EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2017
EMA/169793/2017
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/0131

Note

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

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Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
BMD	bone mineral density
CD4	cluster determinant 4
CI	confidence interval
CSR	clinical study report
d4T	stavudine
DAVG	difference between time-weighted average postbaseline and baseline
$DAVG_{xx}$	time-weighted average change from baseline at Week xx
ddI	didanosine
EFV	efavirenz
eGFR	estimated glomerular filtration rate
FTC	emtricitabine (Emtriva®)
GSS	genotypic sensitivity score
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HIV, HIV-1	human immunodeficiency virus, type 1
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LPV/r	lopinavir boosted with ritonavir
m	Module
M = F	missing = failure
mo	month
NA	not applicable
NC = F	noncompleters = failure
NFV	nelfinavir
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OBR	optimized background regimen
PACTG	Pediatric AIDS Clinical Trial Group
PCR	polymerase chain reaction
PI	protease inhibitor
PK	pharmacokinetic(s)
PRT	proximal renal tubulopathy
Q1, Q3	first quartile, third quartile

RNA	ribonucleic acid
RT	reverse transcriptase
RTV	ritonavir
SAE	serious adverse event
SD	standard deviation
SmPC	summary of product characteristics
SOC	system organ class
TAM	thymidine analog mutation
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TLOVR	time to loss of virologic response
TVD	emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®)
US	United States
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 Ltd submitted to the European Medicines Agency on 27 July 2016 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 treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years for Truvada.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated.

The Package Leaflet and the Risk Management plan (v.13) are updated in accordance.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) 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 not yet completed as some measures were deferred.

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 and the evaluation teams were:

Rapporteur: Greg Markey Co-Rapporteur: Pierre Demolis

Timetable	Actual dates
Submission date	27 July 2016
Start of procedure:	15 August 2016
CHMP Co-Rapporteur Assessment Report	5 October 2016
CHMP Rapporteur Assessment Report	5 October 2016
PRAC Rapporteur Assessment Report	12 October 2016
Committees comments on PRAC Rapp Advice	19 October 2016
PRAC Rapporteur Updated Assessment Report	21 October 2016
PRAC Teleconference	27 October 2016
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	29 October 2016
CXMP comments	3 November 2016
Rapporteur Revised Assessment Report	4 November 2016
Request for supplementary information	10 November 2016
Submission	22 December 2016
Re-star	26 December 2016
CHMP Rapporteur Assessment Report	24 January 2017
PRAC Rapporteur Assessment Report	26 January 2017
PRAC members comments	1 February 2017
PRAC Rapporteur Updated Assessment Report	2 February 2017
PRAC Outcome	9 February 2017
CHMP members comments	13 February 2017
CHMP Rapporteur Updated Assessment Report	16 February 2017
Opinion	23 February 2017

2. Scientific discussion

2.1. Introduction

Truvada® is a fixed-dose combination of the nucleoside analogue emtricitabine (FTC) and the acyclic nucleotide analogue tenofovir disoproxil fumarate (TDF). Truvada tablets were first authorised by the European Commission (EC) on 21 February 2005, for treatment of HIV-infected adults over 18 years of age, in combination with other antiretroviral products. The individual components of Truvada are both approved for the treatment of HIV-1 infection in adults, adolescents, and younger paediatric patients. Emtriva® (FTC) was first approved in the EU on 24 October 2003, and is indicated in combination with other antiretroviral products for the treatment of HIV-1 infected children aged 4 months and over.

Viread® (TDF) was first approved in the EU on 05 February 2002, and is indicated for the treatment of HIV-1 infected children and adolescents aged 2 to < 18 years with nucleoside reverse transcriptase inhibitor resistance or toxicities precluding the use of first line agents.

This Type II variation application proposes to add the following new indication for Truvada,

'treatment of HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

The new indication proposed for TVD in HIV-1 infected adolescents relies upon the results of 3 studies with FTC and 2 studies with TDF in paediatric populations. Data from these studies supported the approval of the use of Emtriva® (FTC) and Viread® (TDF) in paediatric patients.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The new indication proposed for TVD in HIV-1 infected adolescents relies upon the results of 3 studies with FTC and 2 studies with TDF in paediatric populations. Data from these studies supported the approval of the use of Emtriva® (FTC) and Viread® (TDF) in paediatric patients. These are considered sufficient as they demonstrated efficacy of the single entities.

Tabular overview of clinical studies

Table 1. Studies with emtricitabine

Study	Study Design	Number of Subjects by Treatment Regimen	Data Presented
HIV-1 infected pediatric subjects			
FTC-202	Multicenter, open-label study in ART-naive male or female pediatric subjects. Subjects had no or very limited prior ART exposure.	37 subjects enrolled (ITT population), all ART naive; Age groups: 3 months-< 3 years: n = 0 3-12 years: n = 21[a] 13-21 years: n = 16	Week 48 efficacy and safety, and PK of FTC
FTC-203	Multicenter, open-label study in ART-naive and ART-experienced male or female pediatric subjects.	116 subjects enrolled (ITT population); 71 ART-naive and 45 ART-experienced Age groups: 3-24 months: n = 16 25 months-6 years: n = 68 7–12 years: n = 29 13–17 years: n = 3	Week 48 efficacy and safety, and PK of FTC
FTC-211	Multicenter, open-label study in ART-naive 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: 3-24 months: n = 0 7-12 years: n = 1 13-17 years: n = 15	Week 48 efficacy and safety, and PK of FTC

Table 2. Studies with tenofovir

Study	Study Design	Number of Subjects by Treatment Regimen	Data Presented
HIV-1 infected adolescents (12 to < 18 years) with HIV-1 RNA ≥ 1000 copies/mL			
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) 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
HIV-1 infected subjects (2 to < 16 years) with HIV-1 RNA < 400 copies/mL			
GS-US-104-0352	Phase 3, randomized, open-label, to evaluate the safety and efficacy of switching from d4T or ZDV to TDF vs. continuing d4T or ZDV in HIV-1 infected children, who were virologically suppressed (HIV-1 RNA < 400 copies/mL), taking HAART regimen.	97 randomized and treated in the randomized phase (TDF subgroup 48, [d4T or ZDV]/TDF subgroup 49) 89 randomized and treated through the extension phase (TDF subgroup 48, [d4T or ZDV]/TDF subgroup 41)	Up to Week 336 efficacy and safety, and PK of TFV

2.3.2. Pharmacokinetics

The pharmacokinetic parameters from three studies (FTC-202, FTC-211, and FTC-203) for FTC and two Phase 3 studies (Studies GS US 104 0321 and GS US 104 0352) for TDF are summarized.

Emtricitabine

Study FTC-202

Study Title: An Open-label Study to Evaluate the Safety, Tolerance, Antiviral Activity and Pharmacokinetics of Emtricitabine in Combination with Efavirenz and Didanosine in a Once daily Regimen in HIV infected Antiretroviral Therapy Naïve or Very Limited Antiretroviral Exposed Pediatric Subjects

This study evaluated the safety, tolerance, antiviral activity and pharmacokinetics (PK) of emtricitabine (FTC) when combined with efavirenz (Sustiva®, EFV) and didanosine (Videx®/Videx®EC; ddI) in a once-daily (q.d.) regimen in HIV-infected antiretroviral therapy (ART) naïve or very limited ART exposed paediatric subjects. Eligible subjects were stratified, based on their age at study entry as follows:

Age Group 1: from 90 days to < 3 years of age – 0 subjects enrolled

Age Group 2: from 3 to 12 years of age, and - 21 subjects enrolled

Age Group 3: from 13 to 21 years of age – 16 subjects enrolled

The objective of the PK section of the study in terms of FTC was to characterise the PK disposition.

Serial blood samples (0-24 hours post-dose administration) were obtained from all subjects at Week 2 for analysis of the plasma concentrations of all three drugs. In addition, single blood samples for measuring plasma concentrations of all three drugs collected from all subjects at Weeks 4, 8, 12, 20, 28, 36 and 48.

Results

Week 2 pharmacokinetic evaluations are available for 31 children (17/21 subjects in Age Group 2, and 14/16 subjects in Age Group 3).

Table 3. Summary Demographic and Dosing Information by Age Group for Subjects with Pharmacokinetic Evaluations

Characteristics	Age Group 2 N = 17	Age Group 3 N = 14
Formulation Solution Capsule	 13 4	 0 14
Race (n) Black, non-Hispanic Hispanic White, non-Hispanic	 8 7 2	 10 2 2
Age (yr)[a]	7.0 (4.1-11.7)	17.8 (14.6-21.1)
Weight (kg)[b]	22.3 (13.3-40.4)	72.1 (44.0-110.7)
BSA (m^2)[b]	0.83 (0.58-1.27)	1.85 (1.49-2.33)
Dose[a] mg mg/kg mg/m^2	 135 (85-200) 6.1 (5.0-6.7) 160 (142-191)	 200 (200-200) 2.9 (1.8-4.5) 109 (86-134)

a Mean (range) age on day of pharmacokinetic evaluation
b Mean (range)

Among subjects with pharmacokinetic data in Age Group 2, 13 of 17 received the emtricitabine solution formulation, while all subjects in Age Group 3 received the 200 mg emtricitabine capsule formulation. All subjects > 33 kg received capsules and all subjects but 2 weighing ≤ 33 kg (27 and 30 kg) received emtricitabine solution. All children over the age of 10.5 years received capsules, and all subjects ≤ 10.5 years old received the solution formulation except two who were 8.7 and 9.9 years old

Table 4. Mean (CV%) Values for Emtricitabine Pharmacokinetic Parameters at Steady-State by Age Group for All Subjects

Age Group	N		C_{max} (µg/mL)	C_{min} (µg/mL)	t_{max} (hr)	AUC_{tau} (hr•µg /mL)	$t_{1/2}$ (hr)	CL/F (mL/min)	CL/F (mL/min /kg)	CL/F (mL/min /m^2)
2	17	Mean	2.28	0.058	1.46	10.24	12.35	243	11.6	300
		CV%	36	56	61	38	50	38	44	41
3	13[a]	Mean	2.52	0.079	1.68	12.37	11.54	280	3.8	149
		CV%	37	38	55	20	37	19	23	19

a Subject XXXXXX was excluded from the means

Study FTC-203

Study Title: An Open-Label Study of a Once Daily Dose of Emtricitabine in Combination with Other Antiretroviral Agents in HIV-Infected Pediatric Subjects

This study evaluated the safety, antiretroviral activity and pharmacokinetics of emtricitabine in combination with other antiretroviral agents in paediatric HIV-infected subjects aged < 18 years old. 116 antiretroviral therapy (ART) naïve (i.e., no or only very limited prior ART) and ART-experienced paediatric subjects were enrolled into the study. Subjects were enrolled into the following age-groups:

Age Group 1: from 3 to 24 months of age – 13 subjects ART-naïve/ 3 subjects ART-experienced

Age Group 2: from 25 months to 6 years of age – 45 subjects ART-naïve/23 ART-experienced

Age Group 3: from 7 to 12 years of age, inclusive – 13 subjects ART-naïve/ 16 ART-experienced

Age Group 4: from 13 to 17 years of age, inclusive – 0 subjects ART-naïve/ 3 ART-experienced

The objective of the objective of the PK section of the study was to determine the steady-state emtricitabine concentrations in HIV-1 infected paediatric subjects and, if necessary, to refine the dose of emtricitabine to achieve plasma concentrations comparable to those in adults given 200 mg emtricitabine once daily.

ART-naïve subjects received Emtricitabine (6 mg/kg once daily [QD]; up to a maximum of 200 mg QD using the capsule formulation or up to 240 mg QD plus stavudine (1 mg/kg twice daily [BID] if < 30 kg; 30 mg BID if 30 to 59 kg; 40 mg BID if ≥ 60 kg) plus lopinavir/ritonavir (12/3 mg/kg BID if ≥ 7 to < 15 kg; 10/2.5 mg/kg BID if ≥ 15 to ≤ 40 kg; 400/100 mg BID if > 40 kg).

ART-experienced subjects: Replaced the lamivudine in their existing ART regimens with emtricitabine (6 mg/kg once daily [QD]; up to a maximum of 200 mg QD using the capsule formulation or up to 240 mg QD - changed from a maximum of 200 mg QD.

For the full-profile (0-24 hour post-dose) pharmacokinetic evaluation, serial blood samples were collected at Week 2 from the first 6 to 8 subjects enrolled in each age group, irrespective of ART strata, starting

pre-dose and continuing at 1, 2, 4, 8, 12 and 24 hours following the administration of that day's dose of emtricitabine.

For the trough pharmacokinetic analysis at Weeks 8, 16, 24 and 36, one blood sample were collected immediately prior to administration of that day's dose of emtricitabine. At Weeks 4, 12, 20 and 32, after dosing with emtricitabine, two plasma samples for potential population pharmacokinetic analysis and adherence monitoring were to be collected from all subjects at random times, at least 1 hour apart. Random samples were to be analyzed for plasma concentrations of emtricitabine only, regardless or ART stratum.

Results

Full-profile pharmacokinetic evaluations were conducted in 36 children. Pharmacokinetic data are available from 35 children; 14/16 subjects in Age Group 1, 9/68 subjects in Age Group 2, 9/29 subjects in Age Group 3 and 3/3 subjects in Age Group 4

Table 5. Summary Demographic and Dosing Information by Age Group for Subjects Providing 24–Hour Pharmacokinetic
Data

Characteristics	Age Group			
	1: 3 - 24 mo (N = 14[a])	2: 25 mo – 6 yr (N = 9)	3: 7 - 12 yr (N = 9)	4: 13 – 17 yr (N = 3)
Formulation (n)				
Solution	14	9	4	0
Capsule	0	0	5	3
ART Stratum (n)				
Naïve	10	4	2	0
Experienced	4	5	7	3
Ethnic Origin (n)				
Black	13	2	3	3
Other	1	7	6	0
Gender				
Male	7	6	1	1
Female	7	3	8	2
Age (yr)[b]	1.4 (0.4 - 2.0)	5.0 (3.0 - 6.8)	9.9 (7.1 - 12.6)	14.8 (13.9 - 15.9)
Weight (kg)[c]	9.1 (4.8 - 12.0)	18.7 (13.0 - 26.4)	35.3 (20.0 - 64.5)	46.2 (39.0 - 49.5)
BSA (m^2)[c]	0.43 (0.28 - 0.54)	0.74 (0.60 - 0.91)	1.14 (0.81 - 1.64)	1.42 (1.34 - 1.46)
Dose[c]				
mg	56 (27 - 75)	112 (78 - 160)	175 (118 - 200)	200 (200 - 200)
mg/kg	6.1 (5.5 - 6.8)	5.9 (5.7 - 6.3)	5.4 (3.1 - 6.5)	4.4 (4.0 - 5.1)
mg/m^2	128 (96 – 142)	150 (135 - 176)	157 (122 - 186)	141 (137 - 149)

a subject XXXX excluded from summary statistics

b b Mean (range) age on day of pharmacokinetic evaluation

c Mean (range)

All children ≤ 33 kg received the emtricitabine solution formulation and all children > 33 kg received as the 200 mg capsule formulation. All children under 8 years of age received the solution formulation and all but two children over 8 years of age received the capsule formulation.

Table 6. Mean (CV%) Values for Emtricitabine Pharmacokinetic Parameters at Steady–State by Age Group for All Subjects

Age Group	N		C_{max} (µg/mL)	T_{max} (hr)	C_{min} (µg/mL)	AUC_{tau} (hr•µg/mL)	$T_{1/2}$ (hr)	CL/F (mL/min)	CL/F (mL/min/kg)
1	13[a]	Mean	1.93	1.6	0.059	8.70	8.87	115	13.2
(3 – 24 mo)		CV%	34	54	52	37	36	27	34
2	9	Mean	1.90	1.5	0.060	8.98	7.44	242	13.7
(25 mo – 6 yr)		CV%	46	58	90	39	45	48	58
3	9	Mean	2.59	2.2	0.071	13.00	7.71	240	7.1
(7 – 12 yr)		CV%	32	103	31	18	42	34	26
4	3	Mean	2.42	2.33	0.079	14.46	8.34	233	5.1
(13 – 17 yr)		CV%	20	65	38	12	26	13	11

Study FTC- 211

Study Title: An Open-label Study of a Once-daily Dose of Emtricitabine in Combination with Other Antiretroviral Agents in HIV-infected Pediatric Subjects

This was an open-label, non-randomized clinical study designed to evaluate the safety, pharmacokinetics, and activity of antiretroviral therapy (ART) regimens containing a once-daily dose of emtricitabine in ART-naïve or ART-experienced, HIV-1 infected paediatric subjects. Subjects were enrolled into the following age-groups:

Age Group 1: from 3 to 24 months,

Age Group 2: from 7 to 12 years – 1 subject

Age Group 3: from 13 to 17 years – 15 subjects

The objective of the PK section was to determine the steady-state emtricitabine concentrations in

HIV-1 infected paediatric subjects and, if necessary, to refine the dose of emtricitabine to achieve plasma concentrations comparable to those in adults given 200 mg emtricitabine once daily.

Trough blood samples for plasma concentrations of emtricitabine were collected from all subjects at Weeks 8, 16, 24, and 36. Random (population) blood samples for plasma concentrations of emtricitabine were collected from all subjects at Weeks 4, 12, 20, and 32 for the purpose of potential adherence monitoring and population pharmacokinetic evaluations

Results

Week 2 pharmacokinetic evaluations are available for 15 of the 16 children entered in the study (1/1 subject in Age Group 2, and 14/15 subjects in Age Group 3. All subjects received the 200 mg capsule formulation with the exception of one subject in Age Group 3.

Table 7. Summary Demographic and Dosing Information by Age Group for Subjects with Pharmacokinetic Evaluations

Characteristics	Age Group 2 N = 1	Age Group 3 N = 14	Overall N = 15
Formulation Capsule Solution	 1 0	 13 1	 14 1
Race (n) Black Caucasian Others	 0 1 0	 0 14 0	 0 15 0
Gender Female Male	 0 1	 8 6	 8 7
Age (yr)[a]	12.8	14.2 (13.2 -15.2)	14.1 (12.8 – 15.2)
Weight (kg)[a]	38.0	37.6 (23.0 – 49.0)	37.7 (23.0 – 49.0)
BSA (m^2)[a]	1.24	1.24 (0.90 – 1.48)	1.24 (0.90 – 1.48)
Dose[a] mg mg/kg mg/m^2	 200 5.3 162	 197 (160 – 200) 5.4 (4.1 – 7.0) 161 (136 -180)	 197 (160 – 200) 5.4 ((4.1 – 7.0) 161 (136 -180)

a Mean (range)

Table 8. Mean (CV%) Values for Emtricitabine Pharmacokinetic Parameters at Steady-State by Age Group for Subjects Receiving 200 mg Capsules

Age Group	N		C_{max} (µg/mL)	C_{min} (µg/mL)	t_{max}, (hr)	AUC_{τ} (hr•µg /mL)	$t_{1/2}$ (hr)	CL/F (mL/min)	Vd/F (L)
2	1	Mean	3.43	0.068	1.0	13.38	7.55	249	163
		CV%	-	-	-	-	-	-	-
3	13	Mean	2.92	0.035	1.31	10.61	7.30	330	214
		CV%	23	53	65	23	30	23	50

The data from the three studies above have been combined and summarised according to age for FTC,

Age Group 1: from 3 to 24 months of age, inclusive,

Age Group 2: from 25 months to 6 years of age, inclusive,

Age Group 3: from 7 to 12 years of age, inclusive,

Age Group 4: from 13 to 17 years of age, inclusive

Table 9. Summary Demographic and Dosing Information by Age Group (3 months to < 18 years) for Subjects Receiving Capsules and Solution in FTC Pediatric Clinical Studies FTC-202, FTC-211, and FTC-203

Age Group / Characteristics	1 (3 to 24 mo) (N = 15)[c]	2 (25 mo to 6 yr) (N = 19)	3 (7 to 12 yr) (N = 17)	4 (13 to 17 yr) (N = 27)
Formulation Capsule Solution	 0 15	 0 19	 10 7	 26 1
Race (N) Black White Hispanic	 14 0 0	 4 2 6	 9 1 1	 11 15 1

Other	1	7	6	0
Gender Male Female	 8 7	 10 9	 7 10	 11 16
Age (yr)[a]	1.4 (0.4–2.1)	5.0 (3.0–6.8)	10.0 (7.1–12.8)	15.2 (13.2–17.9)
Weight (kg)[b]	9.4 (4.8–13.4)	18.5 (13.0–26.4)	32.5 (19.1–64.5)	51.3 (23.0–111)
Body Surface Area (m^2)[b]	0.44 (0.28–0.58)	0.73 (0.58–0.91)	1.09 (0.75–1.64)	1.487 (0.90–2.33)
Dose (mg/kg)[a]	6.1 (5.5–6.8)	6.1 (5.6–6.7)	5.6 (3.1–6.6)	4.4 (1.8–7.0)

a Mean (range) age on day of PK evaluation

b Mean (range)

c Includes subject XXXX (study FTC-203) who was excluded from the PK analysis

Table 10. Combined Analysis: Mean (CV%) Values for FTC Pharmacokinetic Parameters at Steady-State by Age Group (All Subjects)

Age Group	N		C_{max} (µg/mL)	C_{min} (µg/mL)	T_{max} (h)	AUC_{tau} (h•µg/mL)	$t_{1/2}$ (h)	CL/F (mL/min/kg)
1	14[a]	Mean	1.93	0.059	1.6	8.70	8.87	13.2
(3–24 mo)		CV%	34	52	54	37	36	34
2	19	Mean	1.91	0.059	1.6	9.03	11.29	13.0
(25 mo–6 yr)		CV%	38	71	62	33	57	46
3	17	Mean	2.72	0.066	1.7	12.57	8.19	8.4
(7–12 yr)		CV%	30	45	99	28	39	54
4	27	Mean	2.73	0.064	1.7	12.55	8.94	6.4
(13–17 yr)		CV%	31	94	65	43	37	45

The overall mean Cmax, Cmin, and AUCtau across all age groups (N = 77) were 2.38 µg/mL, 0.062 µg/mL and 10.99 h•µg/mL, respectively. AUC appears to increase with age. Apparently there was no trend observed between virologic failures and AUCtau.

TFV

Pharmacokinetic data are available for 8 HIV 1 infected adolescent subjects who received TDF plus a background ARV regimen for at least 4 weeks in **Study GS US 104 0321**. Of the 8 subjects in the PK sub-study, 5 were male and 3 were female; 7 were white and 1 was black. The mean age was 14 years and mean weight at screening was 44.06 kg

Tenofovir was rapidly absorbed with a median T_{max} of 1.98 hours and mean C_{max} of 377.5 ng/mL. A mean AUC_{tau} of 3390.6 ng•h/mL and a median $t_{1/2}$ of 10.54 hours were achieved. Comparison of the data in this study with historical data in HIV-1 infected adults under steady-state conditions revealed similar TFV exposures, as assessed by mean AUC_{tau}, C_{max}, and C_{tau}, as well as median T_{max} and $t_{1/2}$ estimates.

Table 11. GS-US-104-0321: Plasma TFV Pharmacokinetic 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.

In study **GS US 104 0352** pharmacokinetic data are also available for 23 HIV 1 infected paediatric subjects who had replaced stavudine or zidovudine with TDF as part of their ART regimen. There were 12 subjects in the 2 to < 6 years group out of which 50% of whom were female. There were 11 subjects in the 6 to < 12 years group out of which 63.6% were female.

A summary of TFV steady-state PK parameters for children enrolled in the PK sub-study is presented by age group and overall in Table 12.

Tenofovir was rapidly absorbed with a median Tmax of 1.93 hours and mean Cmax of 238.7 ng/mL. A mean AUC_{tau} of 2586.3 ng•h/mL and a median t1/2 of 13.65 hours were achieved. In addition, PK by age group (2 to < 6 years and 6 to < 12 years) are presented in Table 12. Analysis by age group (2 to < 6 and 6 to < 12 years) revealed similar TFV absolute exposures by AUC_{tau}, Cmax, and C_{tau}, and similar Tmax and t1/2 estimates.

Comparison of the data in this study to historic data in HIV 1 infected adults (GS-97-901, GS 99 907) under steady state conditions revealed similar TFV exposures, as assessed by AUC_{tau}, C_{max}, and C_{tau}, as well as median T_{max} and t1/2 estimates.

Table 12. GS-US-104-0352: Summary of Steady-State Pharmacokinetic Parameters for TFV Overall and by Age Group (PK Substudy Analysis Set)

	TDF 8 mg/kg		
TFV PK Parameter	**Overall (N = 23)**	**2 to < 6 years (N = 12)**	**6 to < 12 years (N = 11)**
AUC_{tau} (ng•h/mL)[a] Mean (% CV)	2586.3 (40.9)	2679.1 (39.9)	2485.0 (43.8)
C_{max} (ng/mL) Mean (%CV)	238.7 (53.4)	257.2 (58.9)	218.5 (44.8)
C_{tau} (ng/mL)[a, b] Mean (%CV)	54.5 (43.4)	55.4 (47.3)	53.4 (41.0)
CL/F (L/h)[a] Mean (%CV)	34.7 (71.4)	22.7 (40.6)	47.8 (62.5)
T_{max} (h) Median (Q1, Q3)	1.93 (1.08, 2.30)	1.98 (1.20, 2.24)	1.22 (1.00, 4.00)
$t_{1/2}$ (h)[a, c] Median (Q1, Q3)	13.65 (11.43, 16.00)	13.85 (9.96, 16.54)	12.31 (11.43, 15.99)

Parameter was estimated using pre-dose concentration as a surrogate for the concentration at the 24-hour timepoint.

2.3.3. Pharmacodynamics

There are no new data since the efficacy of TFV and FTC within regimens for treatment of HIV-1 infection is well established.

2.3.4. PK/PD modelling

None provided.

2.3.5. Discussion on clinical pharmacology

No clinical pharmacology studies in which FTC and TDF have been used together have been provided. For the well-established single agents (FTC and TDF) also no new clinical pharmacology studies have been provided. PK data from studies conducted in HIV –infected paediatric subjects for the individual components FTC and TDF were provided in support of this application. These studies have previously been evaluated in support of the use of the single entities in children. These data show that in the paediatric age groups for the single entity FTC and TDF, the PK of both are in the range of those observed in adults.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of FDC and TDF are well-known. There are no issues to be highlighted.

2.4. Clinical efficacy

2.4.1. Dose response studies

No clinical dose response studies were provided to support the proposed use in HIV-1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

2.4.2. Main studies

No new studies have been conducted using the FDC or the single components in combination together. The variation application relies on the efficacy data generated for FTC i.e. studies FTC-202, FTC-211 and FTC-203 and on the efficacy data from two studies conducted with TDF, studies GS US-104-0321 and GS US 104-0352

Studies FTC-202, FTC-211 and FTC-203

FTC-202

An open-label study to evaluate the safety, tolerance, antiviral activity and pharmacokinetics (PK) of emtricitabine (FTC) in combination with efavirenz (Sustiva®, EFV) and didanosine (Videx®/Videx®EC; ddI) in a once-daily (q.d.) regimen in HIV-infected antiretroviral therapy (ART) naïve or very limited ART exposed paediatric subjects.

Methods

A multi-centre, open-label Phase 2 study in ART-naive or very limited ART exposed male or female paediatric subjects to evaluate the safety, tolerance, antiviral activity and pharmacokinetics (PK) of emtricitabine (FTC) in combination with efavirenz (Sustiva®, EFV) and didanosine (Videx®/Videx®EC; ddI) in a once-daily (q.d.) regimen . Subjects had no or very limited prior ART exposure

Study Participants

Paediatric subjects (3 mo-21 y) with HIV-1 infection, ART-naive or very limited ART exposure, and plasma HIV-1 RNA ≥ 5000 copies/mL

Eligible subjects were stratified based on their age

- Age Group 1: from 90 days to < 3 years of age (cohort not yet open to enrolment awaiting efavirenz dose specification),
- Age Group 2: from 3 to 12 years of age, and
- Age Group 3: from 13 to 21 years of age.

Treatments

All subjects receive a triple-drug regimen comprising: FTC: 6 mg/kg q.d., up to a maximum of 200 mg q.d.; ddI: 240 mg/m2 q.d., up to a maximum of 400 mg q.d., and EFV: based on body weight, up to a maximum of 600 mg q.d. as a capsule or up to 720 mg q.d. as an oral solution (Age Groups 2 and 3).

Objective

To determine long-term safety, tolerance, and antiviral activity of FTC+ddI+EFV in HIV-1 infected ART-naive or very limited ART exposed paediatric subjects

Statistical approach

There was an interim analysis at week 2 to review PK data. A second interim analysis was done to summarise the results of analysis of safety and activity data and a third interim analysis was to be performed after 24 weeks of treatment. However no subjects were enrolled in age group one therefore the 3rd analysis was performed on Groups 2 and 3 subjects. This analysis was done to assess the overall results. A 4th analysis was conducted due to study extension after all subjects had on Groups 2 and 3, this particular analysis focussed on the safety and efficacy of the study regimen

Outcomes/endpoints

- Development of Grade 3 or 4 adverse events, attributed to the study treatment.
- Suppression of HIV-1 RNA to:

  a) <400 copies/mL at Week 16, and

  b) <50 copies/mL, at Week 16.
- Time to virologic failure at or after Week 16, defined as:

  a) the first measurement ≥400 copies/mL or permanent discontinuation of study treatment, or

  b) the first measurement ≥50 copies/mL or permanent discontinuation of study treatment

Baseline data

Seventeen (46%) of the 37 subjects enrolled were female and 23 (62%) were black. Mean age was 11.6 years (range: 3.2 to 21.1 years). The median CD4 count at Baseline was 310 cells/µL (range: 2 to 1893

cells/μL) and the median CD4 percentage was 17% (range 1 to 40%). The median HIV-1 RNA viral load at Baseline was 47,775 copies/mL (range: 3,655 – 2,370,884 copies/mL).

Outcome and estimation

Table 13. Number (%) of Subjects with Plasma HIV-1 RNA Suppression by Study Week

	Age Group 2[a] N = 21	Age Group 3[b] N = 16	Overall N = 37
< 400 copies/mL			
Baseline (Week 0)	0/21 (0.0%)	0/16 (0.0%)	0/37 (0.0%)
Week 2	9/21 (42.9%)	8/16 (50.0%)	17/37 (45.9%)
Week 4	14/21 (66.7%)	12/16 (75.0%)	26/37 (70.3%)
Week 8	15/21 (71.4%)	13/16 (81.3%)	28/37 (75.7%)
Week 12	19/21 (90.5%)	13/16 (81.3%)	32/37 (86.5%)
Week 16	18/21 (85.7%)	12/16 (75.0%)	30/37 (81.1%)
Week 24	18/21 (85.7%)	12/16 (75.0%)	30/37 (81.1%)
Week 36	17/21 (81.0%)	12/16 (75.0%)	29/37 (78.4%)
Week 48	17/21 (81.0%)	13/16 (81.3%)	30/37 (81.1%)
< 50 copies/mL			
Baseline (Week 0)	0/21 (0.0%)	0/16 (0.0%)	0/37 (0.0%)
Week 2	2/21 (9.5%)	1/16 (6.3%)	3/37 (8.1%)
Week 4	4/21 (19.0%)	3/16 (18.8%)	7/37 (18.9%)
Week 8	7/21 (33.3%)	6/16 (37.5%)	13/37 (35.1%)
Week 12	13/21 (61.9%)	10/16 (62.5%)	23/37 (62.2%)
Week 16	15/21 (71.4%)	11/16 (68.8%)	26/37 (70.3%)
Week 24	17/21 (81.0%)	12/16 (75.0%)	29/37 (78.4%)
Week 36	15/21 (71.4%)	11/16 (68.8%)	26/37 (70.3%)
Week 48	14/21 (66.7%)	13/16 (81.3%)	27/37 (73.0%)

a 3 to 12 years of age

b 13 to 21 years of age.

Overall, 81% of children had plasma HIV-1 RNA < 400 copies/mL, 73% were suppressed below 50 copies/mL (ITT, missing=failure), and the median decline in plasma HIV-1 RNA was 3.3 log10 copies/mL at 48 weeks.

Study FTC-203

An Open-Label Study of a Once Daily Dose of Emtricitabine in Combination with Other Antiretroviral Agents in HIV-Infected Paediatric Subjects

Methods

A multi-centre open-label, non-randomized, Phase 2 clinical study was designed to evaluate the safety, antiretroviral activity and pharmacokinetics of emtricitabine in combination with other antiretroviral agents in paediatric HIV-infected subjects aged < 18 years old.

Study participants

A total of 116 subjects who met the inclusion and exclusion criteria, including 71 ART-naïve and 45 ART experienced subjects, with a confirmed HIV-1 infection were actually enrolled and treated with at least one dose of emtricitabine. Subjects were enrolled into the following age-groups:

Age Group 1: from 3 to 24 months of age – 13 subjects ART-naïve/ 3 subjects ART-experienced

Age Group 2: from 25 months to 6 years of age – 45 subjects ART-naïve/23 ART-experienced

Age Group 3: from 7 to 12 years of age, inclusive – 13 subjects ART-naïve/ 16 ART-experienced

Age Group 4: from 13 to 17 years of age, inclusive – 0 subjects ART-naïve/ 3 ART-experienced

Treatments

ART-naïve subjects: Emtricitabine (6 mg/kg once daily [QD]; up to a maximum of 200 mg QD using the capsule formulation or up to 240 mg QD - changed from a maximum of 200 mg QD, per protocol amendment no. 5 – using the oral solution formulation) plus stavudine (1 mg/kg twice daily [BID] if < 30 kg; 30 mg BID if 30 to 59 kg; 40 mg BID if ≥ 60 kg) plus lopinavir/ritonavir (12/3 mg/kg BID if ≥ 7 to < 15 kg; 10/2.5 mg/kg BID if ≥ 15 to ≤ 40 kg; 400/100 mg BID if > 40 kg). ART-experienced subjects: Replaced the lamivudine in their existing ART regimens with emtricitabine (6 mg/kg once daily [QD]; up to a maximum of 200 mg QD using the capsule formulation or up to 240 mg QD - changed from a maximum of 200 mg QD, per protocol amendment no. 5 - using the oral solution formulation). At the Investigator's discretion, one or more of the subject's background antiretroviral medication(s) could be replaced with different drug(s) at the same time that lamivudine was replaced with emtricitabine.

Objectives

- To obtain long-term safety experience for antiretroviral regimens containing emtricitabine in HIV-1 infected paediatric subjects.
- To obtain antiviral activity data for antiretroviral regimens containing emtricitabine in HIV-1 infected paediatric subjects.

Outcomes/endpoints

The primary efficacy endpoint as defined by the protocol was the proportion of subjects at Week 48 with suppression of plasma HIV-1 RNA to below the LLOQ for the assay, i.e., ≤ 400 and ≤ 50 copies/mL for the Standard and UltraSensitive Tests, respectively. The protocol-defined analysis of the endpoint was based on an intent-to-treat (ITT), non-completer = failure (NC = F) analysis. In addition, the proportion

of subjects who achieved and/or maintained HIV viral load at ≤ 400 and ≤ 50 copies/mL based on the FDA defined time to loss of virologic response (TLOVR) algorithm were also completed and are presented as co-primary efficacy variables.

Secondary endpoints include the incidence of virologic failure, effectiveness failure and efficacy failure, as well as the change from baseline in plasma HIV-1 RNA viral load and absolute and percent CD4+ cell counts and the incidence of subjects experiencing clinical disease progression.

Sample size

No formal sample size calculations were performed for this study. Sixty (60) to 120 subjects were planned for enrolment to provide sufficient data to characterize the preliminary safety, antiviral activity and pharmacokinetic profile of emtricitabine in a paediatric population.

Randomisation

This was an open-label, non-randomized study. As previously described Eligible subjects were stratified into four age groups:

- Age Group 1: from 3 to 24 months of age
- Age Group 2: from 25 months to 6 years of age
- Age Group 3: from 7 to 12 years of age, inclusive
- Age Group 4: from 13 to 17 years of age, inclusive

Statistical methods

Statistical analyses for safety and anti-HIV activity are presented by subject population (i.e., ART-naïve and ART-experienced subjects). In addition, for each ART population, analyses are presented by age group (1-4, as defined above) and emtricitabine dosage form (oral solution or capsules).

Virologic response parameters that were continuous data (e.g., log10 HIV-1 RNA) are summarized by the mean, standard error, median, minimum and maximum. Categorical data (e.g., proportion of subjects with plasma HIV-1 RNA below the LLOQ at Week 48, proportion of subjects who were virologic, effectiveness or efficacy failures, and the respective times to failure) are summarized by the number and percent of subjects belonging to a specific classification. Time-to-event methods (e.g., Kaplan-Meier estimates) were used to summarize time-to-event data.

Analyses were conducted according to the intent-to-treat (ITT) principle. The ITT population was defined as all subjects with a confirmed HIV-1 infection and who received at least one dose of the study drug, emtricitabine, regardless of whether the subject completed the planned duration of the study.

Results

Table 14. Summary (n, %) of Subject Disposition at Week 48 by ART Stratum

	ART Stratum					
	Naïve		Experienced		Overall	
Subjects enrolled and treated with at least one dose of study drug	72		45		117	
Subject censored[a]	1	(1.4)	0	(0)	1	(0.9)
Subjects in the ITT population	71	(98.6)	45	(100)	116	(99.1)
Status of subjects in ITT population:						
Completed Week 48[b]	67	(94.4)	42	(93.3)	109	(94.0)
Premature Discontinuation[c]	4	(5.6)	3	(6.7)	7	(6.0)
Reason for Discontinuation:						
Virologic failure	2	(2.8)	1	(2.2)	3	(2.6)
Adverse Event	1	(1.4)	1	(2.2)	2	(1.7)
Investigator and/or subject decision to withdraw	1	(1.4)	1	(2.2)	2	(1.7)

a Subject XXXXas not HIV infected and was therefore censored from all analyses.

b Percent is % of ITT Population

c Prior to Week 48

Baseline data

Overall, the majority of subjects were black (69.0%) and about half (52.6%) were female. Mean age was 5.8 years (range: 0.3 to 15.9 years). Median baseline plasma HIV-1 RNA was 4.53 log10 copies/mL (range of 1.70 to 5.88 log10 copies/mL) and median baseline (N = 115) absolute and percent CD4+ cell counts were 817 cells/mm3 (range: 186 to 2,650 cells/mm3) and 25.3% (range: 6.6 to 50.6%), respectively. Twenty-two (22/116, 19.0%) subjects had a history of a CDC Class C event

Numbers analysed

The ITT population was the primary population for the efficacy analysis. A total of 116 subjects with confirmed HIV-1 infection and who received at least one dose of study drug, emtricitabine, were included in the ITT Population. Analyses were also performed by subject subgroup, including age group (3 to 24 months, 25 months to 6 years, 7 to 12 years, and 13 to 17 years); ART stratum (ART-naïve and ART-experienced); and emtricitabine dosage form (capsule and oral solution).

Outcomes and estimation

In the analysis for the ITT population, overall 89.7% (93.0% naïve stratum, 84.4% experienced stratum) of the subjects achieved and/or maintained suppression of plasma HIV-1 RNA to ≤ 400 copies/mL. 75.9% of the subjects overall (78.9% naïve stratum, 71.1% experienced stratum) achieved and/or maintained suppression of plasma HIV-1 RNA to ≤ 50 copies/mL.

The incidence of TLOVR-defined virologic failure (LLOQ ≤ 400 copies/mL) was low at 6.9% overall through Week 48 (4.2% naïve stratum, 11.1% experienced stratum).

Table 15. Summary of TLOVR-Defined Outcome through Week 48

TLOVR Outcome through Week 48	ART Stratum		Overall N = 116
	Naïve N = 71	Experienced N = 45	
TLOVR Classifications (n, %)			
Responder[a] at 400 copies/mL	66 (93.0)	38 (84.4)	104 (89.7)
Responder[a] at 50 copies/mL	56 (78.9)	32 (71.1)	88 (75.9)
Virologic Failure[b]	3 (4.2)	5 (11.1)	8 (6.9)
Study Discontinuation Due to			
Death	0	0	0
Adverse Event	1 (1.4)	1 (2.2)	2 (1.7)
Other Reasons[c]	1 (1.4)	1 (2.2)	2 (1.7)

a Subjects achieved and maintained confirmed HIV-1 RNA < LLOQ through Week 48.

b Includes subjects who failed to achieve virologic suppression or rebounded after achieving virologic suppression at the 400 copy/mL LLOQ.

c Includes loss to follow-up, subject withdrawal, non-compliance, protocol violation and other reasons.

Study FTC-211

Method

An open-label, non-randomized clinical study designed to evaluate the safety, pharmacokinetics, and activity of antiretroviral therapy (ART) regimens containing a once-daily dose of emtricitabine in ART-naïve or ART-experienced, HIV-1 infected paediatric subjects. Depending on their age, 30 to 50 eligible HIV-1 infected paediatric subjects < 18 years of age were to receive one of two emtricitabine-containing treatment options. However due to slower than expected enrolment, enrolment into this study was stopped before the targeted minimum of 30 subjects was reached. A total of 16 subjects were actually enrolled in this study, 1 in Age Group 2 and 15 in Age Group 3.

Study participants

Male and female paediatric subjects with documented HIV-1 infection were eligible to participate in this study if they were from 3 to 24 months of age (and ART-naïve) or from 7 to 17 years of age (either ART-naïve or ART-experienced).

ART-naïve was defined as having no prior exposure to any ART (with the exception of ≤ 56 days of perinatal prophylaxis for the prevention of maternal-to-child transmission or ≤ 6 weeks of cumulative postnatal treatment with zidovudine [Retrovir®, ZDV] monotherapy) and having a plasma HIV-1 RNA level of ≥ 5,000copies/mL at Screening. Children ≥ 7 years of age (i.e., Age Groups 2 and 3) also had to have a screening plasma HIV-1 RNA level of ≤ 600,000 copies/mL.

ART-experienced was defined as having previously been treated with an ART regimen(s) that did not include either lamivudine (3TC) and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI) and having a Screening plasma HIV-1 RNA level of ≤ 600,000 copies/mL.

Treatments

Subjects in Age Group 1 (ART-naïve) were to receive Treatment 1, a combination of emtricitabine, stavudine, and lopinavir/ritonavir. No subjects were actually enrolled into Age Group 1 or received Treatment 1.

Treatment 1: Emtricitabine (6 mg/kg QD) plus stavudine (Zerit®, d4T;1 mg/kg BID if < 30 kg) plus lopinavir/ritonavir (Kaletra®, LPV/r; 12/3 mg/kg BID if ≥ 7 to < 15 kg; 10/2.5 mg/kg BID if ≥ 15 to ≤ 40 kg).

Subjects in Age Groups 2 and 3 (ART-naïve and ART-experienced) received Treatment 2, a combination of emtricitabine, didanosine, and efavirenz.

Treatment 2: Emtricitabine (6 mg/kg QD, up to a maximum of 200 mg QD using the capsule formulation or up to 240 mg QD using the oral solution formulation) plus didanosine (Videx® or Videx®EC, ddI; 240 mg/m2 QD, up to a maximum of 400 mg QD) plus efavirenz (Stocrin, EFV; based on body weight, up to a maximum of 600 mg QD using the capsule formulation or up to 720 mg QD using the oral solution formulation).

Objectives

- To obtain safety experience for antiretroviral regimens containing emtricitabine in HIV-1 infected paediatric subjects.
- To determine the steady-state emtricitabine concentrations in HIV-1 infected pediatric subjects and, if necessary, to refine the dose of emtricitabine to achieve plasma concentrations comparable to those in adults given 200 mg emtricitabine once daily.
- To obtain antiretroviral activity data for antiretroviral regimens containing emtricitabine in HIV-1 infected paediatric subjects.

Outcomes

The primary efficacy parameter was defined as the suppression of plasma HIV-1 RNA levels below 50copies/mL at Week 48.

Secondary efficacy endpoints included:

- Plasma HIV-1 RNA change from baseline was summarized at Week 48. Summary statistics (n, mean, median, minimum, maximum, and interquartile range) were displayed for this endpoint.
- The proportion of subjects with plasma HIV-1 RNA levels below 400 copies/mL was summarized at Week 48, as well as, the 95% confidence interval for the percentage. Any subject that was missing an HIV-1 RNA value at Week 48 was considered a failure, unless the missing data point was preceded (at Week 44) and followed (at Week 52) by a value that was less than 400 copies/mL. In this case, the missing data point was censored.
- CD4 change from baseline was summarized by study visit. Summary statistics (n, mean, median, minimum, maximum, and interquartile range) were displayed for this endpoint.
- The proportion of virologic failures that occurred during the study was summarized. A subject was as a virologic failure if s/he had a lack of virologic response or a loss of virologic response. A lack of virologic response was defined as not having at least one plasma HIV-1 RNA value ≤ 400 copies/mL by Week 24. A loss of virological response was defined as having > 1 log10 increase from nadir on 2 consecutive HIV-1 RNA measurements, preferably within 1 month of each other

or > 400 copies/mL plasma HIV-1 RNA measured on 3 consecutive visits over approximately 2 months while on study drug(s) after having had at least 2 consecutive plasma HIV-1 RNA measurements at ≤ 400 copies/mL.

Statistical methods

The number and percentage of patients that met the primary endpoints were summarised as well as, the 95% confidence interval for the percentage. Any patient that was missing an HIV-1 RNA value at Week 48 was to be considered a failure, unless the missing data point was preceded (at Week 44) and followed (at Week 52) by a value that was less than 50 copies/mL. In this case, the missing data points were to be censored.

Results

Participant flow

A total of 16 subjects were enrolled in this study at 2 study centers in Romania. All 16 subjects enrolled received at least one dose of study medication. One subject was enrolled in Age Group 2 (7 to 12 years) and fifteen subjects in Age Group 3 (13 to 17 years).

Baseline data

Overall, 8 subjects were female (50%) and all were Caucasian. The mean age for study participants was 14.1 years. The median plasma HIV-1 RNA at baseline was 4.88 log10 copies/mL and median CD4+ cell count and percentage were 372 cells/mm3 and 23 %, respectively.

Four (4/16, 25.0%) subjects had a history of a CDC Class C event, with Bacterial Pneumonia, Herpes simplex virus stomatitis and Mycobacterium tuberculosis reported in 2 (12.5%), 1 (6.3%) and 2 (12.5%) subjects, respectively.

Numbers analysed

Safety and efficacy analyses were conducted according to the intent-to-treat (ITT) principle. The ITT population was defined as all subjects who received at least 1 dose of the study drug, emtricitabine. Of the 16 subjects in the ITT Population, 15 (93.8%) subjects completed 48 weeks of the study, with 1 (6.3%) subject discontinuing the study prematurely.

Outcomes and estimation

In the ITT population NC=F analysis at Week 48, 75% of the subjects achieved complete suppression of plasma HIV-1 RNA to ≤ 50 copies/mL with 94% of subjects achieving suppression of plasma HIV-1 RNA to ≤ 400 copies/mL.

The median decrease from baseline in HIV-1 RNA was – 3.03 $\log^{10}$ copies/mL (range: -4.05, -2.30) (n=15) and the median change from baseline in CD4+ cell count was +201 cells/mm^3 (range: -107,366) (n=15) and +8% (range: +3-+29) at Week 48 in the ITT population.

Table 16. Summary of Primary and Secondary Endpoints at Week 48: ITT Population

Primary Endpoint (NC=F)	**Overall N=16**
≤ 50 copies/mL (n/N) % 95% CI	 (12/16) 75.0 53.8-96.2
Secondary Endpoint (NC=F)	**Overall N=16**
≤ 400 copies/mL (n/N) % 95% CI	 (15/16) 93.8 81.9-100.0
Week 48 Change from baseline in HIV-1 RNA (median, min-max)	-3.0 -4.0, -2.3
Week 48 Change from baseline in CD4+ cell count (median, min-max)	+201 -107.0, 366.0

Table 17. Summary of TLOVR Defined Outcome through Week 48

TLOVR Outcome through Week 48	**Overall N = 16**
TLOVR Classifications (n/N %)	
Responder[a] at 400 copies/mL [50 copies/mL]	11 (68.8) [9 (56.2)]
Non-Responder	5 (31.2)
Virologic Failure	
Rebound	4 (25.0)
Insufficient Virologic Response	0
Never suppressed	0
Study Discontinuation Due to	
Subject withdrawal	1 (6.3)

Studies GS US-104-0321 and GS US 104-0352

Study GS US-104-0321

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1-Infected Adolescents

Method

This was a Phase 3, randomized, double-blind, placebo-controlled, multi-centre study of the safety and efficacy of tenofovir DF as part of an OBR in HIV-1 infected adolescents, 12 years to < 18 years of age, who were failing their current antiretroviral regimen, with plasma HIV-1 RNA levels ≥ 1000 copies/mL at screening. The first 48 weeks of this study consisted of a randomized, double-blind, placebo-controlled, treatment period (the randomized phase). Eligible subjects were randomized in a 1:1 ratio to receive

either tenofovir DF plus OBR or placebo plus OBR. Each OBR was designed based on the subject's antiretroviral history and genotyping results at screening. At Week 24, subjects who were adherent to study drug, but did not demonstrate a ≥ 0.5 $\log^{10}$ copies/mL decrease from base-line in HIV-1 RNA, were considered to be non-responders and were unblinded. Non-responders randomized to the placebo group were given the option to switch to open-label tenofovir DF plus an appropriate background regimen determined by the investigator, while non-responders randomized to the tenofovir DF treatment group were discontinued from the study.

Study participants

The study enrolled HIV-1 infected male and female subjects, 12 to < 18 years of age, with plasma HIV-1 RNA ≥ 1000 copies/mL and weight ≥ 35 kg. Subjects were naive to tenofovir DF and had no K65R mutation on genotypic testing, had prior treatment experience with at least 2 antiretroviral drug classes, and were receiving combination antiretroviral therapy for at least 12 weeks at the time of study entry. Subjects also had adequate hematologic, renal and hepatic functions, and based upon resistance testing, were able to receive an OBR not containing didanosine.

Treatments

Tenofovir DF 300-mg tablets were administered during the randomized phase (Weeks 0 to 48) with a genotype-guided OBR. During the randomized phase, the OBR was defined as at least 3, but no more than 5 antiretroviral agents, not including the randomized study treatment (tenofovir DF or placebo) or pharmacokinetic boosting agents such as low-dose ritonavir.

During the extension phase, subjects received open-label tenofovir DF 300-mg tablets with a background regimen consisting of at least 2, but no more than 5 antiretroviral agents, not including tenofovir DF or pharmacokinetic boosting agents.

Objectives

- To assess the efficacy of tenofovir DF plus a genotype-guided OBR compared to placebo plus OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥ 1000 copies/mL through 24 weeks of drug exposure.
- To assess the efficacy of tenofovir DF plus a genotype-guided OBR compared to placebo plus OBR in the treatment of HIV-1 infected antiretroviral treatment-experienced adolescents with plasma HIV-1 RNA levels ≥ 1000 copies/mL through 48 weeks of drug exposure.
- To evaluate the safety and tolerability of tenofovir DF plus OBR compared to placebo plus OBR.
- To measure changes in BMD in the two treatment groups.

Outcomes

The primary efficacy endpoint was time-weighted average change from baseline through Week 24 (DAVG24) in plasma HIV-1 RNA (log10 copies/mL). DAVG24 was defined as the time-weighted average between the first post-baseline value through the last value up to Week 24 minus the baseline value.

Secondary endpoints

- Time-weighted Average Change from Baseline through Week 48 (DAVG48) in Plasma HIV-1 RNA

- Change from Baseline in log10 HIV-1 RNA, CD4 cell count, and CD4%
- Proportion of Subjects with an HIV-1 RNA Decrease of ≥ 1.0 log10 copies/mL from Baseline
- Proportions of Subjects with HIV-1 RNA < 400 copies/mL and < 50 copies/mL
- Time to Virologic Failure

Statistical method

The RAT analysis set included all subjects who were randomised into the study and received at least one dose of double-blind study medication. During the double-blind period of the study, data from subjects who received open-label tenofovir DF were excluded from the date the subject initiated open-label tenofovir DF onward. Data from subjects who received double-blind study medication other than their assigned treatment were to be analyzed according to the double-blind study medication received.

The ITT analysis set included all subjects who were randomised into the study and received at least one dose of study medication. Subjects with major eligibility violations (e.g., subject not of paediatric age, presence of the K65R mutation at screening, or prior experience with tenofovir DF identifiable based on pre-randomization characteristics) and subjects with plasma HIV-1 RNA < 1000 copies/mL at baseline were excluded.

The analyses of primary and selected secondary efficacy endpoints (DAVG48, change from baseline in HIV-1 RNA, and change from baseline in CD4 cell count and CD4%) were stratified by baseline genotypic sensitivity score (GSS ≤ median or > median) across all randomized and treated subjects.

For DAVG endpoints, data for subjects who discontinued the double-blind phase of the study early were included for summary statistics up until the point of discontinuation from the study (i.e., missing data were not imputed).

Missing data for the other efficacy endpoints were handled using missing = excluded (M = E), missing = failure (M = F), and/or last observation carried forward (LOCF) analyses.

M = E analyses include non-missing reported data in calculations; M = F analyses include the subject in the denominator for missing data points, but not in the numerator when calculating the percentage of subjects who met the endpoint criteria; and LOCF analyses pull forward the subject's last available post-baseline value (taken within 2 days of last study drug dose) for missing data. If no post-baseline value was available prior to the visit, this value remained missing in the analysis.

For secondary endpoints assessing change from baseline in log10 HIV-1 RNA and the proportion of subjects with a ≥ 1.0 log10 copies/mL decrease from baseline in HIV-1 RNA, LOCF and M = E analyses were performed. For secondary endpoints assessing the proportion of subjects with HIV-1 RNA < 50 copies/mL and < 400 copies/mL, M = E, M = F, and LOCF analyses were performed. Changes from baseline in CD4 cell count and percentage were analyzed using only M = E analysis.

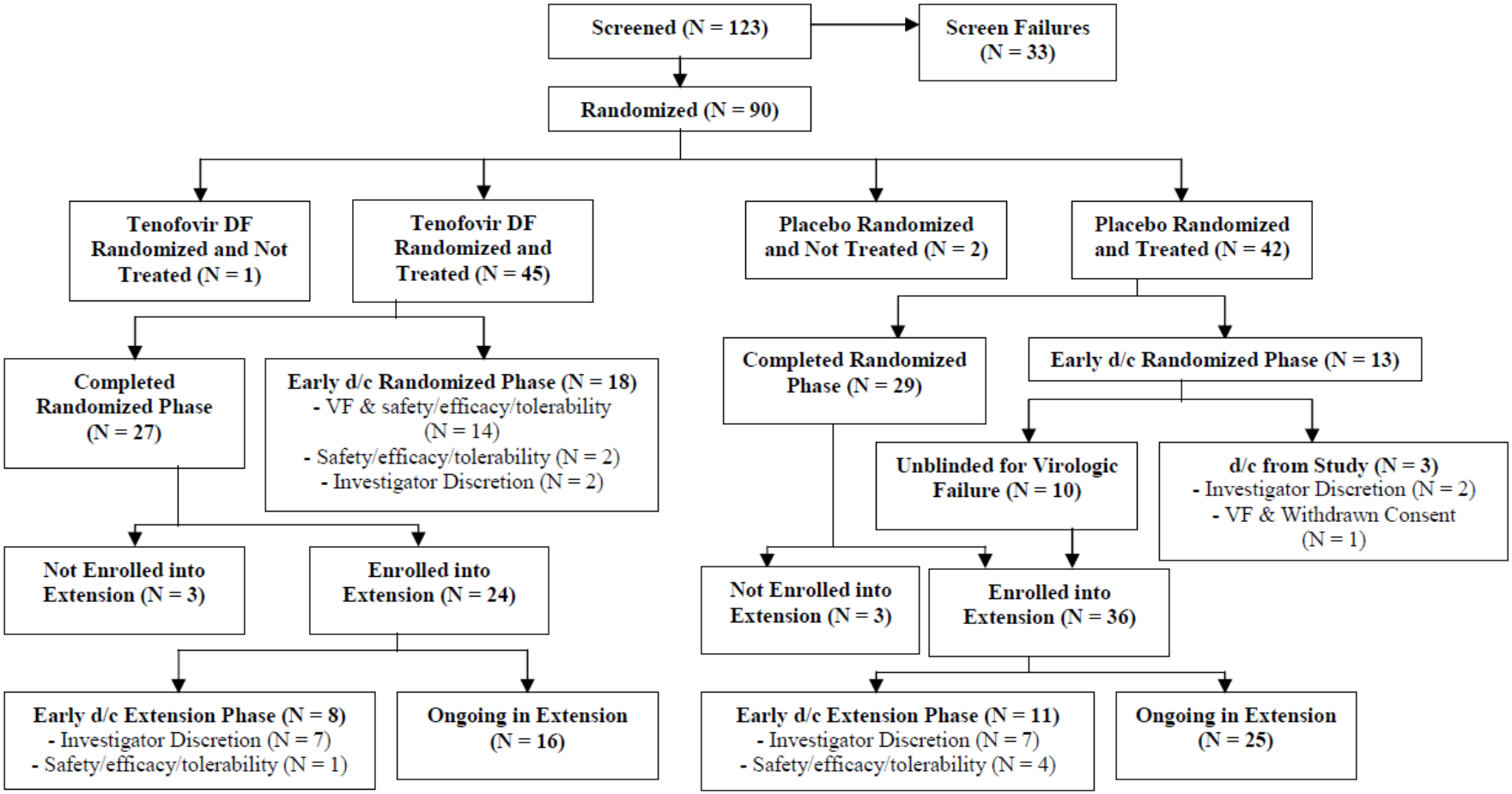
The All TDF group was descriptively summarized using an M = E analysis for all endpoints described above, except DAVG.

Logarithmic transformations were made for the following HIV-1 RNA endpoints: DAVG, change from baseline in HIV-1 RNA, and the proportion of subjects with an HIV-1 RNA decrease of ≥ 1.0 $\log^{10}$ copies/mL from baseline

Descriptive statistics included the number of subjects (n), mean, median, standard deviation (SD), quartiles (Q1 and Q3), minimum, and maximum in a sample with a continuous measurement, and the number and percentage of subjects meeting the criteria in a sample with categorical measurement.

Results

Participant flow



d/c = discontinued; VF = virologic failure;

Note: Subjects unblinded for virologic failure and randomized to placebo were given the option to receive open-label TDF; those randomized to TDF were discontinued.

Note: Six subjects (three per group) terminated from study at the end of the randomized phase. All six had reached their 18th birthday on the date of last randomized dose.

Baseline data

Subjects in the RAT analysis set in the randomized phase of this study were 56.3% female, with a mean age of 14 years (range, 12 to 17 years), and most were white (51.7%) or black (28.7%). The mean value for BMI at screening was 19.33 kg/m2. Overall, the mean (SD) baseline HIV-1

RNA value was 4.64 (0.734) log10 copies/mL, CD4 cell count was 374 (223.5) cells/mm3, and CD4% was 17.7 (9.00). Two subjects (one in each treatment group) had HIV-1 RNA levels at baseline less than 3.0 log10 copies/mL (i.e., < 1000 copies/mL) and were excluded from the ITT analysis set. In the All TDF group, the mean (SD) baseline HIV-1 RNA value was 4.02 (1.395) log10 copies/mL, CD4 cell count was 422 (260.8) cells/mm3, and CD4% was 19.4 (9.92).

Numbers analysed

All 87 subjects who were randomized and received at least one dose of study drug were included in the RAT analysis set (45 subjects in the tenofovir DF group and 42 subjects in the placebo group.

The ITT analysis set included 85 subjects; 44 subjects in the tenofovir DF group and 41 subjects in the placebo group.

Table 18. GS-US-104-0321: Analysis Sets

Analysis Set	TDF (N = 45)	Placebo (N = 42)	Total (N = 87)	All TDF (N = 81)[a]
	n	n	n	n
RAT	45	42	87	81
ITT	44	41	85	79
PK[b]	1	7	8	8

a The All TDF group included double-blind phase and extension phase data (through the cutoff date) for subjects who were initially randomized to double-blind tenofovir DF, or who were initially randomized to double-blind placebo and were later switched to open-label tenofovir DF, from the date of the subject's first dose of tenofovir DF.

b Pharmacokinetic specimens were collected from a subset of subjects at selected sites. Subjects initially randomized into the placebo group were switched to open-label tenofovir DF at Week 24. All subjects had been taking tenofovir DF for at least 4 weeks before pharmacokinetic assessments were performed.

Outcome and estimations

Both the TDF and placebo groups showed decreases from baseline in plasma HIV-1 RNA; the median time-weighted average change from baseline through Week 24 (DAVG24) in plasma HIV-1 RNA was −1.580 log10 copies/mL in the TDF group and −1.549 log^{10} copies in the placebo group. However, there were no statistically significant differences between treatment groups in DAVG24 in plasma HIV-1 RNA or for any of the secondary efficacy endpoints at any of the time points analysed.

Table 19. GS-US-104-0321: Time-Weighted Average Change from Baseline to Week 24 in Plasma HIV-1 RNA (ITT Analysis Set)

Time-Weighted Average Change in HIV-1 RNA (log_{10} copies/mL) from Baseline through Week 48 (DAVG48)[a, b, c]	Tenofovir DF (N = 44)	Placebo (N = 41)	p-value[d]
DAVG Through Week 48			
N	44	41	0.40
Mean (SD)	−1.276 (1.1894)	−1.457 (1.2401)	
Median	−1.423	−1.352	
Q1, Q3	−2.25, −0.25	−2.72, −0.53	
Min, Max	−3.14, 0.83	−3.14, 0.87	

a DAVG through time X is the time weighted average between the first post-baseline value through the last value up to week X minus the baseline value.
b HIV-1 RNA analyzed using Roche PCR Ultrasensitive assay (range 50 to 100,000 copies/mL); or PCR COBAS as a reflex test.
c HIV-1 RNA collected after first dose of open-label tenofovir DF or after last randomized dose date + 2 days (if terminated) for double-blind groups was excluded.
d p-value is from a Van Elteren test stratified by baseline genotypic sensitivity score (GSS) (without tenofovir DF) <= or > median [median GSS is 2].

In terms of the secondary endpoints, there was no difference between treatment groups in decreases in plasma HIV-1 RNA from baseline at Week 48; the median time-weighted average change from baseline through Week 48 (DAVG48) in plasma HIV-1 RNA was −1.423 log10 copies/mL in the TDF group and −1.352 log10 copies/mL in the placebo group (p = 0.40).

The differences between treatment groups for change from baseline in HIV-1 RNA levels at Weeks 24 and 48 was not statistically significant. The median change at Week 48 (last observations carried forward) was −0.97 log^{10} copies/mL in the TDF group and −1.53 log10 copies/mL in the placebo group (p = 0.37).

Nine of 45 TDF subjects compared to 2 of 42 placebo subjects developed NRTI-associated resistance mutations at Week 48. This difference was due to more subjects developing K65 (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, n = 2, and n = 1, respectively). The resistance development in ARV-experienced adolescents with extensive resistance in their HIV at screening was comparable to that observed in heavily treatment-experienced adults.

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

Study GS US 104-0352

A Phase 3, randomized, Open-Label study comparing the safety and efficacy of switching stavudine or zidovudine to Tenofovir Disoproxil Fumarate versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy.

Methods

The first 48 weeks of this study consisted of a randomized, open label, parallel group treatment period. Eligible subjects were randomized in a 1:1 ratio to either replace d4T or ZDV with TDF (Treatment Group A) or to continue d4T or ZDV (Treatment Group B) in their existing HAART regimen for 48 weeks.

Randomization was stratified by whether a subject was currently on d4T or ZDV. Subjects completing 48 weeks of randomized treatment who continued to be < 18 years old were given the option to either continue or initiate TDF in the first of three 96 week study extensions (collectively referred to as the extension phase). Subjects initially randomized to d4T or ZDV could only switch to TDF if the investigator determined that TDF would be safe and beneficial for the subject. After completing the first and second 96 week study extensions, currently enrolled subjects who were benefiting from TDF and who continued to be < 18 years old were given the option to continue receiving TDF for an additional 96 weeks, or until TDF becomes commercially available in the country where the subjects are enrolled, whichever occurs first. The criterion that subjects be < 18 years of age upon entry into the first and second study extensions was only applicable in those regions where TDF is commercially available for the treatment of HIV 1 infection in adults.

After completing the third 96-week study extension, currently enrolled subjects who were benefiting from TDF and who continued to be < 18 years old were given the option to continue receiving TDF until: a) the subject turned 18 and TDF was commercially available for use in adults in the country in which the subject was enrolled or b) TDF became commercially available for use in children or adolescents in the country in which the subject was enrolled or c) Gilead Sciences elected to terminate development of TDF in the applicable country. If a paediatric formulation of TDF became commercially available in the country in which the subjects were enrolled, subjects could choose to continue in the study until they reached 18 years of age and receive investigational supplies, or they could choose to discontinue their participation. Non-responders randomized to the placebo group were given the option to switch to open-label tenofovir DF plus an appropriate background regimen determined by the investigator, while non-responders randomized to the tenofovir DF treatment group were discontinued from the study.

After completing the 48-week randomized phase, subjects who were less than 18 years of age at the beginning of each enrolment period, and who, in the opinion of the investigator, would derive clinical benefit from the use of tenofovir DF, had the option to receive open-label tenofovir DF in addition to a background regimen in up to three 96-week study extensions (collectively referred to as the extension phase). For subjects completing the extension phase, tenofovir DF was provided until the subject reached 18 years of age, until tenofovir DF became commercially available in the country in which the subject was enrolled,

Study participants

The study enrolled HIV-1 infected male and female subjects, (2 to < 12 years, and 2 to < 16 years for subjects enrolled in Study GS US 162 0111 at the time of enrolment into GS US 104 0352) who were currently receiving a d4T or ZDV containing HAART regimen, and who were virologically suppressed, with HIV 1 RNA levels < 400 copies/mL.

Treatments

Tenofovir DF 300-mg tablets were administered during the randomized phase (Weeks 0 to 48) with a genotype-guided OBR. During the randomized phase, the OBR was defined as at least 3, but no more than 5 antiretroviral agents, not including the randomized study treatment (tenofovir DF or placebo) or pharmacokinetic boosting agents such as low-dose ritonavir.

During the extension phase, subjects received open-label tenofovir DF 300-mg tablets with a background regimen consisting of at least 2, but no more than 5 antiretroviral agents, not including tenofovir DF or pharmacokinetic boosting agents**.**

Objectives

Primarily to assess the efficacy of switching to tenofovir DF compared to continuing stavudine or zidovudine in maintaining virologic suppression (plasma HIV-1 ribonucleic acid [RNA] < 400 copies/mL) in HIV-1 infected children at Week 48 and secondarily to

- To evaluate the safety and tolerability of tenofovir DF in HIV-1 infected children
- To evaluate the effects of switching from stavudine or zidovudine to tenofovir DF versus continuing stavudine or zidovudine on bone mineral density, fasting lipid parameters and fat distribution
- To evaluate the pharmacokinetics of tenofovir in a subset of HIV-1 infected children receiving tenofovir DF oral powder formulation

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA concentrations < 400 copies/mL at Week 48.

Statistical methods

The planned sample size of 100 subjects (50 per group) was supposed to have at least 80% power to establish non-inferiority with respect to the difference in the proportion of subjects maintaining HIV-1 RNA < 400 copies/mL at Week 48 between subjects who switched from stavudine or zidovudine to tenofovir DF (Treatment Group A) and those who continued on stavudine or zidovudine (Treatment Group B). The equivalence limit was set at −15% for the lower boundary of a two-sided 95% confidence interval (CI) on the difference in proportions of subjects maintaining HIV-1 RNA < 400 copies/mL at Week 48. Power calculations were performed using nQuery Version 6.0.

Randomised and Treated (RAT)

All subjects who were randomised into the study and received at least one dose of study medication. Data from subjects who received study medication other than their assigned treatment were analysed according to the study medication received.

Intent-to-Treat (ITT)

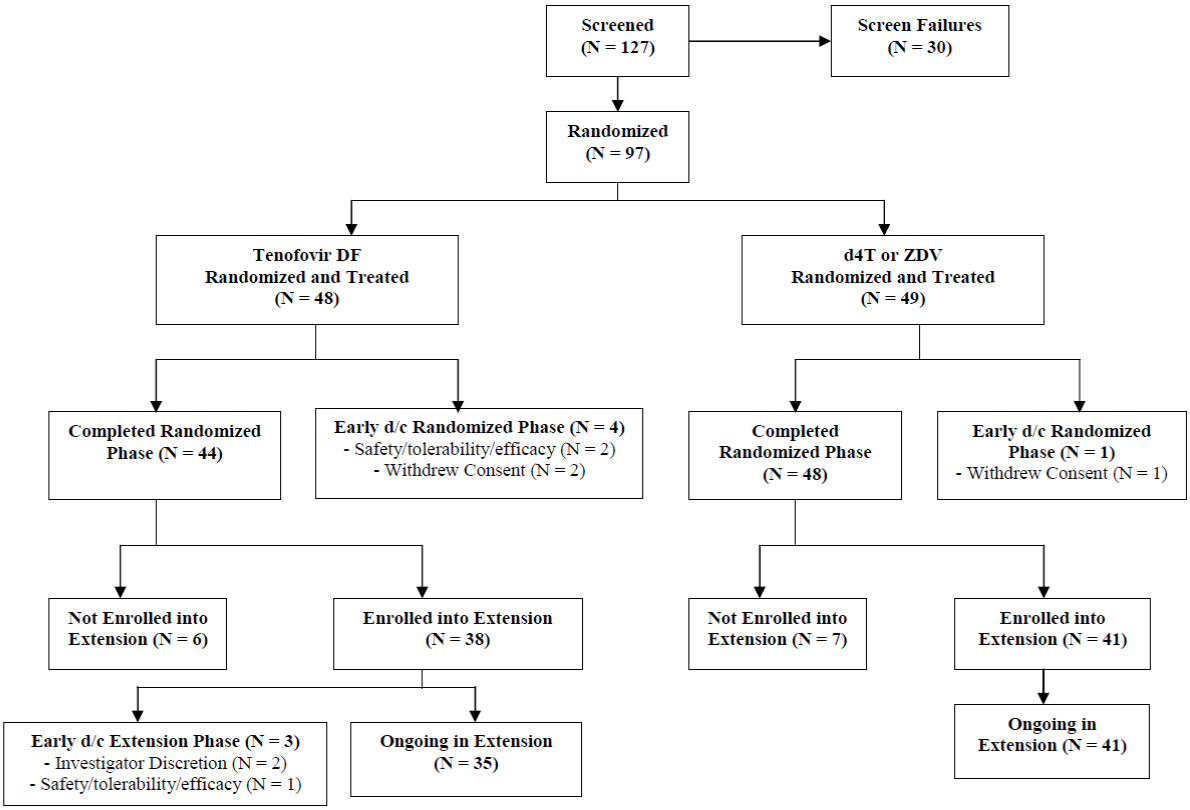
All subjects who were randomized into the study and received at least one dose of study medication; subjects with major eligibility violations (i.e., HIV infection not documented, did not meet paediatric age entry criteria) identifiable based on pre-randomisation characteristics were excluded. Data from subjects who received study medication other than their assigned treatment were analyzed according to the subject's randomized treatment group.

Per Protocol (PP)

Subjects who received at least one dose of study medication, did not have any major eligibility violations at study entry, and did not commit any major protocol deviation (i.e., baseline HIV-1 RNA > 400 copies/mL). Subjects who received study medication other than their assigned treatment were analyzed according to the study medication received.

Results

Participant flow - GS-US-104-0352: Disposition of Study Subjects (All Subjects)



Baseline data

Subjects in the All TDF group in the RAT analysis set were 49.4% male, with a mean age of 8 years (range: 2 to 15 years), and most were Mestizo or black. Mean values for weight, height, and BMI at baseline were 25.9 kg, 121.0 cm, and 17.1 kg/m2, respectively.

In the All TDF group, 78.7% of subjects (70/89) had plasma HIV-1 RNA levels < 50 copies/mL and 16.9% of subjects (15/89) had plasma HIV-1 RNA levels 50 to < 400 copies/mL. Four subjects had plasma HIV-1 RNA levels > 400 copies/mL. The mean (SD) baseline CD4 cell count was 1179 (464.2) cells/mm3 and the mean (SD) baseline CD4 percentage was 33.6% (6.69).

Numbers analysed

Randomized and treated (RAT), and intent-to-treat (ITT): 48 in the tenofovir DF subgroup, 41 in the (d4T or ZDV)/TDF subgroup, and 89 in the All TDF group. Per Protocol (PP): 47 in the tenofovir DF subgroup, 38 in the (d4T or ZDV)/TDF subgroup, and 85 in the All TDF group.

Table 20. GS-US-104-0352 – Analyses sets

Analysis Set	TDF (N = 48) n	d4T or ZDV (N = 49) n	Total (N = 97) n	All TDF (N = 89) n
Randomized	48	49	97	—
RAT	48	49	97	89
ITT	48	49	97	89
PP	47	47	94	86
PK[a]	23	0	NA	NA

Outcomes and estimations

At Week 48, 83.3% of subjects (40/48) in the tenofovir DF group and 91.8% of subjects (45/49) in the stavudine or zidovudine group had HIV-1 RNA concentrations < 400 copies/mL (M = F, ITT analysis set). An estimate of the difference in proportions and a two-sided 95% CI about the difference in proportions (tenofovir DF group minus stavudine or zidovudine group) for the primary endpoint was constructed (−8.5%; 95% CI [−21.5% to 4.5%]). Since the lower confidence bound of the difference between treatment groups was −21.5%, tenofovir DF did not meet the criteria (lower confidence bound of the difference between treatment groups greater than −15%) for treatment non-inferiority.

At Week 24, 93.8% of subjects (45/48) in the tenofovir DF group and 89.8% of subjects (44/49) in the stavudine or zidovudine group had HIV-1 RNA < 400 copies/mL (M = F, ITT analysis set). The difference in proportions was 4.0% and the 95% CI was −6.9% to 14.9%. The lower bound of the 95% CI on the difference between treatment groups was greater than −15% from baseline through Week 24, suggestive of treatment non-inferiority through Week 24 For M = E using the ITT analysis set, 90.9% of tenofovir DF subjects (40/44) and 93.8% of stavudine or zidovudine subjects (45/48) had HIV-1 RNA concentrations < 400 copies/mL at Week 48 (ITT analysis set). The difference in the proportion of subjects with HIV-1 RNA concentrations < 400 copies/mL was −2.8% and the 95% CI was −13.8% to 8.1%. Since the lower confidence bound of the difference in proportions between treatment groups was −13.8%, tenofovir DF met the criteria for treatment non-inferiority. For M = E using the ITT analysis set, the lower confidence bound of the difference in proportions between treatment groups was greater than −15% at all time-points from baseline to Week 48.

Table 21. GS-US-104-0352: Proportion of Subjects with Plasma HIV-1 RNA < 400 Copies/mL at Week 48 (ITT Analysis Set)

Subjects with Plasma HIV-1 RNA < 400 copies/mL at Week 48 (n, %)[a]	TDF (N = 48)	d4T or ZDV (N = 49)	p-value[a]	Difference (95% CI)[b, c]
Missing = Failure[d]				
At Week 48	40/48 (83.3%)	45/49 (91.8%)	0.23	–8.5% (–21.5% to 4.5%)
Missing = Excluded[e]				
At Week 48	40/44 (90.9%)	45/48 (93.8%)	0.71	–2.8% (–13.8% to 8.1%)

Note: Roche polymerase chain reaction (PCR) Ultrasensitive assay. Data collected after 1st dose open-label tenofovir DF or last dose + 2 days (if terminated) excluded.

a p-values displayed to test for between group differences (randomized phase) are from a Fisher's Exact test.

b The confidence interval for the proportion estimate for a treatment group is based on the Exact method.

c The 95% confidence interval on the difference in proportions between randomized treatment groups is based on the normal approximation.

d Denominator (for %) is the number of ITT Subjects (subjects with missing HIV-1 RNA data counted as failure).

e Denominator (for %) is the number of ITT Subjects with non-missing HIV-RNA data at the visit

Secondary efficacy endpoints up to Week 336

In the All TDF group, the proportion of subjects with plasma HIV-1 RNA concentrations < 400 copies/mL at Week 336 was 75.0% (21/28) using the M = F method and 91.3% (21/23) using the M = E method. The proportion of subjects in the All TDF group with HIV-1 RNA concentrations < 50 copies/mL at Week 336 was 71.4% (20/28) using the M = F method and 87.0% (20/23) using the M = E method. No clinically relevant differences in efficacy were seen between the TDF and (d4T or ZDV)/TDF subgroups.

In the All TDF group, 100% (11/11) of subjects in the 2 to < 6 years group and 57.1% (8/14) of subjects in the 6 to < 12 years group had HIV 1 RNA concentrations < 400 copies/mL at Week 336 (M = F). The proportion of subjects in the All TDF group with HIV-1 RNA concentrations < 400 copies/mL at Weeks 48, 96, 144, 240, and 336 was consistently lower in the 6 to < 12 years group than in the 2 to < 6 years group (although with overlapping CIs). No clinically relevant differences were seen between the TDF and (d4T or ZDV)/TDF subgroups.

Analysis performed across trials (pooled analyses and meta-analysis)

Table 22. Summary of Plasma HIV-1 RNA Suppression at Week 48 by FTC Studies (Protocol-defined Endpoints)

Plasma HIV-1 RNA Level Endpoint n/N (%)	Study FTC-202[a,b] N = 37	Study FTC-203[c, d] N = 116	Study FTC-211[c] N = 16	Total N = 166
≤ 400 copies/mL	30/37 (81.1)	102/113 (90.3)	15/16 (93.8)	147/166 (88.6)
≤ 50 copies/mL	27/37 (73.0)	88/113 (77.9)	12/16 (75.0)	127/166 (76.5)

a ITT, missing=failure (M=F)
b Endpoints were < 400 copies/mL and < 50 copies/mL in FTC-202
c ITT, noncompleter=failure (NC=F)
d The data from 3 ART-naive subjects were censored, as they had no Week 48 data and were below the LLOQ (≤ 50 copies/mL) at the visits immediately prior toand after Week 48.

Table 23. 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)

Table 24. Summary of Incidence of TLOVR-defined Virologic Failure by FTC Studies and ART Experience

Study n/N (%)	ART Stratum		Overall
	ART-naive	ART-experienced	
Study FTC-203[a]	4/71 (5.6)	8/45 (17.8)	12/116 (10.3)
Study FTC-211[b]	4/15 (26.7)	0/1 (0)	4/16 (25.0)
Overall	8/86 (9.3)	8/46 (17.4)	16/132 (12.1)

2.4.3. Discussion on clinical efficacy

This type II variation application proposes the inclusion of a new indication in HIV-1 infected adolescents with NTRI resistance or toxicities precluding the use of first line agents aged 12 to <18 years.

Design and conduct of clinical studies

Data from 3 studies with FTC and 2 studies with TDF are included to support the proposed new indications. These data supported the approval of the use of FTC and TDF as single entities in paediatric patients.

FTC

The three open-label studies assessed the suppression of plasma HIV-1 RNA to undetectable levels through 48 weeks of treatment as measured by the percentage of subjects achieving and maintaining plasma HIV-1 RNA viral load of ≤ 400copies/mL. Subjects were stratified by age group. In study FTC-202, 21 subjects aged between 3 to 12 years and 10 subjects aged 13 to 21 years were included in the

study. In study FTC-203, 29 subjects aged 7 to 12 and 13 to 17 years of age were included in the study. While in study FTC-211 1 subject aged 7 to 12 and 15 aged 13 to 17 years were included in the study.

TDF

The two studies were double-blind placebo controlled. Study GS US-104-0321 assessed the efficacy of TDF plus a genotype-guided OBR compared to placebo plus OBR in the treatment of HIV-1 infected adolescents (treatment experienced). While study GS US 104-0352 assessed the efficacy of switching to TDF compared to continuing stavudine or zidovudine in maintaining virologic suppression < 400 copies/ml in HIV-1 infected children at week 48. The primary efficacy endpoint of GS US-104-0321 was the time-weighted average change from baseline through week 24 (DAVG 24) in plasma HIV-1 RNA (log10 copied/ml). For study GS US 104-0352, the primary efficacy endpoint was the proportion of subjects with HIV-1 RNA concentrations < 400 copies/mL at Week 48. The non-inferiority margin was set at −15%

The general design of all studies (three for FTC and two for TDF) are considered acceptable and there are no issues to highlight regarding the conduct of the studies as in any case these studies have previously been reviewed

Efficacy data and additional analyses

FTC

The results of the three studies adequately demonstrate the efficacy of FTC when given in combination with other ART. 88.6% of the subjects achieved plasma HIV-1 RNA viral load of ≤ 400copies/mL by week 48, while 76.5% of the subjects achieved and maintained complete suppression of HIV-1 RNA viral load to ≤50 copies/mL at week 48. Generally the response rates in the different age groups were similar taking into consideration the few numbers in some age groups. In terms of virologic failure, 16 subjects (8 ART-naïve and 8 ART experienced) were considered virologic failures. 4 subjects were confirmed to have M184V mutation.

TDF

Study GS US-104-0321

The results showed that the median time weighted average change from baseline through week 24 in plasma HIV-1 RNA was -1.580 $\log_{10}$ copies/ml and -1.549 log10 copies/ml in the placebo group with no difference between treatment groups in terms of decreases in plasma HIV-1 RNA from baseline at Week 48. Nine subjects on TDF developed NRTI-associated resistance mutations at Week 48. One subject developed K65R; 4 developed M184V (n = 4) while 4 subjects developed thymidine-analogue associated mutations.

Study GS-US-104-0352

The results showed that at week 48 83.3% of subjects (40/48) in the tenofovir DF group and 91.8% of subjects (45/49) in the stavudine or zidovudine group had HIV-1 RNA concentrations < 400 copies/mL. The bound of the difference between treatment groups was −21.5%, therefore TDF did not mean the criteria for demonstrating non-inferiority. At week 24, 93.8% of subjects (45/48) in the TDF group and 89.8% of subjects (44/49) in the d4T or ZDV group had HIV-1 RNA < 400 copies/mL (ITT analysis set). The difference in proportions was 4.0% and the 95% CI was −6.9% to 14.9%. The lower bound of the 95% CI on the difference between treatment groups was greater than −15% from baseline through Week 24 and therefore suggestive of treatment non-inferiority.

2.4.4. Conclusions on the clinical efficacy

Overall, the results of all the studies provided for FTC and TDF are considered to be demonstrative of efficacy of the single entities for the treatment of HIV-1 in the proposed age group of 12 to 18 years of age. These data are considered applicable for Truvada for the proposed indication in adolescents with extrapolation of adult data and the demonstrated comparative PK data.

The proposal to limit the indication to subjects NRTI resistance or toxicities precluding the use of first-line agents is considered acceptable as this is in line with the label for Viread and is considered to be applicable also for Truvada.

2.5. Clinical safety

Introduction

Data from the three long-term paediatric studies for FTC (studies **FTC-202, FTC-211** and **FTC-203)** and two long term studies for TDF (studies **GS US-104-0321** and **GS US 104-0352)** are provided to demonstrate safety of the proposed indication in adolescents.

Patient exposure

FTC

Overall, a total of 169 subjects received FTC in the paediatric safety and efficacy studies. 164 subjects were < 18 years of age; of these, 42 received FTC capsules and 122 received FTC oral solution. The 5 subjects who were at least 18 years of age received FTC capsules.

Table 25. Extent of Exposure to FTC in Long-term Paediatric Clinical Studies Through the Data Cut-off Date

Study	No. of Patients Exposed to FTC	No. of Patients On-study			Median (range) Duration of Exposure to FTC (in Weeks)	Median Exposure to FTC in Years
		≥ 24 Weeks	≥ 48 Weeks	≥ 96 Weeks		
Overall < 18 years	164	157	152	88	96.1 (0.1 to 172.3)	1.8
ART-naive or very limited prior ART exposure patients						
FTC-202 (PACTG 1021)	37	34	32	20	96.3 (0.6 to 133.1)	1.8
FTC-203	71	70	67	45	96.1 (21.3 to 132.3)	1.8
FTC-211	15	14	14	NA	48.1 (0.1 to 48.1)	0.9
Total No < 18 years	118	113	109	64	96.1 (0.1 to 133.1)	1.8
ART-experienced patients (on stable, suppressive 3TC-containing regimen)						
Total	46	44	43	24	99.7 (6.1 to 172.3)	1.9

Data cutoff dates: FTC-202 (P1021), 14 June 2004; FTC-203, 4 May 2004 (date on which the last patient enrolled reached Week 48).

Table 26. Number of Paediatric Subjects Exposed to FTC by Age Group and by FTC Dosage Form in Long term Paediatric Clinical Studies

Age Range	No. of Subjects in FTC-203	No. of Subjects in FTC-202	No. of Subjects in FTC-211	Total No. of Subjects	No. of Subjects Receiving FTC Solution	No. of Subjects Receiving FTC Capsule
3 to 24 Months	16	0[a]	0	16	16 [all 203]	0
25 Months to 6 Years	68	13	0	81	81 [68 (203) + 13 (202)]	0
7 to 12 Years	29	8	1	38	24 [20 (203) + 4 (202)]	14 [9 (203) + 1 (211) + 4 (202)]
13 to 17 Years	3	11	15	29	1 (211)	28 [3 (203) + 14 (211) + 11 (202)]
18 to 21 Years	0	5	0	5	0	5 (202)
All Pediatric Subject (< 18 years)	116	32	16	164	122 [104 (203) + 1 (211) + 17 (202)]	42 [12 (203) + 15 (211) + 15 (202)]
Overall Subjects	116	37	16	169	122	47

TDF

87 adolescents were included in study GS-US-104-0321 (45 were on TDF and 42 on placebo) and 97 paediatric subjects were included in study GS-US-104-0352 (48 on TDF, 49 were on d4T or ZDV). All patients included were ART-experienced.

Adverse events

FTC

In study FTC-203, through Week 48, the most frequent adverse events (AEs) (> 25%) were infection (62%), increased cough (37%), hyperpigmentation (36%), vomiting (30%), rhinitis (29%), and otitis media (28%). Among AEs with an incidence ≤ 25%, the most common and clinically relevant given the general context of expected childhood conditions were diarrhoea (25%), rash (22%), fever (21%), gastroenteritis (15%), pneumonia (18%), abdominal pain (14%), and anaemia (10%).

TDF

Study GS-US-104-0321

In the TDF group, the most commonly reported AEs were as follows: vomiting (16 subjects [35.6%]), sinusitis (14 subjects [31.1%]), nausea (11 subjects [24.4%]), and cough (11 subjects [24.4%]). In the placebo group, the most commonly reported AEs were as follows: nasopharyngitis (7 subjects [16.7%]), sinusitis (6 subjects [14.3%]), and cough (6 subjects [14.3%]). By the end of the study at Week 336, 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 as follows: vomiting (4 subjects [4.9%]), osteopenia (5 subjects [6.2%]), and gastritis (2 subjects [2.5%]). One subject discontinued study drug due to vomiting.

Study GS-US-104-0352

In the TDF group, the most frequently reported AEs were as follows: nasopharyngitis (16 subjects [33.3%]), otitis media (7 subjects [14.6%]), and vomiting, upper respiratory tract infection, and cough (6 subjects each [12.5%]). In the d4T or ZDV group, the most frequently reported AEs were as follows: nasopharyngitis (17 subjects [34.7%]), cough (6 subjects [12.2%]), and gastroenteritis and otitis media (4 subjects each [8.2%]). Up to Week 336, AEs considered related to study drug by the investigator were reported for 34 subjects (38.2%) in the All TDF group, including 20 subjects (41.7%) in the TDF subgroup and 14 subjects (34.1%) in the (d4T or ZDV)/TDF subgroup. The most common study drug related AEs reported in the All TDF group were as follows: arthralgia (14 subjects [15.7%]), vomiting and proteinuria (4 subjects each [4.5%]), and hypophosphatemia and myalgia (3 subjects each [3.4%]).

Serious adverse event/deaths/other significant events

FTC

In study FTC-203, a total of 24 patients (20.7%) experienced at least one SAE. The only specific SAEs that occurred in more than one patient were as follows: pneumonia (n = 7, 6%), hepatitis A (n = 4, 3.4%), pharyngitis and accidental injury (n = 3, 2.6% for each), and pancreatitis (n = 2, 1.7%). Three patients (2.6%) had an SAE that was assessed by the reporting investigator as possibly or probably related to study drug: 1 patients with Grade 3 anaemia considered unrelated to background ARV medications (nelfinavir [NFV] and ZDV) and 2 patients with pancreatitis assessed as related to the use of FTC and d4T, and remotely related to the use of LPV/r. All 3 events led to premature discontinuation from the study, although one was recorded as an SAE after the clinical data cut-off date. In FTC-202 there was no consistent pattern of SAEs or recorded signs and symptoms.

A total of 12 patients developed SAEs, including 6 who were hospitalized. No SAE occurred in more than two patients.

Serious adverse events reported were as follows: elevated creatine kinase (n = 2); liver function tests increased, decreased glucose, nausea with asthenia and dizziness, abdominal pain with headache (patient was also hospitalized for lymphadenitis), mild cervical dysplasia with human papilloma virus, rash with diarrhoea, rectal pain, herpes zoster, otitis media, and major depression (n = 1 for each). A total of 11 patients developed Grade 3 or 4 signs or symptoms, the majority overlapping with SAEs, with the exception of additional cases of rash (n = 1), low glucose (n = 1), and ear pain (n = 1), none of which were considered related to study treatment.

In Study FTC-211, 1 subject had 2 SAEs, a case of mumps and orchitis both considered not related to FTC by the investigator

TDF

Study GS-US-104-0321

Serious adverse events reported for more than 1 subject were as follows: pneumonia (TDF: 3 subjects [6.7%]; placebo: 1 subject [2.4%]); and pneumocystis jiroveci pneumonia and sinusitis (TDF: 2 subjects

[4.4%]; placebo: 0 subjects). 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. Serious adverse events reported for > 1 subject in the All TDF group were as follows: pneumonia (5 subjects [6.2%]), herpes zoster (3 subjects [3.7%]), pneumocystis jiroveci pneumonia (2 subjects [2.5%]), and sinusitis (2 subjects [2.5%]). No SAE was considered related to study drug by the investigator.

Study GS-US-104-0352

2 subjects (4.2%) in the TDF group and 2 subjects (4.1%) in the d4T or ZDV group had an SAE. Up to Week 336, SAEs were reported for 12 subjects (13.5%) in the All TDF group, including 6 subjects (12.5%) in the TDF subgroup and 6 subjects (14.6%) in the (d4T or ZDV)/TDF subgroup. The only SAE reported for > 1 subject in the All TDF group was pneumonia (2 subjects [2.2%]). One subject experienced a spontaneous abortion. Renal safety data for 4 subjects who discontinued study drug due to renal AEs were clinically consistent with proximal renal tubulopathy (PRT). One further subject met the case definition for PRT at the Week 144 data cut-off, while continuing study drug; renal AEs of glycosuria and proteinuria were reported for this subject after Week 144, and were ongoing when the subject discontinued from the study due to being 18 years old. Thus there was a total of 5 cases clinically consistent with PRT (5/89 subjects, 5.6%). No new cases were clinically consistent with PRT after the Week 144 analysis.

Laboratory findings

FTC

Through Week 48 in study FTC-203, treatment-emergent grade 3/4 laboratory abnormalities occurred in 6 of 116 patients (5%). The overall incidence of Grade 3/4 laboratory abnormalities in FTC-203 through a median follow up of 96 weeks was 8.6% (10 patients): elevated alanine aminotransferase (ALT; 3 patients); neutropenia, hyperbilirubinemia, and elevated amylase [normal lipase] (each in 2 patients); and elevated aspartate aminotransferase (AST), low haemoglobin, elevated lipase, and low platelets (each in 1 patient). An additional subject with hepatitis A had local laboratory data documenting Grade 3 total bilirubin, and Grade 4 ALT and AST. The incidence of Grade 3 and 4 laboratory abnormalities was low in FTC-211 and FTC-202.

TDF

Study GS-US-104-0321

At Week 48, Grade 3 or 4 abnormalities were reported for 10 subjects in the TDF group and for 9 subjects in the placebo group. Grade 3 or 4 abnormalities were most frequently reported for neutrophil counts (7 subjects in the TDF group and 2 subjects in the placebo group) and total bilirubin (4 subjects in each group). At Week 336, Grade 3 or 4 abnormalities reported remained low, affecting 25 subjects in the All TDF group, including 12 subjects in the TDF subgroup and 13 subjects in the placebo/TDF subgroup. Grade 3 or 4 abnormalities were most commonly reported for neutrophil count (15 subjects) and total bilirubin (7 subjects). Overall, there were no clinically relevant differences between groups in the profile of laboratory abnormalities over the course of the study

Study GS-US-104-0352

During the randomized treatment period, Grade 3 or 4 abnormalities were reported for 3 subjects in the TDF group and for 5 subjects in the d4T or ZDV group. Grade 3 or 4 abnormalities were most frequently reported for amylase (2 subjects in each group) and neutrophil counts (2 subjects in the d4T or ZDV group).

By Week 336, Grade 3 or Grade 4 abnormalities were reported for 19 subjects in the All TDF group, including 13 subjects in the TDF subgroup and 6 subjects in the (d4T or ZDV)/TDF subgroup. Grade 3 or Grade 4 abnormalities were most frequently reported for amylase (8 subjects), ALT (7 subjects), and hypophosphatemia (3 subjects).

Safety in special populations

FTC

Age

There were no clinically relevant differences between age groups in the incidence of AEs in Study FTC-203, either in ART-naive or ART-experienced subjects. A number of events (e.g. rash, eczema, diarrhoea, and otitis media) were reported with decreasing frequency according to increasing age.

Safety in Subjects with Renal Impairment

No new information regarding the safety in subjects with renal impairment is presented.

Safety related to drug-drug interactions and other interactions

Apparently, assessment of the AE profile in the paediatric clinical studies did not indicate any clinically relevant drug-drug interactions.

Adverse Events of Interest

FTC

Hyperpigmentation

The overall incidence of hyperpigmentation was 42 of 132 patients (31.8%) across the two uncontrolled paediatric studies conducted by Gilead (FTC-203 and FTC-211), with all reported cases of skin discoloration (hyperpigmentation) occurring in study FTC-203.

Hematologic toxicities

In FTC-203, anaemia and/or iron deficiency anaemia was reported in 16 patients (13.8%; 4 patients in the 3 to 24 months age group, 8 patients in the 25 month to 6 years age group, and 4 patients in the 7 to 12 years age group). Anaemia was not reported as an AE in FTC-202 or FTC-211.

Thus the overall incidence of anaemia and iron deficiency anaemia in studies FTC-203, FTC-202, and FTC-211 is 9.5%

TDF

Renal Events

Study GS-US-104-0321

During the double-blind treatment period, similar numbers of subjects in each group reported at .least one AE in the renal and urinary disorders system organ class (SOC) in the double-blind treatment period (TDF group: 6 subjects [13.3%]; placebo group: 4 subjects [9.5%]). The only renal AE reported for > 1 subject in the All TDF group was proteinuria in 2 subjects (2.5%).

Study GS-US-104-0352

During the randomized treatment period, up to Week 48, similar numbers of subjects in each treatment group reported at least 1 AE in the renal and urinary disorders SOC (TDF group: 3 subjects [6.3%]; d4T or ZDV group: 1 subject [2.0%]). An AE of enuresis was considered related to study drug by the investigator.

Up to Week 336, renal and urinary disorders SOC AEs were reported for 9 subjects (10.1%) in the All TDF group, including 7 subjects (14.6%) in the TDF subgroup and 2 subjects (4.9%) in the (d4T or ZDV)/TDF subgroup. Events reported in > 1 subject in the TDF subgroup were enuresis and proteinuria (each 3 subjects [6.3%]), and dysuria (2 subjects [4.2%]). No event was reported for > 1 subject in the (d4T or ZDV)/TDF subgroup. Hypophosphatemia was reported as an AE for 3 subjects (3.4%) in the All TDF group and considered related to study drug in each of them.

Hypophosphatemia was reported for 3 subjects (6.3%) in the TDF subgroup, proteinuria for 2 subjects (4.2%) in the TDF subgroup, proteinuria for 1 subject (2.4%) in the (d4T or ZDV)/TDF subgroup, and glycosuria for 1 subject (2.4%) in the (d4T or ZDV)/TDF subgroup led to study drug discontinuation.

Sixteen subjects met the case definition of potential PRT at the Week 336 analysis. Five of these subjects had laboratory data consistent with PRT, including the 4 subjects with renal AEs of hypophosphatemia or glycosuria that led to discontinuation of TDF identified at the time of the Week 96 analysis. The additional subject developed a > 35% reduction from baseline in creatinine clearance prior to Week 96, but did not meet the case definition of PRT until afterwards.

Bone Safety

Study GS-US-104-0321

Fracture AEs were reported for 2 subjects in the TDF group (clavicle fracture and right malleolar fracture) during the double-blind treatment period. Osteopenia was reported as an 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. No AE of osteopenia was serious.

Osteopenia AEs were considered related to study drug for the 3 subjects (6.7%) in the TDF group and 2 subjects (5.6%) in the placebo group.

Study GS-US-104-0352

Up to Week 336, bone fractures were reported for 3 subjects who received TDF during this study, including 1 subject in the TDF subgroup (radius fracture) and 2 subjects in the (d4T or ZDV)/TDF subgroup (forearm fracture and wrist fracture). All fractures were trauma related and none of these events were considered related to study drug by the investigator.

Median spine, total body, and total body less head (TBLH) BMD increased with time in the All TDF group. Median percentage changes in spine, total body, and TBLH BMD from baseline (baseline medians 0.623, 0.803, and 0.657 g/cm2, respectively) at Week 336 were 45.651% (n = 32, p < 0.001), 20.488% (n = 35, p < 0.001), and 33.956% (n = 35, p < 0.001), respectively.

There were no notable changes from baseline (baseline median −0.880) in median values for spine BMD Z-score in the All TDF group. No statistically significant change in spine BMD Z score was seen at any time point in the All TDF group; the median change from baseline at Week 336 was 0.379. Analyses of spine BMD Z-scores by age subgroup and by sex showed no notable change from baseline in median values for the 2 to < 6 and 6 to < 12 years groups, or for male and female subjects. There were decreases from baseline (baseline median −0.505) in median values for spine height-age adjusted BMD Z-scores in the All TDF group up to Week 96, but these appeared to stabilize and were not progressive through Week 336; the median change from baseline at Week 336 was 0.737.

There were decreases from baseline (baseline median −0.032) in median values for TBLH BMD Z-score up to Week 96, but these decreases were not progressive through Week 336. In the All TDF group, median changes from baseline at Weeks 48, 96, 144, 240, and 336 were −0.224, −0.524, −0.519, −0.611, and −0.409, respectively. A similar trend was observed in height-age adjusted TBLH BMD Z-scores.

At baseline, 13% of subjects (11/86) had low spine BMD (Z-score ≤ −2), 1 subject had low total body BMD, and 1 subject had low TBLH BMD; after height-age adjustment, no subject had a baseline BMD Z-score ≤ −2.

Seventeen subjects in the All TDF group had a TDF treatment-emergent shift in BMD Z-score (spine, total body, and/or TBLH) to ≤ −2 (8 subjects in the TDF subgroup and 9 subjects in the [d4T or ZDV]/TDF subgroup). After height age adjustment, 7 subjects had a TDF treatment emergent shift in BMD Z-score (spine, total body, and/or TBLH) to ≤ −2 (3 subjects in the TDF subgroup and 4 subjects in the [d4T or ZDV]/TDF subgroup).

Sixteen of 86 subjects (18.6%) in the All TDF group had decreases from baseline of ≥ 4% in spine, total body, and/or TBLH BMD at 1 or more time points during the study (6 subjects in the TDF subgroup and 10 subjects in the [d4T or ZDV]/TDF subgroup). Six of these 16 subjects discontinued study drug due to a renal AE, with or without laboratory data consistent with proximal renal tubulopathy (PRT).

Discontinuation due to adverse events

FTC

In FTC-203 a total of 3 patients (2.6%) had an AE that led to premature discontinuation from the Study, 1 patient with Grade 3 anaemia while receiving a background regimen of NFV and ZDV treated with transfusion, and 2 patients with pancreatitis on a regimen of FTC, d4T, and LPV/r. All events resolved with treatment. In study FTC-202, 2 of 37 patients discontinued due to rash.

TDF

Study GS-US-104-0321

One subject (1.2%) discontinued the study due to an AE (vomiting).

Study GS-US-104-0352

During the randomized treatment period, up to Week 48, no subjects discontinued study drug due to AEs. Up to Week 336, 9 subjects (10.1%) in the All TDF group discontinued study drug due to an AE. Five of these subjects discontinued prior to the Week 144 data cut-off (hypophosphatemia for 3 subjects [6.3%] in the TDF subgroup [1 of whom also had arthralgia reported as an AE that resulted in study drug discontinuation], glycosuria for 1 subject [2.4%] in the [d4T or ZDV]/TDF subgroup, and brain neoplasm for 1 subject [2.4%] in the [d4T or ZDV]/TDF subgroup), and 4 subjects discontinued after the Week 144 data cut-off (proteinuria for 2 subjects in the TDF subgroup, arthralgia for 1 subject in the TDF subgroup, and proteinuria for 1 subject in the [d4T or ZDV]/TDF subgroup). The 4 discontinuations due to renal AEs of hypophosphatemia or glycosuria were clinically consistent with proximal renal tubulopathy (PRT). These 4 discontinuations were prior to the Week 96 analysis. Three additional discontinuations due to renal AEs (proteinuria) were reported after the Week 144 analysis;

Post marketing experience

There have been no safety concerns specific to paediatric patients identified for TVD or its components based on the post-marketing data available to date.

2.5.1. Discussion on clinical safety

Safety data are derived from the studies of the single entities (FTC and TDF) provided in support of this application. These studies have previously been presented and have been used to support the use of the single entities in children. No new ADRs to FTC or TDF were identified in these studies in addition to those observed in adults. It would appear that anaemia and skin discoloration (hyperpigmentation) occurred more frequently in children when compared to adults. It also appeared that decrease in spine and total body BMD Z-scores occurred with the use of TDF.

Overall it is considered that there are no new safety concerns regarding use in the paediatric population when compared to adults.

2.5.2. Conclusions on clinical safety

The safety profile of the single entities FDC and TDF when used in the paediatric population have been previously characterised and well-known. These data are considered applicable for Truvada since no differences are expected with FDC and TDF used as single entities or combined as a FDC (Truvada).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Update of the Product information

As a consequence of this new indication, several sections of the SmPC and PL have been revised.

2.7. 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 13.1 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 advice without changes.

The CHMP endorsed the Risk Management Plan version 13.1 with the following content:

Safety concerns

Summary of safety concerns

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 ongoing and planned additional pharmacovigilance studies are shown in Table 27.

Table 27. Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan (Categories 1 3)

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-276-0101 A Prospective, Observational Study of Pregnancy Outcomes among Women exposed to Truvada for PrEP indication nested in the Antiretroviral Pregnancy Registry	Observational study collecting data on pregnancy outcome of women who become pregnant while taking Truvada for pre-exposure prophylaxis	*Missing information*: Safety in pregnancy (FTC, TDF)	Ongoing	Final report planned Q1 2017
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

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
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-US-276-0105 A Prospective, Observational, Drug Utilization Study of Subjects Taking Truvada for Pre-exposure Prophylaxis in the USA	Provide nationally representative drug utilization data for use of Truvada for a pre-exposure prophylaxis indication including both TVD and for the single-ingredient products containing emtricitabine or tenofovir disoproxil fumarate.	*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 Q1 2017
GS-EU-276-4027 A Drug Utilization Study of Truvada for Pre-Exposure Prophylaxis in the European Union	To provide information on the effectiveness of the additional risk minimization measures and to describe the usage patterns and reported adherence to the use of Truvada for PrEP	*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)	Planned	To be confirmed
GS-EU-104-0433 An Observational, Drug Utilization Study of Viread in Children and	To assess the clinical management and outcome of renal and	*Important identified risk*: Renal toxicity	Ongoing	Final report planned Q4 2017

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Adolescents with HIV-1Infection	bone events	(TDF) *Important identified risk:* Bone events due to proximal renal tubulopathy/loss of BMD (TDF)		
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

Table 28. Summary Table of Risk Minimization Measures

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 to strictly adhere to the recommended Truvada 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	*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

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	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 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 patients receiving LDV/SOF 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 efavirenz or rilpivirine no dose adjustment is recommended but renal function should be closely monitored. 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:* *Adults* 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	Truvada to pediatric patients.

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	< 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. 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. *Pediatrics* Sections 4.2, 4.4 and 4.8 of the Truvada SmPC include a statement indicating that use of Truvada is not recommended in HIV-1 infected pediatric patients 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 HIV-1 infected 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. *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.	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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 4.8 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 effects of bone and renal toxicity in pediatric patients and the reversibility of renal toxicity 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 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 Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
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. *Pediatrics* Sections 4.2, 4.4 and 4.8 of the Truvada SmPC state that Truvada is not recommended in pediatric patients with renal impairment. *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.	None

3. Benefit-Risk Balance

Benefits

Truvada is a fixed dose combination of FTC and TDF (available as single entities) which offers convenience in terms of reduced pill burden.

Beneficial effects

This current application to add an indication for use of Truvada in the treatment of HIV-1 infected adolescents (12 to <18 years) with NRTI resistance or toxicities precluding the use of line agents relies upon the results of three studies conducted with FTC and two studies conducted with TDF in paediatric populations. Data from these studies supported the approval of the use of Emtriva® (FTC) and Viread® (TDF) in paediatric patients.

For FTC, the results of the three studies demonstrate the efficacy of FTC when given in combination with other ART. 88.6% of the subjects achieved plasma HIV-1 RNA viral load of ≤ 400copies/mL by week 48, while 76.5% of the subjects achieved and maintained complete suppression of HIV-1 RNA viral load to ≤ 50 copies/mL at week 48.

For TDF, the results of Study GS US-104-0321 demonstrated that the median time weighted average change from baseline through week 24 in plasma HIV-1 RNA was -1.580 $\log_{10}$ copies/ml and -1.549 log10 copies/ml in the placebo group with no difference between treatment groups in terms of decreases in plasma HIV-1 RNA from baseline at Week 48. While the results of Study GS-US-104-0352 showed that at

week 48 83.3% of subjects (40/48) in the tenofovir DF group and 91.8% of subjects (45/49) in the stavudine or zidovudine group had HIV-1 RNA concentrations < 400 copies/mL. The bound of the difference between treatment groups was −21.5% therefore TDF did not mean the criteria for demonstrating non-inferiority. At week 24, 93.8% of subjects (45/48) in the TDF group and 89.8% of subjects (44/49) in the d4T or ZDV group had HIV-1 RNA < 400 copies/mL (ITT analysis set). The difference in proportions was 4.0% and the 95% CI was −6.9% to 14.9%. The lower bound of the 95% CI on the difference between treatment groups was greater than −15% from baseline through Week 24 and therefore suggestive of treatment non-inferiority.

Uncertainty in the knowledge about the beneficial effects

No studies have been conducted with Truvada in adolescents and the data is derived entirely from studies conducted with the single entities. However, this is not considered to be a significant issue as these data are considered applicable for Truvada for the proposed indication in adolescents since the studies conducted with adults are also demonstrative of efficacy and there is comparative PK data.

Risks

Unfavourable effects

It would appear that anaemia and skin discoloration (hyperpigmentation) occurred more frequently in children when compared to adults. It also appeared that decrease in spine and total body BMD Z-scores occurred with the use of TDF. Issues have also been identified regarding renal safety.

In terms of virologic failure, 16 subjects (8 ART-naïve and 8 ART experienced) were considered virologic failures. 4 subjects were confirmed to have M184V mutation. In Study GS US-104-0321, nine subjects on TDF developed NRTI-associated resistance mutations at Week 48. One subject developed K65R; 4 developed M184V (n = 4) while 4 subjects developed thymidine-analogue associated mutations.

Overall it is considered that there are no new safety concerns regarding use in the paediatric population when compared to adults other than those already known about the single entities in particular with TDF and the association with renal safety and decrease in spine and total body BMD Z-scores.

Uncertainty in the knowledge about the unfavourable effects

No studies have been conducted with Truvada in adolescents and the data is derived entirely from studies conducted with the single entities. As previously stated this is not considered to be an issue.

Effects Table

Table 29. Effects Table for Truvada for the indication in patients 12 to <18 years of age

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary efficacy end-point	The proportion of subjects achieving HIV-1 RNA < 400	%	FTC: 88.6%	Uncontrolled	Open label studies conducted with FTC alone	Studies FTC 202, 203 and 211

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	copies/mL at Week 48					
Primary efficacy end-point	Time-weighted average change from baseline through week 24 in plasma HIV-1 RNA copies (DAVG24)		TDF: -1.580 log_{10} copies/ml	Placebo: -1.549 log_{10} copies/ml		GS US-104-0321
Primary efficacy end-point	The proportion of subjects achieving HIV-1 RNA < 400 copies/mL at Week 48		TDF: 83.3%	D4T/ZDV : 91.8%	TDF did not meet the criteria for demonstrating non-inferiority	Study GS-US-104-0352
Unfavourable Effects						
	TLOVR defined virologic failure	%	FTC: 12.1%	Uncontrolled	Open label studies conducted with FTC alone	Studies FTC 203 and 211
	Hyperpigmentation		FTC: 31.8%	Uncontrolled	Occurred entirely in study FTC 203	Studies FTC 203 and 211
	Decrease in spine and total body BMD Z-scores		TDF: 18.6%			Study GS-US-104-0352
	Hypophosphatemia		TDF: 6.3%			Study GS-US-104-0352

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The results of all the studies provided for FTC and TDF are demonstrative of efficacy of the single entities for the treatment of HIV-1 in the proposed age group of 12 to 18 years of age. These data are considered applicable for Truvada for the proposed indication in adolescents with extrapolation of adult data and the demonstrated comparative PK data. In terms of safety, no new ADRs to FTC or TDF were identified in these studies in addition to those observed in adults this means that there are no new safety concerns regarding use in the paediatric population when compared to adults. It is important to note the concerns regarding TDF in terms of renal safety and bone safety are well-known and remain but should not alter the benefit risk in terms of the proposal to extend the use to adolescents.

No studies have been conducted with Truvada in adolescents and the data is derived entirely from studies conducted with the single entities. This is not considered to be a significant issue as the presented data are considered applicable for Truvada for the proposed indication in adolescents since the studies conducted with adults are also demonstrative of efficacy and there is comparative PK data. The safety issues are well known

Benefit-risk balance

Discussion on the Benefit-Risk Balance

The benefit risk for the proposed new indication is considered to be positive. The data from studies conducted with the single entities are considered applicable for the proposed indication in adolescents. The studies conducted in adults are demonstrative of efficacy and PK data in adolescent is comparable to data in adults. The safety issues are well known and can be monitored and managed.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 for Truvada in the treatment of human immunodeficiency virus, type 1 (HIV-1) infected adolescents, with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.

As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to include information on the target patient population, posology, warnings, interactions, undesirable effects and pharmacodynamics derived from three studies with emtricitabine (FTC-202, FTC-203 and FTC-211) and two studies with tenofovir disoproxil fumarate in paediatric populations (GS-US-104-0321 and GS-US-104-0352).
The Package Leaflet, Annex II and the Risk Management plan (RMP version 13.1) are updated in accordance.

This CHMP recommendation is subject to the following amended conditions:

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
- 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.

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 for Truvada in the treatment of human immunodeficiency virus, type 1 (HIV-1) infected adolescents, with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to include information on the target patient population, posology, warnings, interactions, undesirable effects and pharmacodynamics derived from three studies with emtricitabine (FTC-202, FTC-203 and FTC-211) and two studies with tenofovir disoproxil fumarate in paediatric populations (GS-US-104-0321 and GS-US-104-0352). The Package Leaflet and the Risk Management plan (RMP version 13.1) are updated in accordance.

Summary

Please refer to the Scientific Discussion Truvada EMEA/H/C/000594/II/0131.