-Exposure Prophylaxis.

In addition, the Applicant has agreed to establish a prospective, longitudinal, observational Registry of Emtricitabine/Tenofovir Disoproxil Fumarate for HIV-1 Pre-exposure Prophylaxis (PrEP) in the European Union for both adult and adolescent PrEP users.

The modifications are highlighted in bold in the below table.

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Non-interventional studies (Category 3)				
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to FTC or TDF during pregnancy	*Missing information*: Safety in pregnancy (FTC, TDF)	Started	In the Truvada PSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs)
GS-US-276-0103 A Prospective, Observational Study of Individuals Who Seroconvert While Taking Truvada® for Pre-Exposure Prophylaxis (PrEP)	Collect and analyze data from individuals who take Truvada for pre-exposure prophylaxis of sexually acquired HIV-1 infections and who seroconvert during follow-up	*Important identified risk:* HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication) *Important identified risk:* Development of resistance in patients with unrecognized or acute infection (TVD PrEP indication)	Ongoing	Final report planned Q3 2018
GS-US-276-0104 Seroconversions, Resistance, Adverse Events and Drug Adherence among Subjects taking Truvada® for PrEP: A Nested Case Control study	Collect and analyze data examining the association between levels of adherence to the once-daily dosing regimen and risk of seroconversion, resistance development, and renal and skeletal adverse events.	*Important identified risk:* HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication) *Important identified risk:* Development of resistance in patients with unrecognized or acute infection (TVD PrEP indication) *Important identified risk:* Renal toxicity (TDF) *Important identified risk:* Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Ongoing	Final report planned Q2 2019
GS-EU-276-4027 A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider's Level	**To determine healthcare providers' level of awareness of Risk Minimisation Materials and appropriate use and risks associated with Truvada for a PrEP**	**Important identified risk: HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication)**	**Ongoing**	**Enrollment progress report planned Q4 2017** **Final study report planned**

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
of Awareness of Risk Minimisation Materials for Truvada for Pre-Exposure Prophylaxis in the European Union	**indication**	**Important Identified risk: Development of resistance in patients with unrecognized or acute infection (TVD PrEP indication)**		**Q3 2018**
GS-EU-104-0433 An Observational, Drug Utilization Study of Viread in Children and Adolescents with HIV-1 Infection	To assess the clinical management and outcome of renal and bone events	Important identified risk: Renal toxicity (TDF) Important identified risk: Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Ongoing	Final report planned Q4 2017
GS-EU-276-4487 **Prospective, Longitudinal, Observational Registry of Emtricitabine / Tenofovir Disoproxil Fumarate for HIV-1 Pre-exposure Prophylaxis in the European Union**	**To characterize the demographics of the prescribers and individuals who are prescribed FTC / TDF for PrEP.** **To characterize the nature and frequency of patient monitoring after initiating FTC / TDF for PrEP and document any cases of development of resistance to FTC / TDF and any cases of seroconversion to HIV-1 positive, any available information on adherence, and any treatment-related renal or bone adverse events.**	**Important identified risks: HIV-1 acquisition, including infection resulting from non-adherence (TVD PrEP indication)** **Development of resistance in patients with unrecognized or acute infection (TVD PrEP indication)** **Renal toxicity (TDF) Bone events due to proximal renal tubulopathy / loss of BMD (TDF)**	**Planned**	**Protocol submission planned** **Q1 2018**
Other data (Category 3)				
Monitoring of reversibility of renal tubulopathy in clinical trials	To collect information on the reversibility of renal tubulopathy following the discontinuation of tenofovir DF in adult and pediatric patients	Important identified risk: Renal toxicity (TDF)	Ongoing activity	Ongoing activity

Risk minimisation measures

The current PrEP materials were modified to include advice on adolescents. The reminder card to support adherence was also modified accordingly.

Modified or updated sections in the table of Risk Minimisation Measures are highlighted below in bold.

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Post-treatment hepatic flares in HBV infected patients (FTC, TDF)	Section 4.4 of the Truvada SmPC warns about the risk of exacerbation of hepatitis in HBV infected patients following discontinuation of Truvada.	None
HIV-1 Acquisition, including infection resulting from non-adherence (TVD – PrEP)	**Section 4.4 of the Truvada SmPC and the Truvada Package Leaflet warn that Truvada should only be taken as part of a comprehensive prevention strategy and that individuals should be counselled at frequent intervals to strictly adhere to the recommended Truvada daily dosing schedule.**	Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe Truvada for PrEP.
Development of resistance in patients with unrecognized or acute HIV-1 infection (TVD – PrEP)	Sections 4.3 and 4.4 of the Truvada SmPC and the Truvada Package Leaflet warn that Truvada should only be used in individuals confirmed to be HIV-negative prior to initiating and routinely while taking Truvada for PrEP.	Distribution of risk minimization material directed to the prescriber and the individual at risk, to healthcare providers who are likely to prescribe Truvada for PrEP.
Renal toxicity (TDF)	Section 4.4 of the Truvada SmPC provides guidance on calculating creatinine clearance at baseline and the regular monitoring of renal function during Truvada use. In individuals at risk for renal impairment, more frequent monitoring of renal function is required. Section 4.4 of the Truvada SmPC states that use of Truvada should be avoided with concurrent or recent use of nephrotoxic medicinal products and that if concomitant use of Truvada and nephrotoxic agents is unavoidable, renal function should be monitored weekly. Section 4.4 of the Truvada SmPC states that cases of acute renal failure after initiation of high dose or multiple NSAIDS have been reported in HIV-1 infected patients treated with Truvada and with risk factors for renal dysfunction. If tenofovir disoproxil fumarate is coadministered with an NSAID, renal function should be monitored adequately. Section 4.4 of the Truvada SmPC states that the potential risks and benefits associated with coadministration of LDV/SOF or SOF/VEL with tenofovir disoproxil fumarate given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction, and that	*Educational initiatives* 'HIV and the Kidney' educational program. HIV renal educational brochure (including creatinine clearance slide ruler) for prescribers of Truvada to adult patients. HIV educational brochure for prescribers of Truvada to pediatric

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	patients receiving LDV/SOF or SOF/VEL concomitantly with tenofovir disoproxil fumarate and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil fumarate. Section 4.5 of the Truvada SmPC provides guidance that coadministration of tenofovir disoproxil fumarate with LDV/SOF and atazanavir/ritonavir or darunavir/ritonavir should be used with caution with frequent renal monitoring if other alternatives are not available, and that when LDV/SOF is coadministered with tenofovir disoproxil fumarate and dolutegravir , efavirenz or rilpivirine no dose adjustment is recommended but renal function should be closely monitored. Section 4.5 of the Truvada SmPC provides guidance on the coadministration of tenofovir DF with SOF/VEL. Section 4.5 of the Truvada SmPC provides information on interactions due to elimination of FTC and TDF by the kidneys and provides recommendations against the use of Truvada with nephrotoxic medications. Section 4.8 of the Truvada SmPC recommends monitoring of renal function as Truvada may cause renal damage. Renal ADRs associated with the TDF component of Truvada are provided in Section 4.8 of the Truvada SmPC. Section 4.8 of the Truvada SmPC states that proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil fumarate discontinuation. Individuals at risk of renal impairment (such as individuals with baseline renal risk factors, advanced HIV disease, or individuals receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil fumarate discontinuation. Adults Section 4.2 of the Truvada SmPC states that Truvada should only be used in individuals with creatinine clearance below 80 mL/min if the potential benefits of treatment are considered to outweigh the potential risks. *For treament of HIV-1 infection:* Section 4.2 of the Truvada SmPC also contains recommendations on dosing in mild renal impairment (Cl_{cr} 50-80 mL/min) and moderate renal impairment (Cl_{cr} 30-49 mL/min) and states that Truvada is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min) and patients who require hemodialysis. Section 4.4 of the Truvada SmPC states that a higher risk of renal impairment has been reported in patients receiving tenofovir disoproxil fumarate in combination with a ritonavir or cobicistat boosted protease inhibitor. A close monitoring of renal function is required in these patients. In patients with renal risk factors, the coadministration of tenofovir disoproxil fumarate with a boosted protease inhibitor should be carefully evaluated. Section 4.4 of the Truvada SmPC contains a warning statement that renal function should be re-evaluated within a week should serum phosphate decrease < 1.5 mg/dL, or creatinine clearance decrease to < 50 mL/min in any patient receiving Truvada. Consideration should be given to interrupting treatment with Truvada in patients with creatinine clearance <50mL/min or decreases in serum phosphate to <1.0mg/dL (0.32mmol/L). Interrupting treatment with Truvada should also be considered in case of progressive decline of renal function when no other cause has been identified.	patients. **Truvada for PrEP indication educational brochure for prescribers of adults and adolescents, which includes renal educational statements.**

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Section 4.4 of the Truvada SmPC contains a recommendation that dose interval adjustments for HIV-1 patients with creatinine clearance 30-49 mL/min should be made. Section 4.4 of the Truvada SmPC contains a warning that a careful benefit-risk assessment is needed when Truvada is used in patients with creatinine clearance < 60 mL/min and that renal function should be closely monitored. Section 4.4 of the Truvada SmPC contains a warning that the clinical response to treatment should be closely monitored in patients receiving Truvada at a prolonged dosing interval. Section 4.4 of the Truvada SmPC states that Truvada is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min) or on dialysis as the appropriate dose adjustments cannot be achieved with the combination tablet. ***For PrEP:*** **Section 4.2 and 4.4 of the Truvada SmPC states that Truvada has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 ml/min and is therefore not recommended for use in this population. Section 4.4 of the Truvada SmPC also contains a warning statement that renal function should be re-evaluated within a week should serum phosphate decrease < 1.5 mg/dL, or creatinine clearance decrease to < 60 mL/min in any individual receiving Truvada. Consideration should be given to interrupting use of Truvada in individuals with creatinine clearance < 60mL/min or decreases in serum phposphate to <1.0mg/dL (0.32 mmol/L). Interrupting use of Truvada should also be considered in case of progressive decline of renal function when no other cause has been identified.** ***Pediatrics, for the HIV-1 treatment and for PrEP;*** **Sections 4.2, 4.4 and 4.8 of the Truvada SmPC include a statement indicating that use of Truvada is not recommended in individuals under the age of 18 years with renal impairment.** Section 4.4 of the Truvada SmPC states that renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected pediatric patients aged 2 to <12 years in clinical study GS-US-104-0352. **Section 4.4 of the Truvada SmPC recommends monitoring renal function (creatinine clearance and serum phosphate) as recommended for adults.** **Section 4.4 of the Truvada SmPC recommends to measure serum potassium and blood and urine glucose levels in any pediatric patient within one week if serum phosphate is < 3.0mg/dL (0.96 mmol/L); consultation with a nephrologist should be obtained to consider interruption of treatment if renal abnormalities are suspected or detected. Interrupting treatment with Truvada should also be considered in case of progressive decline of renal function when no other cause has been identified.** **Section 4.4 of the Truvada SmPC recommends that, when Truvada is prescribed for PrEP, the individual should be reassessed at each visit to ascertain whether they remain at high risk of HIV-1 infection and that the risk of HIV-1 infection should be balanced against the**	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	potential for renal and bone effects with long-term use of Truvada.	
Bone events due to proximal renal tubulopathy/loss of BMD (TDF)	Section 4.4 of the Truvada SmPC warns about loss of BMD associated with TDF and that more pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil fumarate as part of a regimen containing a boosted protease inhibitor and provides guidance that alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures. Sections 4.4 and 4.8 of the Truvada SmPC provide a description of bone events associated with TDF-associated proximal renal tubulopathy. Section 4.4 of the Truvada SmPC recommends that if bone abnormalities are detected or suspected in pediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained. **Section 4.4 of the Truvada SmPC recommends that, when Truvada is prescribed for PrEP, the individual should be reassessed at each visit to ascertain whether they remain at high risk of HIV-1 infection and that the risk of HIV-1 infection should be balanced against the potential for renal and bone effects with long-term use of Truvada.** Section 4.8 of the SmPC states that reductions in BMD have been reported in HIV-1 infected pediatric and adolescent patients who received TDF.	None
Interaction with didanosine (TDF)	Sections 4.4 and 4.5 of the Truvada SmPC warn that coadministration of tenofovir DF and didanosine is not recommended.	None
Pancreatitis (TDF)	Sections 4.4 and 4.5 of the Truvada SmPC warn about the risk of pancreatitis associated with the interaction between TDF and didanosine and state that co-administration is not recommended. Pancreatitis is included as an ADR to TDF in Section 4.8 of the Truvada SmPC.	None
Missing Information		
Safety in children (including long-term safety) (TDF)	Section 4.2 of the Truvada SmPC notes that the safety and efficacy of Truvada has not been established in children < 12 years old. **Section 4.4 of the Truvada SmPC states that there are uncertainties associated with the long term renal and bone effects of tenofovir disoproxil fumarate in the pediatric population during the treatment of HIV-1 infection.** **Section 4.4 of the Truvada SmPC states that there are no data on the long-term renal and bone effects of Truvada when used for PrEP in uninfected adolescents and the reversibility of renal toxicity after cessation of TDF for treatment of HIV-1 or Truvada for pre-exposure prophylaxis cannot be fully ascertained.**	None
Safety in elderly patients (FTC, TDF)	Sections 4.2 and 4.4 of the Truvada SmPC note that Truvada has not been studied in individuals over the age of 65 years, and should be administered with caution in this patient population.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Safety in pregnancy (FTC, TDF)	Section 4.6 of the Truvada SmPC provides information on pregnancy in humans for the FTC and TDF components and in animals for all components of Truvada and notes that Truvada may be considered during pregnancy, if necessary.	None
Safety in lactation (FTC, TDF)	Section 4.6 of the Truvada SmPC provides information on secretion of FTC and TDF in human milk and notes that Truvada should not be used during breastfeeding.	None
Safety in patients with renal impairment (TDF)	*Adults* Section 4.2 of the Truvada SmPC states that Truvada should only be used in individuals with creatinine clearance below 80 mL/min if the potential benefits are considered to outweight the potential risks. *For treatment of HIV-1 infection* Section 4.2 of the Truvada SmPC states that Truvada should only be used in HIV-1 infected patients with creatinine clearance below 80mL/min if the potential benefits are considered to outweight the potential risks. Section 4.2 of the Truvada SmPC states that limited data support once daily dosing of Truvada in patients with mild renal impairment (CL_{cr} 50-80 mL/min). In patients with moderate renal impairment (CL_{cr} 30-49 mL/min) Truvada every 48 hours is recommended but Truvada is not recommended for patients with severe renal impairment (CL_{cr} <30 mL/min) and patients who require hemodialysis. *For PrEP* Sections 4.2 and 4.4 of the Truvada SmPC states that Truvada has not been studied in HIV-1 uninfected individuals with creatinine clearance < 60 mL/min and is therefore not recommended for use in this population. ***Pediatrics*** **Sections 4.2, 4.4 and 4.8 of the Truvada SmPC state that Truvada is not recommended in individuals under the age of 18 with renal impairment.**	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

2.8. Significance of paediatric studies

The CHMP is of the opinion that Study 2 (Extrapolation study to support the use of Truvada in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adolescents at high risk), which is contained in the agreed Paediatric Investigation Plan P/0294/2015 and has been completed after 26 January 2007, is considered as significant.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Available therapies and unmet medical need

Truvada is approved for use in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults at high risk in the EU, US and several other countries worldwide. There remains a need for additional methods of HIV prevention to further reduce new HIV infections, especially among adolescents.

3.1.2. Main clinical studies

Data from studies with FTC, TDF, and TVD in HIV-infected and uninfected subjects were provided. Exposure, efficacy, and safety data from TDF and/or FTC treated HIV-infected adults and adolescents, and from uninfected subjects receiving TVD for PrEP support extrapolation to high risk adolescents for the use of TVD in combination with safer sex practices for PrEP to reduce the risk of sexually acquired HIV-1 infection. In addition, this data is further supplemented by Study ATN-113 investigating TVD PrEP in HIV-uninfected adolescents (aged 15 to 17 years).

3.2. Favourable effects

The current application to extend the use of daily Truvada for PrEP from adults to adolescents is principally based on the adult PrEP studies that were previously assessed in II/126 and on a comparison of safety and PK between HIV-1-infected adolescents and adults dosed with FTC 200 mg and/or TDF 300 mg QD as part of a complete ART regimen. There are minimal data available from the actual target population and these are confined to 79 adolescent males aged from 15-17 years, many of whom did not complete 48 weeks of treatment and had poor adherence.

The iPrEx study was conducted in adult MSM (mean age ~27 years) and reported relative effectiveness of 44% (mITT) and 47% (ITT) in the primary analysis. The lower bounds of the 95% CI were above zero but below the pre-defined cut-off of 30%. In mITT subjects reporting ≥90% pill adherence the relative efficacy was 73% (41%, 88%) and for those with quantifiable plasma or intracellular drug levels the relative efficacy was 92% (40%, 99%), even in those reporting unprotected receptive anal intercourse (URAI). Thus, the efficacy of oral Truvada for PrEP depended on adherence. Adherence and efficacy were related to age, level of education and reporting URAI at screening.

In the open label extension (OLE) phase the HIV incidence on PrEP was 53% (95% CI 26 to 70) lower than in the placebo group of the randomised phase (3.93 infections per 100 p-y) and 51% (95% CI 23 to 69) lower than during the gap between the randomised phase and the OLE (3.81 infections per 100 p-y). HIV incidence was strongly inversely related to detection of TFV-DP in dried blood spots (DBS).

The Partner's PrEP study provided efficacy data in HIV-1 serodiscordant couples (mean age ~33 years) in which the index cases were not considered to be in need of HIV treatment at the time of study conduct. In the mITT population the HRs indicated a 67% reduction (95% CI: 44%–81%) in risk of HIV-1 acquisition with TDF and a 75% reduction (95% CI: 55%–87%) in risk of HIV-1 acquisition with TVD. Overall, similar protective trends for TDF and FTC/TDF compared with placebo were observed in each sub-group including gender. Cases were much less likely than controls to have detectable TFV in plasma.

Those who had been assigned to placebo were offered re-randomisation (in a 1:1 ratio) to TDF or Truvada in a blinded fashion. In total, 52 infections occurred after randomisation in subjects taking active treatment, including 31 in the TDF arm (0.71 per 100 p-y) and 21 in the Truvada arm (0.48 per 100 p-y). The difference between these arms was not significant (HR 0.67, 95% CI 0.39–1.17; p=0.16). Having detectable plasma TFV was associated with an estimated relative risk reduction for acquiring HIV-1 of 85% for TDF and 93% for Truvada. HIV-1 incidences in subjects receiving PrEP were similar before and after the DSMB intervened to stop the placebo group, in which the HIV-1 incidence was 2 per 100 p-y.

Additional data came from the PROUD study in MSM with a mean age of 35 years. At the time when the steering committee recommended that all deferred treatment group participants should be offered PrEP, three HIV infections had occurred in the immediate treatment group (1.2/100 person-years) vs. 20 in the deferred group (9.0/100 person-years) despite 174 non-study prescriptions for PrEP in the deferred group (leaving 167 without prior use of PrEP). These results give a relative reduction of 86% (90% CI 64–96, p=0·0001) and an absolute difference of 7.8/100 person-years (90% CI 4.3–11.3).

Based on plasma exposures to FTC and TFV when dosed (200 mg and 300 mg QD) to steady state, the efficacy of daily TVD for PrEP in male adolescents who have sex with other males can be expected to be the same as that previously described in older MSM provided that they have the same level of treatment adherence. Unfortunately, available evidence indicates that adherence in adolescents and adults aged 18-22 years is lower than that in older adults and wanes rapidly, with implications for efficacy.

3.3. Uncertainties and limitations about favourable effects

There are two issues that are expected to negatively impact on the benefit of once daily Truvada for PrEP when it is used over longer periods than have been studied within formal clinical trial settings.

The first is the potential for dwindling adherence to daily dosing, which has already been shown very clearly to impact on efficacy. The second is that taking an oral PrEP will prompt some individuals to engage in more risky behaviours, which could result in a higher rate of HIV seroconversion despite PrEP compared to the trial settings, especially if behavioural change is accompanied by dwindling adherence. In iPrEx and Partner's PrEP the assessment of behavioural change suggested that being in a study without knowledge of treatment assignment reduced risky behaviours compared to subjects' screening visit reports but this finding cannot be extrapolated to non-study settings or to adolescents.

There are very few data available on the use of TVD for PrEP in adolescent males aged 15-17 years and in young adult males aged 18-22 years with a history of URAI. What data there are indicate lesser efficacy than was observed in the prior MSM studies. Poor efficacy was associated with a marked drop in adherence to treatment over time. Through 48 weeks of treatment with TVD for PrEP in adult males aged 18-22 in ATN 110 the HIV incidence was 3.3 per 100 person-years. In the adolescents in ATN 113 the HIV seroconversion rate was 6.4 per 100 person-years. Thus, ATN 100 and 113 gave HIV seroconversion rates similar to or higher than the rate observed in the placebo group in the randomised phase of iPrEX (3.9 infections per 100 person-years). In reality, PrEP may be far less successful in subjects aged < 18 years (or indeed in adults aged 18-22 years) compared to older adults simply due to poor adherence.

There is a lack of information on PrEP in female teenagers. There is a suggestion from publications that adherence may be even more critical for women at risk of HIV-1 acquisition via the genital tract compared to men at risk from rectal transmission. Overall, the Partners PrEP study supported an association between high rates of adherence and high rates of efficacy among study participants of both sexes. Therefore similar levels of adherence in female adolescents should provide protection comparable to that observed in women in Partners PrEP but there are no fully reported and published data to support this assumption. One study (CHAMPS) has completed in S. Africa. Over the course of this 12-month study in 148 teenagers (98 female) adherence based on detectable plasma TFV waned from 57% at week 12 to

38% at week 24 and 38% at study end but there was no gender-specific trend in adherence. One HIV seroconversion occurred (0.76/100 person-years) in a 19-year-old female who had stopped PrEP 24 weeks prior to diagnosis.

3.4. Unfavourable effects

The safety profile of each of FTC and TDF, as well as that of Truvada, is very well known. When used for PrEP in HIV-1 uninfected adults the safety profile was much as expected based on the wealth of experience with this combination within complete ART regimens. There were lower rates of factors associated with renal abnormalities during TDF exposure (including higher age, lower CrCL, underlying diabetes and concomitant nephrotoxic agents) in adults suitable for PrEP vs. HIV-1 infected adults, which may explain why there were not major differences in renal markers between active and placebo groups in adult PrEP studies.

Safety data on use of FTC and TDF in adolescents come mostly from small numbers of HIV-1 infected subjects enrolled in clinical trials. The available data suggest that the overall safety profile is similar to that in infected adults. There are very limited safety data available from ATN113 but there are several ongoing studies known to the MAH that are enrolling HIV uninfected teenagers. These trials should provide more safety information in the future.

Whilst FTC is not without its safety issues, the main concern is the use of TVD in uninfected adolescents due to the renal and bone effects of TFV.

Renal effects

During the double-blind treatment period of Study GS-US-104-0321, 6 TDF (13.3%) and 4 placebo subjects (9.5%) reported at least one AE in the renal and urinary disorders SOC but none in the TDF group was considered related to study drug by the investigator. By Week 336, the he only renal AE reported for > 1 subject in the All TDF group was proteinuria in 2 subjects (2.5%). One subject had findings consistent with PRT although some of these resolved during continued therapy with TDF and treatment was continued. Reductions from baseline to Week 48 in eGFR were −11.00 mL/min/1.73 m2 in the TDF group and −5.35 mL/min/1.73 m2 in the placebo group and at Week 144 the median change from baseline was –38.1 mL/min/1.73 m2 in the All TDF group. The changes were considered to be consistent with normal changes in renal function in an adolescent population progressing towards adulthood but there was no control group after Week 48 to put the changes into context.

In GS-US-236-0112, with cobicistat in the STB, there were expected initial increases in serum creatinine and decreases in eGFR that stabilised through Week 48. At baseline, 4/50 (8.0%) had proteinuria as assessed by dipstick analysis (all Grade 1). Post-baseline, Grade 1 or 2 proteinuria, generally isolated and transient, was reported for 22 subjects (44%; 15 Grade 1, 7 Grade 2). There was an increase in proteinuria as assessed by urine protein to creatinine ratio, an increase in urine retinol binding protein to creatinine ratio and a decrease in the urine beta-2-microglobulin to creatinine ratio. There were no reported cases of PRT or Fanconi syndrome.

Bone effects

Peak bone mass is generally achieved by 30 years of age, and 80% of peak bone mass is attained by age 18 years. The greatest gains in bone mass at the spine and the hip occur between 11 and 14 years of age in girls and 13 and 17 years of age in boys. Adolescent subjects in Study GS-US-104-0321 were within the period of greatest gain and BMD increased. Over 48 weeks the differences between the TDF and placebo groups in the percentage change from baseline in spine or total body BMD were not statistically significant. Increases from baseline in lumbar spine BMD at Week 48 were 3.148% for TDF and 3.807%

for placebo (p = 0.54). After the double-blind treatment period, the median percentage change for the All TDF group in spine BMD from baseline to Week 144 was 12.702% (n = 26).

There were no clinically relevant changes in spine BMD Z-scores in either TDF or placebo group at Weeks 24 or 48. After the double-blind treatment period, among the 28 subjects who received TDF for 96 weeks, a decrease in the spine BMD Z-score was observed (−0.341). Increases from baseline in total body BMD to Week 48 were 1.495% for TDF and 1.518% for placebo (p = 0.96). The median percentage change in total body BMD from baseline to Week 144 was 4.322%. At Week 48, the mean change in total bone BMD Z-score was −0.254 in the TDF group and −0.179 in the placebo group. Among the 15 subjects who received TDF for 96 weeks, the mean (SD) total body BMD Z-score had decreased by −0.403.

By Week 336, 13/81 (16.05%) in the All TDF group had decreases from baseline of > 4% in spine and/or total body BMD at ≥1 time points. Decreases > 4% were persistent in 5/13 subjects. Also, 3/13 had low BMD at any visit (spine or total body unadjusted Z-score ≤ −2.0).

In GS-US-236-0112, with no control group, the percentages of subjects with ≥ 4% decrease from baseline in spine BMD were 10/47 (21.3%) at Week 24 and 7/46 (15.2%) at Week 48 (6 had≥ 4% decrease at both Weeks 24 and 48). Similar decreases on TBLH were observed in 1/49 (2.0%) at Week 24 and 2/48 (4.2%) at Week 48 (1 had ≥ 4% decrease at both Weeks 24 and 48). Five of the 50 subjects showed a worsening from baseline (change from > −2 to ≤ −2) in their spine and/or TBLH height-age BMD Z-scores at Week 24 and/or Week 48.

The overall picture in these HIV-infected adolescents points to a slightly greater effect of TDF over 48 weeks vs. placebo and a negative effect over time that cannot be put into context due to lack of a longstanding control group.

In Study ATN 110, in HIV uninfected male subjects aged 18-22 years, the median BMD decreased over 24 weeks in the hip (−0.44%), spine (−0.23%) and whole body (−0.61%). Median BMD also decreased from baseline at Week 48 in the hip and whole body (approximately −1.0% and −0.7%, respectively; p < 0.001 for the change from baseline), but increased in the spine (approximately 0.4%). Decreases from baseline in all Z-scores were small but statistically significant at Weeks 24 and 48 (median absolute change from baseline at Week 24: spine approximately −0.08, hip approximately −0.02 [p = 0.02], whole body approximately −0.09; at Week 48: spine approximately −0.10, hip approximately −0.04, whole body approximately −0.10; p < 0.001 for all other parameters at both time points). Bone loss in participants with TFV-DP in the range considered to be highly protective in adults (> 700 fmol/punch) was significantly greater than in those with drug levels below the limit of quantitation.

In Study ATN 113, in uninfected male subjects aged 15-17 years, baseline BMD was in the normal range for age, based on Z-scores. At week 48, results for 43 participants showed statistically significant increases from baseline in spine (median +2.6%, IQR 0.0-4.6, P<0.001), hip (+1.2%, IQR -0.9-4.3, P=0.02) and total body BMD (+0.7%, IQR -0.2-2.6, P<0.001). Z-scores in the hip and spine did not change significantly from baseline to week 48, but total body BMD Z-score decreased (-0.20, p<0.001).

In adults and adolescents another important risk is that subjects could acquire HIV-1 despite PrEP and continue to expose the virus to Truvada until such time as the infection is discovered and a full ART regimen is commenced as necessary. This raises the risk of development of clinically important resistance. The SmPC already contains warnings on this issue but the apparent lower adherence and efficacy of PrEP in adolescents means that the risk of such occurrences can be expected to be greater.

3.5. Uncertainties and limitations about unfavourable effects

In addition to the few and mostly uncontrolled safety data available in adolescents, plasma exposures to FTC and TFV were not determined in uninfected adolescents who received 200 mg FTC and 300 mg TDF

QD for PrEP. Based on all the available data, it is reasonably expected that plasma exposures to FTC and TFV in HIV-uninfected adolescents will be slightly higher than those in uninfected adults at the same level of adherence to TVD for PrEP. This observation underlines the potential safety concerns regarding TFV effects on renal function and bone formation and maintenance, especially in adolescents who are pre-pubertal and in those who have not completed their growth spurt. Furthermore, it cannot be ruled out that plasma exposures may differ between genders, possibly being even greater in post-pubertal females compared to post-pubertal males. Unfortunately, there are insufficient data at this time to assess this possibility.

3.6. Effects Table

Effect	Short Description	Truvada	Prior MSM studies	Uncertainties / Strength of evidence
ATN 113 HIV seroconversion rate over 48 weeks on study	Open label non-comparative study in males aged 15-17 years engaged in URAI	6.4 per 100 patient-years	Placebo rate in DB phase of IPrEX was 3.9 per 100 patient-years	N=79; 32 prematurely discontinued Adherence markedly dropped over 48 weeks
ATN 110 HIV seroconversion rate over 48 weeks on study	Open label non-comparative study in males aged 18-22 years engaged in URAI	3.3 per 100 patient-years	See above	N=200; 58 prematurely discontinued Adherence markedly dropped over 48 weeks
Decrease in BMD	Known risk with TDF in HIV-infected persons, including adolescents treated with TVD	ATN 110 BMD decreased in hip, spine and whole body by Week 24 and hip and whole body at Week 48 No data from ATN 113	iPrEx BMD decreased in TVD group and increased in placebo group	In iPrEX there were significant differences (-0.4 to -1.0% across total hip, spine, femoral neck and trochanter) between the groups by Week 24.
Proximal renal tubulopathy and Fanconi's syndrome	Known risk with TDF in HIV-infected persons	No cases in ATN 110 or adolescent treatment studies	No cases so far in PrEP use	Risk can be expected especially with prolonged use; patients most at risk of renal effects may not be common users of PrEP

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Truvada has been shown to provide some degree of protection against HIV-1 infection in treatment-adherent adult persons who put themselves at risk due to their sexual practise. The degree of protection provided by PrEP has been repeatedly shown to be related to the level of adherence, supported by finding drug in plasma, although the minimum concentrations that are needed to provide protection have not been identified. Thus, if taken regularly, Truvada can be regarded as having a benefit in persons unwilling or unable to take adequate non-pharmacological and behavioural steps to prevent HIV-1 infection.

Use of TVD from the age of 12 years is supported by efficacy and pharmacokinetic data. It can be agreed that if adherence were to be similar in adolescents as in the older subjects enrolled into iPrEX and

Partners' PrEP then protection should be similar. However, the few data available indicate that adherence is poor and dwindles rapidly in male and female subjects aged < 18 years. Indeed, this seems to apply even in male subjects aged 18-22 years. Thus, the benefit of prescribing TVD to adolescents appears very likely to be less than that achievable in motivated adults.

There are no clinical data on PrEP below 15 years of age. Based on plasma exposures to FTC and TFV when dosed (200 mg and 300 mg QD) to steady state, the efficacy of daily TVD for PrEP in male adolescents who have sex with other males can be expected to be the same as that previously described in older MSM provided that they have the same level of treatment adherence. Subjects aged 12-15 years could be even more vulnerable to the considerations that were reported to lead to poor adherence in older subjects.

As was the case in the adult PrEP studies, there were no confirmed and clear cases of PT or Fanconi's syndrome in the small number of adolescents exposed to TDF in clinical trials for treatment. In uninfected adolescents, total TDF consumption was limited to 48 weeks and adherence was poor, so that exposure was lower than likely occurred in HIV-infected adolescents.

The available data in HIV-1 infected adolescents and in uninfected adult males do suggest some negative effects of TDF on bone tissue. It is not possible to directly compare the data between uninfected adolescents and adults. The MAH's conclusion that the effects are lesser in adolescents vs. adults cannot be supported by available data.

The TVD SmPC already warns about the renal and bone effects of TVF but this is in the context of the considerable efficacy that has been demonstrated for TVD-containing regimens in HIV-1 infected persons.

The benefit-risk relationship when Truvada is used for treatment vs. prophylaxis in adolescents rests on two problems: firstly the risk in uninfected adolescents cannot be quantified from the available data and secondly the benefit that may be expected is not known but can be expected to be substantially lower compared to adults due to differences in adherence levels. Finally, the benefit-risk relationship must consider that the proposed usage is in subjects in whom HIV-1 infection could be prevented if appropriate non-pharmacological measures were to be adequately and consistently employed.

3.7.2. Balance of benefits and risks

Ultimately, since it has been concluded that oral PrEP with Truvada is effective if it is taken, it is for subjects and their physicians to discuss to what extent adequate non-pharmacological preventive measures will be applied and to weigh up the benefit of the additional protection that may be afforded by daily oral prophylaxis with TVD against the risks of renal and bone effects as well as the more minor side effects that can occur. Truvada can be used for PrEP in adolescents.

The MAH committed to set up a PrEP registry to evaluate the effectiveness of the risk minimization materials. The establishment of the PrEP Registry is expected to enable monitoring of outcome measures such as seroconversion rates and renal/ bone effects.

3.8. Conclusions

The overall B/R of Truvada is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by a majority the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include pre-exposure prophylaxis of HIV in adolescents; as a consequence, sections 4.1, 4.2, 4.4,4.5, 4.8, 5.1 and 5.2 of the SmPC are updated based on extrapolation of data for emtricitabine, tenofovir disoproxil fumarate, and Truvada in HIV-infected and uninfected subjects.

Annex II, the Package Leaflet and Risk Management Plan (v.15.4) are updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and Risk Management Plan (RMP).

In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor linguistic amendments

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of

an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Truvada are provided with a physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure
- HIV pediatric renal educational brochure
- PrEP educational brochure for prescribers entitled 'Important Safety Information for Prescribers About Truvada for a Pre-exposure Prophylaxis (PrEP) Indication'
- PrEP Checklist for prescribers
- PrEP educational brochure for the individual at risk entitled 'Important Information About Truvada to Reduce the Risk of getting Human Immunodeficiency Virus (HIV) Infection'
- PrEP reminder card

HIV renal educational brochure:

The HIV renal educational brochure should contain the following key messages:

- That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Truvada
- That Truvada should only be used in patients with impaired renal function if the potential benefits are considered to outweigh the potential risks
- That use of Truvada should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Truvada is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule
- That patients should have their baseline renal function assessed prior to initiating Truvada therapy
- The importance of regular monitoring of renal function during Truvada therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- Instructions on the use of the creatinine clearance slide ruler

HIV paediatric renal educational brochure:

The HIV paediatric renal educational brochure should contain the following key messages:

- That a multidisciplinary approach is recommended for the management of paediatric patients
- That there is an increased risk of renal disease in HIV infected patients associated with tenofovir disoproxil fumarate-containing products such as Truvada
- That Truvada is not recommended for use in paediatric patients with renal impairment
- That use of Truvada should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Truvada is used with nephrotoxic medicinal products, renal function should be closely monitored according to the recommended schedule

- That paediatric patients should have their baseline renal function assessed prior to initiating Truvada therapy
- The importance of regular monitoring of renal function during Truvada therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is confirmed to be < 3.0 mg/dL (0.96 mmol/L) in any paediatric patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week. If renal abnormalities are detected or suspected then consultation with a nephrologist should be obtained to consider interruption of Truvada treatment
- That Truvada may cause a reduction in BMD and the effects of Truvada associated changes in BMD on long term bone health and future fracture risk are currently unknown in paediatric patients
- That if bone abnormalities are detected or suspected then consultation with an endocrinologist and/or nephrologist should be obtained

PrEP educational brochure for prescribers:

- Reminder of the key safety information regarding the use of Truvada for PrEP **in adults and adolescents**
- Reminder of factors to help identify individuals at high risk of acquiring HIV-1
- Reminder on the risk of development of HIV-1 drug resistance in undiagnosed HIV-1–Infected individuals
- Provides safety information on adherence, HIV testing, renal, bone and HBV status.

PrEP Checklist for prescribers:

- Reminders for evaluations/counselling at the initial visit and follow-up.

PrEP educational brochure for the individual at risk (to be provided by healthcare provider [HCP]):

- Reminders on what the individual should know before and while taking Truvada to reduce the risk of getting HIV infection
- Reminder on the importance of strict adherence to the recommended dosing regimen
- Provides information on how to take Truvada
- Provides information on the possible side effects
- Provides information on how to store Truvada.

PrEP reminder card for the individual at risk (to be provided by HCP):

- Reminders to adhere to the dosing schedule
- Reminder to attend scheduled clinic visits.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0294/2015 and the results of these studies are reflected in the Summary of Product

Characteristics (SmPC) and, as appropriate, in the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0294/2015 have been completed after the entry into force of that Regulation.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include pre-exposure prophylaxis of HIV in adolescents as a consequence, sections 4.1, 4.2, 4.4,4.5, 4.8, 5.1 and 5.2 of the SmPC are updated based on extrapolation of data for emtricitabine, tenofovir disoproxil fumarate, and Truvada in HIV-infected and uninfected subjects. Annex II, the Package Leaflet and Risk Management Plan (v.15.4) are updated in accordance.

Summary

Please refer to the scientific discussion in Truvada (EMEA/H/C/0594/II/0135)