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Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000419/II/0098

Invented name/name:	Viread
International non-proprietary name/common name:	tenofovir disoproxil fumarate
Indication summary (as last approved):	treatment of HIV-1 infection and hepatitis B infection
Marketing authorisation holder:	Gilead Sciences International Ltd.

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Tenofovir disoproxil fumarate (tenofovir DF, TDF) is a nucleotide reverse transcriptase inhibitor (NtRTI). Viread tablets (containing 245 mg of tenofovir disoproxil as fumarate, equivalent to 300 mg tenofovir DF or 136 mg of tenofovir) was first approved in United States (US) (26 October 2001), European Union (EU)(5 February 2002), and other countries worldwide for the treatment of human immunodeficiency virus type 1 (HIV-1) in combination with other antiretroviral (ARV) medicinal products in infected adults age 18 years and older. Viread was subsequently approved for the treatment of chronic hepatitis B in EU (23 April 2008) and US.

In the US, Viread tablets were approved for the treatment of HIV-1 infected subjects 12 to < 18 years of age and with body weight ≥ 35 kg on 25 March 2010.

This type II variation for Viread 245 mg film-coated tablets sought to extend the indication for the treatment of HIV-1 to include treatment-experienced adolescents 12 to < 18 years of age and with body weight ≥ 35 kg.

This submission presented pharmacokinetic (PK), efficacy, and safety data for tenofovir DF that are pertinent to the assessment of the tenofovir DF 300-mg tablet for the treatment of HIV-1 infected subjects in the EU who are 12 to < 18 years of age and with body weight ≥ 35 kg.

The principal PK, efficacy, and safety data for tenofovir DF in HIV-1 infected subjects 12 to < 18 years of age are from an ongoing, long-term, Phase 3 clinical study sponsored by Gilead Sciences, GS-US-104-0321.

This application was further supported by final clinical study reports from earlier PK and safety paediatric studies of tenofovir DF: GS-01-926 (96 weeks), GS-01-927 (96 weeks), and GS-02-983 (single dose). Data from these studies supported Viread dose selection in Study GS-US-104-0321, and the overall safety and activity profile of Viread for paediatric use. This application also included cumulative assessments of paediatric safety and efficacy data for tenofovir DF from the Gilead Drug Safety and Public Health's database and from published and unpublished literature.

Overview of Gilead-Sponsored Studies in this Submission

Study (Module 5 Reference)	Design	Geographic Location	Study Population	Treatment	Subjects Treated	Duration (Status)
GS-US-104-0321 (m5.3.5.1)	Randomized, double-blind, placebo-controlled, multicenter Phase 3 study in HIV-1 infected adolescent subjects.	17 sites in Brazil; 1 site in Panama	HIV-1 infected subjects (12 to < 18 years old) with plasma HIV-1 ribonucleic acid (RNA) ≥ 1000 copies/mL, naive to tenofovir DF, failing current regimen	Tenofovir DF 300-mg tablets + optimized background regimen (OBR) or placebo plus OBR	87 (tenofovir DF 45, placebo 42; All TDF 81)	240 weeks (ongoing; 48-week randomized period completed)
GS-01-926 (m5.3.5.2)	Open-label, Phase 1 study in HIV-1 infected pediatric subjects	1 site in the United States	HIV-1 infected subjects (4 to < 18 years old); plasma HIV-1 RNA ≥ 10,000 copies/mL; failed 2 prior ARV regimens	Tenofovir DF 75 mg tablets, administered based on body surface area at 175 mg/m^2 (150, 225, or 300 mg/day) as monotherapy for 1 week, then with ≥ 2 other ARVs	18	96 weeks (completed)
GS-01-927 (m5.3.5.2)	Open-label, 96-week, Phase 1/2 study in HIV-1 infected pediatric subjects	1 site in France	HIV-1 infected subjects (4 to 17 years old) with plasma HIV-1 RNA ≥ 10,000 copies/mL; failed 2 prior ARV regimens	Tenofovir DF 75 mg tablets, administered based on body weight (75, 150, 225, or 300 mg/day) as part of an ARV regimen	7	96 weeks (completed)
GS-02-983 (m5.3.3.2)	Open-label, single-dose, single-center, Phase 1 study in HIV-1 infected pediatric subjects	1 site in the United States	HIV-1 infected male or female children, aged 2 to 8 years, inclusive	Tenofovir DF oral suspension, 8 mg/kg with other ARV agents	12	Single dose (completed)

In addition to the studies described above, Tenofovir DF 75-mg tablets (4 × 75 mg) were shown to be bioequivalent to one 300-mg tablet in Study GS-00-914.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/18/2010 for the following conditions:

- Human immunodeficiency virus (HIV) disease resulting in other conditions.
- Chronic viral hepatitis B

The PIP is not yet completed.

The paediatric investigation plan (PIP) for Viread was agreed on 08 February 2010 (EMEA-000533-PIP01-08. It has to be noted that the PIP for Viread was submitted at a late stage regarding the HIV indication since the proposed studies for the paediatric development had been almost completed. The pivotal studies presented in the setting of the PIP were the currently analyzed study GS-US-104-0321

(in adolescents aged 12-<18 years) and study GS-US-104-0352 (in children aged 2-<12 years). Although the PDCO could agree upon the MAH's approach, concerns were raised as regards bone toxicity and maturation.

2. Scientific overview and discussion

2.1. Introduction

The pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy (ART) are similar between HIV-1 infected adults and HIV-1 infected paediatric patients. However, there are some important and unique issues for infants, children, and adolescents, including the following:

• Acquisition of infection through perinatal exposure for many infected children

• In utero, intrapartum, and/or postpartum neonatal exposure to zidovudine and other ARV medications in most perinatally infected children

• Age-specific differences in CD4 cell counts

• Changes in PK parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance

• Special considerations associated with adherence to ART for infants, children, and adolescents.

As was specified in the PIP report, few direct HIV surveillance data are available for children. Estimates for the prevalence of HIV in children are obtained through modelling that is based primarily on HIV prevalence estimates in adult women (ages 15 to 49 years), fertility rates, and assumptions about the survival of HIV 1 infected children. Such estimates show that the number of children living with HIV globally continues to increase steadily; however, new HIV infections in children appear to have peaked between 2000 and 2002. Globally, an estimated 370,000 children aged up to 14 years became infected with HIV in 2007 (UNAIDS report on the Global AIDS epidemic, 2008, accessed at www.unaids.org, 13 February 2009).

Currently, highly active combination regimens including at least three drugs are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children. At present, in EU, the treatment of choice for HIV-infected children comprises 2 NRTIs with either a NNRTI or a ritonavir-boosted PI.

International treatment guidelines list tenofovir DF as a preferred NRTI/NtRTI in an ARV regimen for initial therapy in HIV-1 infected adults. US guidelines listed tenofovir DF as a preferred NRTI/NtRTI in an ARV regimen for initial therapy in HIV-1 infected postpubertal or Tanner stage 4 adolescents only. TDF is not recommended in children in Tanner stages 1 to 3 due to lack of paediatric dosing data, an age-appropriate formulation, and concerns related to bone toxicity (Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children. Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection: February 23, 2009).

In Europe, 2009 treatment guidelines indicate that tenofovir DF is not licensed for use in patients < 18 years of age, and that data on safe long-term use from a young age are lacking; however, the guidelines suggest that tenofovir DF can be used as first-line therapy in adolescents, particularly as part of a fixed-dose combination, i.e., Truvada or Atripla (PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. HIV Med 2009).

2.2. Non clinical aspects

The (Marketing authorisation holder) MAH provided a comprehensive programme of pharmacology, pharmacokinetics and toxicology studies with tenofovir DF in nonadult animals that was undertaken in support of the Marketing Authorization Application. The preclinical studies were conducted in rats, dogs and monkeys in order to characterize the potential toxicity of tenofovir in nonadult animals, especially bone and renal toxicity, to assess the reversibility in newborn and juvenile animals, to determine the safety margins from exposure data, and to compare effects between juvenile and adult animals.

Given that the toxicological profile of Tenofovir DF is characterized in multiple juvenile animals and the long-term effects of tenofovir DF on growth have been identified in those species, no additional juvenile animal studies are requested to support the use of tenofovir DF for the treatment of HIV-infected treatment-experienced adolescent patients. As a result of those studies, bone toxicity findings in juvenile animals are known and included in section 5.3 of the SmPC. This section was further reworded (see section 3.5).

Finally, findings in the rat and monkey studies indicated that there was a substance-related decrease in intestinal absorption of phosphate with potential secondary reduction in bone mineral density. For this reason, the MAH plans to conduct *in vitro* nonclinical studies to evaluate a potential inhibitory effect of tenofovir DF on absorption of phosphate in the gastrointestinal tract. This study is reflected in the last submitted RMP version 9 (under evaluation).

2.2.1. Environmental risk assessment

In the context of this variation, the MAH has provided a new environmental risk assessment with an updated analysis regarding the outcome of tier A and effects analysis.

The outcome of Tier A Fate and effects analysis calculations (Predicted Environmental Concentration/Predicted No Effect Concentration ratios) have been reviewed, and the values for tenofovir DF remain substantially less than 1 based on use for all indications.

Based on the above results, there should be no significant increase in the risk to the environment arising from the introduction of Viread film-coated tablets for treatment of HIV-1 treatment-experienced adolescents from 12 to < 18 years of age and with body weight ≥ 35 kg.

2.3. Clinical aspects

2.3.1. Clinical pharmacology

2.3.1.1. Clinical pharmacokinetics

Age-related differences in pharmacology may occur due to increased apparent clearance and/or lower bioavailability in children relative to adults. These factors were taken into account with dose selection for paediatric subjects, with the aim of targeting tenofovir systemic exposure similar to that seen in adults receiving the tenofovir DF 300-mg.

The MAH provided a summary of the available pharmacokinetic data for tenofovir that are pertinent to the assessment of tenofovir DF for the treatment of HIV-1 infected subjects 12 to < 18 years of age. Results from 4 clinical studies were presented:

Pharmacokinetic Evaluations in HIV-1 Infected Paediatric Subjects

Study	Study Design	Age Group (years)	Number of Subjects Evaluated
GS-US-104-0321	Multidose, Phase 3	12 – < 18	8
GS-01-926	Multidose, Phase 1	6 – 16 inclusive	18
GS-01-927	Multidose, Phase 1/2	9 – 16 inclusive	7
GS-02-983	Single-dose, Phase 1	2 – 8 inclusive	12

Initial clinical studies were undertaken using an oral suspension formulation (GS-02-983 in HIV-1 infected subjects 2 to 8 years of age) and 75-mg tablets of tenofovir DF (GS-01-926 and GS-01-927 in HIV-1 infected subjects 6 to 16 years of age). Each of these studies included pharmacokinetic assessments for all subjects. Based on data from these studies, the dose of tenofovir DF selected for investigation in study GS-US-104-0321 was 8 mg/kg of actual body weight to a maximum of 300 mg/day.

2.3.1.1.1. Initial PK studies

- **study GS-01-926**

Pharmacokinetic evaluations were conducted for all 18 treated paediatric subjects after the first dose of tenofovir DF 175 mg/m2, and for 16 subjects for whom data were available at the Week 4 time point.

On Day 1 (n = 18), the median doses of tenofovir DF adjusted for body weight and BSA were 7.07 mg/kg (range, 3.74 to 10.04 mg/kg) and 208.03 mg/m2 (range, 160.52 to 255.14 mg/m2), respectively.

At Week 4 (n = 15), the median doses of tenofovir DF adjusted for body weight and BSA were 7.03 mg/kg (range, 3.63 to 9.78 mg/kg) and 207.47 mg/m2 (range, 158.31 to 250.96 mg/m2), respectively.

Following a single dose of tenofovir DF, mean maximum observed concentration of drug in serum, plasma, or peripheral (Cmax) and AUCinf were lower than target exposures. At steady state, mean Cmax and area under the concentration versus time curve from time zero (predose) over the blood mononuclear cells (AUCtau) in subjects receiving multiple doses of tenofovir DF with other ARVs, including those known to increase tenofovir concentrations, were consistent with those observed in adults receiving tenofovir DF at 300 mg/day.

This study has been previously assessed by the CHMP in the setting of FUM56 in 2006. On the basis of the limited data available and in view of the marked inter- variability observed, it was concluded that the 8mg/kg dose for paediatric patients would need to be further substantiated in future studies.

- **Study GS-01-927**

The mean tenofovir DF daily dose was 5.7 mg/kg (range 4.7-6.8 mg/kg).

Following a single dose of tenofovir DF, mean Cmax and AUCinf were lower than target exposures. Mean Cmax and AUCtau in subjects receiving multiple doses of tenofovir DF with other ARVs, including those known to increase tenofovir concentrations, were consistent with those observed in adults receiving tenofovir DF at 300 mg/day.

This study has been previously assessed by the CHMP in the setting of FUM OTH57 in 2006, where it was concluded that the study was too limited to support any TDF target dose in children.

- **Study GS-02-983**

Administration of tenofovir DF oral suspension with food at a dose of 8 mg/kg of body weight to HIV-1 infected subjects 2 to 8 years of age resulted in systemic exposures that were similar to those observed in HIV-1 infected adults administered a single dose of the commercially available 300-mg tablet with food (Study GS-97-901). The median T½ was also similar between paediatric subjects and adults.

This study has been previously assessed by the CHMP in the setting of FUM 193 in 2006. The similarity of exposures between adults (historical data) and children aged 2-8 years of age who received TDF oral suspension at a dose of 8mg/kg was endorsed. However, considering the apparent lack of a bioequivalence study between the approved TDF 300 mg tablets and TDF (20 mg/mL) oral suspension, it was questioned whether the data collected in study GS-02-983 with the oral suspension could be extrapolated to carry out the paediatric development with an alternative formulation.

2.3.1.1.2. Study GS-US-104-0321 (also named -0321)

All subjects in the tenofovir DF group in the pivotal Phase 3 study, GS-US-104-0321, were 12 to < 18 years of age at enrolment and received the tenofovir 300 mg tablet once daily. A substudy (n = 8) was included to assess tenofovir PK parameters following administration of the tenofovir DF tablet for at least 4 weeks in order to confirm the appropriateness of the 300 mg dose in this population. Mean (± SD) C_{max} and AUC_{tau} are 0.38 ± 0.13 µg/ml and 3.39 ± 1.22 µg·h/ml, respectively.

Steady-state tenofovir exposures achieved in subjects 12 to < 18 years of age receiving tenofovir DF 300 mg/day were similar to those observed in adults receiving tenofovir DF 300 mg/day (Studies GS-97-901 and GS-99-907). These data confirm the appropriateness of the 300 mg once-daily dose of tenofovir DF for subjects 12 to < 18 years of age.

GS-US-104-0321: Plasma Tenofovir Pharmacokinetic Parameters Following Multiple Doses of Tenofovir DF (PK Analysis Set) and Comparative Historical Data in Adults

TFV Steady-state PK Parameter	GS-US-104-0321 300 mg/day (N = 8)[a]	Historical Adult Data in HIV-1 Infected Adults					
		GS-97-901 300 mg/day		GS-99-907 300 mg/day			
		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_{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
$T_{½}$ (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 tenofovir DF; 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.

2.3.1.1.3. Renal Impairment

Tenofovir DF dose-interval adjustment is required for adult patients with calculated creatinine clearance < 50 mL/min. No data are available to make recommendations for dose adjustment in patients 12 to < 18 years of age with renal impairment.

2.3.1.1.4. Potential for Drug Interactions

The PK drug-drug interaction potential of tenofovir DF and various ARVs have been extensively evaluated in adults, and results from these studies are considered appropriate for extrapolation to the paediatric population.

2.3.1.1.5. Discussion

Although the 3 Phase I-I/II studies in HIV-infected children provided some grounds in favour of the 8mg/kg dose, some doubts on the appropriateness of this dose were raised by the CHMP at the time of their assessment in 2006. Furthermore, two of these studies were conducted with a 75mg tablet and the remaining study with an oral suspension, all 3 formulations had been abandoned by the MAH.

The overall PK data available, including the PK data in adolescent from the study -921, show an almost similar exposure in adolescents and adults dosed with the 300mg tablet. The proposed 300mg dose (equivalent to a 8mg/kg dose for patient with 37.5kg weight) in adolescents aged 12 to <18 years and weighting ≥ 35kg is therefore supported. Therefore, extrapolation of interaction data from adults to the adolescent population can be acknowledged.

Of note, to be eligible in the pivotal adolescent study -321, patients should have estimated creatinine clearance ≥ 80 mL/min/1.73m2 (Estimated by Schwartz Formula).

No data are available to make recommendations for dose adjustment in patients 12 to < 18 years of age with renal impairment.

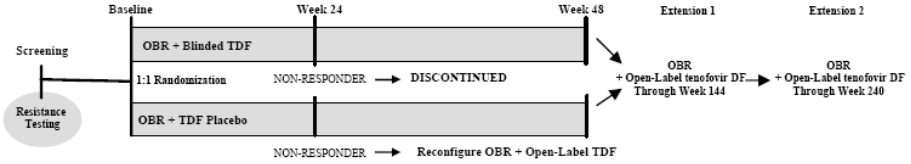
Results from PK drug-drug interaction in adults are considered appropriate for extrapolation to the paediatric population.

2.3.2. Clinical efficacy

2.3.2.1. Study design

Design aspects for study GS-US-104-0321 are summarized below:

Title of the study	A Phase 3, double-blind, randomized, placebo-controlled study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents
Study Centers	18 study centers: 17 in Brazil and 1 in Panama (US sites were initiated but did not enroll any subjects)
Study Period:	13 June 2006 (first subject screened) 09 March 2009 (last subject observation for this report) Anticipated date for completion (last patient, last visit): By March 2013
Objectives	The primary objective of this study was as follows: • To assess the efficacy of tenofovir DF plus a genotype-guided optimized background regimen (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. The secondary objectives of this study (Weeks 0–48) were as follows: • 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 bone mineral density (BMD) in the two treatment groups. A secondary objective that will be evaluated beyond Week 48 (Weeks 0–240) is as follows: • To evaluate the long-term efficacy, safety, and tolerability of treatment with tenofovir DF through up to 240 weeks of drug exposure.
Population and main inclusion criteria	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 two antiretroviral drug classes, and were receiving combination antiretroviral therapy for at least 12 weeks at the time of study entry. Subjects also had to have adequate hematologic, renal and hepatic functions, and based upon resistance testing, were able to receive an OBR not containing didanosine. Patients with history of significant renal or bone disease were excluded.
Number of subjects	Planned: 100 evaluable (50 in each treatment group) Randomized and treated (RAT): 87 (tenofovir DF 45, placebo 42; All TDF 81 [double-blind and extension phase data for subjects who received tenofovir DF in the study])
Study duration	240 weeks

Criteria for evaluation	Efficacy: The primary efficacy endpoint was time-weighted average change from baseline through Week 24 (DAVG24) in plasma HIV-1 RNA. Among secondary endpoints: DAVG48, change from baseline in log10 HIV-1 RNA at Weeks 24 and 48, change from baseline in CD4 cell count and CD4% at Weeks 24 and 48, proportion of subjects with HIV-1 RNA < 400 copies/mL and < 50 copies/mL at Weeks 24 and 48, time to virologic failure Safety: Safety data were collected for the following parameters: adverse events (AEs); clinical laboratory tests; spine and total body BMD (assessed using DEXA); bone biochemical markers; height; weight; vital signs; and physical examinations (complete or symptom-directed).
Dosing regimen	Adolescent (weighing ≥ 35 kg) received the 300mg dose of TDF (i.e. approved adult dose). All subjects were instructed to take their assigned tenofovir DF dose orally, once daily, without regard to meals. The tenofovir DF tablets were film-coated to mask taste.
Study design	This was a 48-week, randomized, double-blind, placebo-controlled, multi-center study of the safety and efficacy of tenofovir DF as part of an optimized antiretroviral regimen in HIV-1 infected adolescents (12 years to < 18 years of age) who were failing their current antiretroviral regimen and had HIV-1 RNA levels ≥ 1000 copies/mL at screening. Two consecutive 96-week study extensions (ongoing) will evaluate the long-term efficacy, safety, and tolerability of open-label tenofovir DF as part of an optimized antiviral regimen, providing data for up to 240 weeks of total drug exposure.  Pretreatment: HIV-1 genotyping was performed as part of the screening assessments to assist in the construction of an OBR, defined as at least 3, but no more than 5 antiretroviral agents, not including tenofovir DF or placebo. Baseline–Week 48: Subjects were randomized in a 1:1 ratio to receive either tenofovir DF + OBR or placebo + OBR. Stopping rules: At Week 24, subjects who were adherent to study drug (in the opinion of the investigator), but did not demonstrate a ≥ 0.5 log10 copies/mL decrease from baseline in HIV-1 RNA, were considered to be nonresponders and were unblinded. Nonresponders randomized to the placebo group were given the option to continue on study and receive open-label tenofovir DF with an appropriate background regimen determined by the investigator. Nonresponders randomized to the tenofovir DF treatment group were discontinued from the study. The majority of efficacy and safety assessments were performed at each clinic visit (Weeks 4, 8, 16, 24, 32, 40, and 48). Bone biochemical markers were assessed at baseline, and at Weeks 4, 16, 24, 32, and 48. Dual energy x-ray absorptiometry (DEXA) scans to assess spine and total body BMD and body fat (including limb fat) were performed at baseline, Week 24, and Week 48.

Disposition of patients

Of the 123 subjects screened, 90 were randomized at 17 sites in Brazil (n = 86) and one site in Panama (n = 4): 46 in TDF arm and 44 in placbo arm.

Of the 87 randomized and treated subjects, 56 completed the 48-week double-blind treatment period (27 subjects [60.0%] in the tenofovir DF group and 29 subjects [69.0%] in the placebo group).

The most common reason for discontinuation of study drug was virologic failure (14 subjects in the tenofovir DF group and 11 subjects in the placebo group).

Demographic and baseline characteristics

Overall, demographic and general baseline characteristics were similar between the two treatment groups.

Subjects in the RAT analysis set in the randomized phase were 56.3% female, with a mean age of 14 years (range, 12 to 17 years). All were of Hispanic/Latino ethnicity, 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).

The disease characteristics reflect a patient population with advanced HIV infection.

The route of contamination (vertical or horizontal) was not available in the report.

Treatment characteristics

Prior antiretroviral experience was similar in the tenofovir DF and placebo groups. The majority of subjects in this study had prior experience with medications from all three of the major antiretroviral drug classes (100.0% with nucleoside and nucleotide reverse transcriptase inhibitors [NRTIs], 82.8% with protease inhibitors [PIs], and 64.4% with nonnucleoside reverse transcriptase inhibitors [NNRTIs]). The most frequently used NRTIs were zidovudine and lamivudine (including the fixed dose combination of these products), didanosine and stavudine. The most frequently used PIs were nelfinavir and lopinavir/ritonavir. The most frequently used NNRTI was efavirenz.

Of note, higher proportions of subjects in the tenofovir DF group compared to the placebo group had baseline genotypic susceptibility scores (GSS) for OBR ≤ 1 (40.0% vs 23.8% [French National Agency for AIDS Research (ANRS) rules]), indicating that the tenofovir DF group had less active concomitant antiretroviral drugs, and baseline GSS for tenofovir DF < 1 (55.6% vs. 40.5%); these subjects would not be expected to respond to tenofovir DF treatment).

Measurement of treatment adherence

Adherence to study drug in the double-blind treatment period was similar in the tenofovir DF and placebo groups (median 93.1% in the tenofovir DF group and 93.8% in the placebo group); however, only 39.1% of subjects overall (TDF: 37.8%, Pbo: 40.5%) maintained an adherence rate to study drug of ≥ 95%.

2.3.2.2. Results

The primary efficacy endpoint was time-weighted average change from baseline through Week 24 ($DAVG_{24}$) in plasma HIV-1 RNA (log10 copies/mL).

Time-Weighted Average Change in HIV-1 RNA (log_{10} copies/mL) from Baseline through Week 24 ($DAVG_{24}$)[a, b, c]	Tenofovir DF (N = 44)	Placebo (N = 41)	p-value[d]
DAVG Through Week 24			
N	44	41	0.55
Mean (SD)	−1.246 (1.1160)	−1.346 (1.2449)	
Median	−1.580	−1.549	
Q1, Q3	−2.15, −0.27	−2.36, −0.34	
Min, Max	−2.81, 0.89	−3.09, 0.88	

a DAVG through time X is the time weighted average between the first postbaseline 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].

Both treatment groups exhibited clinically relevant decreases from baseline in plasma HIV-1 RNA; the median DAVG24 in plasma HIV-1 RNA was −1.580 log10 copies/mL in the tenofovir DF group (n = 44) and −1.549 log10 copies/mL in the placebo group (n = 41) (p = 0.55, Van Elteren test). However, there were no statistically significant differences between treatment groups in the DAVG24 in plasma HIV-1 RNA or for any of the secondary efficacy endpoints at any of the timepoints analysed.

In subjects with an ANRS OBR GSS ≤ 1.0, the difference in median DAVG24 in plasma HIV-1 RNA between treatment groups (tenofovir DF minus placebo) was −0.518 log10 copies/mL (−1.658 log10 copies/mL in the tenofovir DF group [n = 18] and −1.140 log10 copies/mL in the placebo group [n = 10]). Differences between tenofovir DF and placebo in this subgroup were maintained at Week 48 (difference in median DAVG48 in plasma HIV-1 RNA was −0.570 log10 copies/mL). These results were confirmed using the genotypic resistance interpretation rules of the Stanford HIV database.

No significant differences were seen between treatment groups for any subgroup analyses (sex, race, CD4 cell count, HIV-1 RNA level at baseline, and baseline GSS) of DAVG24 in plasma HIV-1 RNA.

No significant differences were seen between treatment groups for secondary virologic endpoints in the intent-to-treat (population) (ITT) analysis set. The median change from baseline in plasma HIV-1 RNA at Week 48 (last observation carried forward (LOCF)) was −0.97 log10 copies/mL in the tenofovir DF group (n = 44) and −1.53 log10 copies/mL in the placebo group (n = 41). The proportion of subjects who had an HIV-1 RNA decrease from baseline of ≥ 1.0 log10 copies/mL at Week 48 (LOCF) was 47.7% in the tenofovir DF group (n = 44) and 53.7% in the placebo group (n = 41). The proportion of subjects with plasma HIV-1 RNA < 400 copies/mL at Week 48 (M = F) was 34.1% (15/44) in the tenofovir DF group and 43.9% (18/41) in the placebo group. The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 (M = F) was 27.3% (12/44) in the tenofovir DF group and 36.6% (15/41) in the placebo group.

Results of post-hoc subgroup analyses for subjects with baseline ANRS OBR GSS ≤ 1 showed clinically relevant differences (in favour of TDF) between tenofovir DF (n = 18) and placebo (n = 10) groups in the median change from baseline in plasma HIV-1 RNA concentration (median of −1.24 log10 copies/mL in the tenofovir DF group vs. −0.63 log10 copies/mL in the placebo group at Week 48, LOCF) and the proportion of subjects with an HIV-1 RNA decrease from baseline of ≥ 1.0 log10 copies/mL (55.6% in the tenofovir DF group vs. 40.0% in the placebo group at Week 48, LOCF). There

were no clinically relevant differences between tenofovir DF and placebo for the number and percentage of subjects with plasma HIV-1 RNA < 400 copies/mL and < 50 copies/mL in the subgroup analyses.

Although an immunologic recovery was seen in both treatment groups, there was no significant difference between treatment groups at baseline or for the change from baseline in CD4 cell count or CD4 percentage at any postbaseline timepoint up to Week 48 (missing = excluded (M = E analysis)). The median change at Week 48 was 152 cells/mm3 in the tenofovir DF group and 148 cells/mm3 in the placebo group (p = 0.47).

Virology results

Ninety subjects randomized to either the tenofovir DF or placebo groups were genotyped for their HIV-1 protease (PR) and reverse transcriptase (RT) genes at screening.

Postbaseline HIV genotypes were performed on subjects who had virologic failure, or had HIV-1 viral load ≥ 400 copies/mL at Week 24, Week 48, Week 96, Early Discontinuation, or their last available plasma sample prior to the Week 48 analysis data cutoff dates. However, a genotypic assay at an earlier time point was not always performed if a later genotype was available.

Screening HIV Genotypic Analysis

The study population had evidence of extensive prior antiretroviral therapy experience at screening, with 90% of subjects having HIV that contained one or more NRTI-associated resistance mutations (NAMs). The mean number of NAMs was 4.8 and 3.9 in the tenofovir DF and placebo groups, respectively. Similarly, 80% of subjects had HIV with thymidine-analog associated mutations (TAMs) at screening (mean 3.0 and 2.2 TAMs in the tenofovir DF and placebo groups, respectively). TAMs were reported in 84% of patients in the tenofovir arm versos 76% in the placebo arm. In the tenofovir DF and placebo groups, 49% and 33% of subjects, respectively, had HIV containing three or more TAMs that included M41L and/or L210W mutations. This pattern of resistance mutations has been associated with poor response to tenofovir DF in previous studies of treatment-experienced, HIV-1 infected adults.

In addition, 53% of subjects in the study had HIV containing an NNRTI-associated resistance mutation, 61% contained major protease resistance mutations, and all subjects had HIV containing at least one secondary protease resistance mutation.

HIV-1 Subtype Distribution at Screening

HIV-1 subtype analyses showed the majority of subjects were infected with subtype B (67%) followed by subtype C (17%).

Emerging Resistance Mutations

During the study, treatment with tenofovir DF or placebo in combination with other antiretroviral drugs resulted in the development of additional NRTI-associated resistance mutations in 24% (11/46) of subjects in the overall resistance analysis population. Numerically, more subjects developed NAMs in the tenofovir DF group 9/29 (31%) than in the placebo group 2/17 (12%). This difference is due to more subjects developing K65R (n = 1), M184V (n = 4), and TAMs (n = 4) in the tenofovir DF group as compared to the placebo group (n = 0, n = 2, and n = 1, respectively). Of note, RAP subjects from the tenofovir DF group were analyzed for resistance development following a longer period of drug exposure than subjects from the placebo group due to the inclusion of the open-label tenofovir DF period for subjects in the tenofovir DF group (mean time from baseline to analysis was 345 days for the tenofovir DF group vs. 275 days for the placebo group).

One subject in the tenofovir DF group developed K65R. This subject had HIV-1 subtype C. No subject developed HIV with K70E, a T69 insertion mutation, or Q151M in RT. TAMs and M184V emerged in HIV

from subjects treated in both arms of the study. These results are similar to the observations of resistance development in treatment-experienced, HIV-1 infected adults.

Data from large genotypic databases have shown the K65R mutation to be generally infrequent. One study[1] has described that HIV-1 subtype C viruses rapidly develop K65R resistance in vitro, and it is concluded that tenofovir based regimens will need close monitoring in subtype C infections by the possibility of selection of K65R. The MAH committed to monitor the literature and clinical trials for the occurrence of K65R among patients infected with subtype C HIV-1. Results of monitoring to be summarized in future PSURs for Viread and other tenofovir DF containing products, as appropriate (see letter of undertaking).

Thirty-six subjects originally randomized to the placebo group entered the open-label extension phase and received tenofovir DF. Sixteen of these subjects (44%) were evaluated for resistance development during the extension phase; HIV genotypic data were available for 14 subjects. NRTI resistance mutations developed in the HIV from 5/14 subjects (36%) and consisted of one TAM (2 subjects with T215F and 1 subject with L210W), A62V+M184V+T215Y (1 subject), or V75I (1 subject). Four of these 5 subjects had HIV with extensive NRTI resistance that included multiple TAMs at screening. Of the 14 subjects in this group, additional NNRTI resistance developed in HIV from 5 subjects and primary PI resistance developed in HIV from 4 subjects. Seven of these 14 subjects did not have further development of NRTI, NNRTI, or primary PI mutations in their HIV. No subject in this group developed K65R.

Long-Term Efficacy and Review of literature

In Study GS-US-104-0321, efficacy outcomes at Week 96 (n = 12) were as follows: the median change from baseline in plasma HIV-1 RNA was −1.97 log10 copies/mL, 58.3% of subjects had plasma HIV-1 RNA < 400 copies/mL, 41.7% of subjects had plasma HIV-1 RNA < 50 copies/mL, and the median change from baseline in CD4 cell count was 216 cells/mm3.

In Study GS-01-926, despite extensive prior ART experience, some children and adolescents were able to achieve and maintain virologic suppression and immunologic responses through 96 weeks of treatment with tenofovir DF as part of the ARV regimen.

In Study GS-01-927, treatment with tenofovir DF as part of the ARV regimen resulted in a decline in median plasma HIV-1 RNA from baseline to Week 108. This overall decline was seen despite high prior exposure and virologic failure/intolerance to multiple ARVs in all subjects. Similarly, the majority of subjects showed modest increases in CD4% during the study.

A review of paediatric efficacy data from published and unpublished literature (to 31 March 2010) describing non-Gilead-sponsored prospective and retrospective clinical studies was performed in support of this submission. Approximately 600 subjects received tenofovir DF in these studies presented in these literature articles. Clinically and immunologically stable subjects who switched to a tenofovir DF-containing regimen maintained virologic suppression and stable CD4 counts/percentages (e.g., Vigano et al., Rosso). Long-term (up to 5 years) maintenance of virologic suppression and immunologic control was demonstrated in subjects receiving tenofovir DF-containing regimens (Cerini).

2.3.2.3. Discussion

To support the extension of the indication for Viread in treatment-experienced adolescents infected with HIV, the MAH submitted the 48 weeks results of an ongoing study, GS-US-104-0321. This study is a Phase 3, double-blind, randomized, placebo-controlled study of the Safety and Efficacy of Tenofovir

[1] Brenner BG, Oliveira M, Doualla-Bell F, et al. HIV-1 subtype C viruses rapidly develop K65R resistance to tenofovir in cell culture. AIDS. 2006;20:F9-F13

DF as part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents. The study initiated in 2006 is characterized by an outdated design and was conducted exclusively in Brazil and Panama. No EU adolescents were included in the pivotal study and few data from EU children are available to support the application. The study population consists in highly treatment experienced adolescents.

The study failed to meet its primary efficacy endpoint. No significant differences were found in virologic response between patients treated with TDF or placebo (+OBR). When considering that 300mg TDF yielded similar exposure in adolescents as compared to adult patients, there is no reason to think that Viread would have different viral efficacy in these populations. The poor efficacy reported in the TDF arm is more likely the reflection of pejorative baseline characteristics (in terms of OBR susceptibility and TDF resistance) in adolescent included in the TDF arm. In the subgroup analysis for subjects with OBR GSS ≤ 1 (TDF n=18, placebo n=10) it was found that TDF exhibited some activity in this highly pretreated patients contrarily to placebo which favours this hypothesis.

Even though the lack of statistical difference between tenofovir and placebo could translate the inability of tenofovir to express its antiviral activity due to the extensive baseline NRTI resistance and the efficacy of the OBR, it is not considered acceptable to judge the benefit of a drug in adolescents on a basis of a "negative" study on virologic endpoints. This raised a major objection.

Due to the major objections raised the MAH has not pursued anymore the request to extend the therapeutic indication for the treatment of HIV-1 infected subjects 12 to < 18 years of age and with body weight ≥ 35 kg. The SmPC was updated to reflect the 48-week results of study GS-US-104-0321 (see section 3.5).

2.3.3. Clinical safety

The safety profile of tenofovir DF has been studied in 118 subjects (including 36 patients that switched from placebo to TDF in the phase 3 study), regardless of the dose and treatment duration. A total of 81 patients aged from 12 to < 18 years old, as requested in the indication, have been treated during 48 weeks with the proposed dose of 300mg once daily in the pivotal study. This study is ongoing and the data are only available for completed randomized period of 48 weeks.

The number of patients with any AE, serious AE, grade ≥3 AE, and withdrawal due to any AE was significantly higher in the tenofovir DF group compared to the placebo group. No death has been reported during the phase 3 study. One death occurred during paediatric development programme in 11-year old boy affected by subarachnoid haemorrhage leading to cardiac arrest and death, previously treated for an episode of staphylococcal infection. No other information on infection status of this patient was given.

The most frequently represented SOCs with tenofovir DF were: Infections And Infestations in more than 90% of subjects, Gastrointestinal Disorders with 64.4% AEs, and Mediastinal, thoracic and respiratory disorders with 35.6% of affected children. A significantly higher rate of AEs for these SOCs was reported in tenofovir-treated subjects compared with placebo group. Vomiting and nausea were reported more than 3-fold. In addition, twice as much of patients experienced sinusitis, upper respiratory infection and diarrhoea in the tenofovir group compared to placebo.

A statistically significant higher number of severe AEs was reported in tenofovir group compared to placebo arm (22.2% vs 7.1%), including 8 cases of infections, 3 pneumonia, 2 sinusitis and 2 pneumocystis jiroveci pneumonia and 1 case of cryptococcosis infection. In addition, one severe case of proteinuria has been reported and is of concern.

One discontinuation due to vomiting, considered to be related to study drug, occurred in tenofovir arm while no discontinuation was reported in placebo arm.

The gastrointestinal disorders, and notably vomiting, were of particularly high frequency in the tenofovir group (64,4% including 35,6% of vomiting) compared to placebo group (38,1% including 11,9% of vomiting). Given this high percentage of vomiting, the long-term tolerance of tenofovir DF is questionable in real life. Additionally, more discontinuations could be expected, which could lead to resistance emergence.

Regarding renal toxicity, renal TEAEs were more frequent in tenofovir group (13,3%) compared to the placebo group (10%). Seven cases of grade 1 proteinuria have been reported in the tenofovir group compared to 2 cases in the placebo group. One case of proteinuria was reported as serious AE. Estimated Creatinine Clearance decreased during the blinding period in both groups but more significantly in tenofovir group (-11 mL/min/1.73 vs -5,35 mL/min/1.73). When considering the updated (from the cut off) safety data from study 0321 where 35 patients are still ongoing in the study, no new AEs were reported related to renal safety. However, treatment-emergent grade 1 hypophosphatemia in 2 patients, 11 grade 1 proteinuria and 1 more case of grade 3 proteinuria are to be noted.

With regard to bone toxicity, 5 cases of osteopenia, of which 2 cases in patients previously treated by placebo, were considered to be related to study drug in the tenofovir group compared to only one case in the placebo group.

In addition, 2 cases of fracture have been reported including a case of 15-year old girl noted to have osteopenia at baseline. Although this fracture was not considered to be related to study drug, subject's bone frailty due to osteopenia could be a risk factor facilitating the occurrence of the fracture.

Regarding bone parameters, although there was no significant difference in the percent change from the baseline to week 24 and 48 in spine BMD and total BMD, a trend of lower increase was noted for tenofovir group compared to placebo as well as the decrease of total body BMD Z-score. Week 96 data available showed for 28 subjects decrease in BMD Z-scores for both spine (mean change of −0.341, median change of −0.353) and total body (mean change of −0.458, median change of −0.407). In addition, 6 subjects in the tenofovir DF group and 1 subject in the placebo group had decreases from baseline in spine BMD of > 4% at Week 48.

A placebo-controlled study in hepatitis B virus in 106 adolescents that could provide further information on safety is ongoing and data are not yet available. A total of 19 SAEs have been reported, including one hand fracture and 1 nephrectomy, but taking into account that treatment assignment remains blinded, it is not known whether it is related to the active treatment.

Furthermore, safety data from Study 0352 in patients 2 to <12 years-old was presented. In this study no fractures were reported. The percentage increases from baseline in total body BMD were smaller in the tenofovir DF group than in the stavudine or zidovudine group (median changes at Week 48: 1.220% versus 2.679%, p = 0.043), and there was a modest reduction in total body BMD Z-score in the tenofovir DF group (median change at Week 48: −0.215) compared to no change in the stavudine or zidovudine group. In the All TDF group, the median changes from baseline to Week 96 were statistically significant (median change at Week 96: −0.267). From baseline to Week 96, the clinical status category for total body BMD Z-score worsened for 11 subjects (n = 64).

According to a Guidelines for the use of ART agents in HIV-1-infected adults and adolescents, "youth who are in their growth spurt period (i.e., Tanner Stage III in females and Tanner Stage IV in males) and who are using adult or paediatric dosing guidelines and those adolescents whose doses have been transitioned from paediatric to adult doses should be closely monitored for medication efficacy and toxicity". In study GS-US-104-0321, the information on Tanner stage at baseline was available in only

30 out of 87 patients (information on Tanner stage was requested post-hoc in response to the query from PDCO at the time of the assessment of the Viread PIP): 17 subjects in tenofovir DF group, and 13 subjects in placebo group (All TDF group contained 25 subjects). Following CHMP request the MAH performed an analysis by Tanner strata, e.g. Tanner ≤ 3 vs. Tanner ≥ 4. Data on subjects according to Tanner stage are too limited to allow any firm conclusion regarding bone toxicity. However, a decrease in spine BMD, spine BMD Z-score, total body BMD and total body BMD Z-score has been reported in subjects with Tanner stage ≤ 3. These results may indicate that the bone toxicity may be more pronounced in younger adolescents with the use of tenofovir DF.

The MAH was requested to further discuss the results of bone markers in the context of values seen in a normal adolescent population. Overall, the MAH response was merely descriptive. Available evidence suggests that HIV-infected children are at risk of poorly mineralized bones. The mechanisms responsible for these alterations are believed to be multifactorial, involving both nutritional, disease related processes and antiretroviral treatment. The design of study 321 does not permit to address the ability of treatment interventions (e.g. ensuring adequate vitamin D and calcium intake, and supplementing these nutrients when necessary) to ameliorate some of the bone density effects of the disease and certain treatments. The MAH has committed to review available data and to provide treatment recommendations on treatment interventions (threshold level for initiating supplementation with vitamin D and calcium and dosing recommendation) for patients receiving tenofovir DF (see letter of undertaking).

Loss of bone mineral density seems higher in the tenofovir DF arm than in the placebo arm. The degree of bone mass loss is also higher in female patients than in males. Overall, the interpretation of DEXA results in the paediatric population should be done with caution due to limitations of DEXA measurements in children. Therefore, a child may most appropriately act as his or her own control, with serial scans to monitor progress. Scan intervals of less than six months should only be considered in special situations such as monitoring the response to a pharmacological intervention, and for most patients annual scans should suffice (Fewtrell MS, 2003). For patients receiving tenofovir, yearly radiologic assessment of bone mineral density by DEXA is indicated (Kim RJ et al, 2010).

Moreover, post-marketing data on tenofovir DF use in children, including 31 renal disorders out of 77 paediatric cases, four reports of rickets, and 6 cases of severe BMD decrease are not reassuring.

In conclusion, the main safety concern of tenofovir DF in adult population is related to renal and bone toxicity. Similar findings have been observed in the current application for the paediatric population. Although the medical need for additional backbone for paediatric use is acknowledged the safety profile of tenofovir is a concern. Therefore, the CHMP raised the following major objection: The bone toxicity of this drug makes it "a priori" a non optimal candidate for the adolescent population as impairment of peak bone mass acquisition is of particular concern for this population. The observed trend for a lower increase of total BMD in the tenofovir group compared to the placebo group as well as the occurrence of osteopenia after a medium term duration reinforce this concern, especially because only medium term data are available.

The CHMP considers that these data are not reassuring to allow the approval of the indication in children from 12-17 year-old, all the more that only limited data are available in term of exposure and duration.

Due to the major objections raised the MAH has not pursued anymore the request to extend the therapeutic indication for the treatment of HIV-1 infected subjects 12 to < 18 years of age and with body weight ≥ 35 kg. The SmPC was updated to reflect the 48-week safety results of study GS-US-104-0321 (see section 3.5).

2.4. Pharmacovigilance system

2.4.1. Risk management plan

The degree to which tenofovir causes bone changes by direct osteoclast/osteoblast toxicity and/or affects proximal renal tubuli is unknown. The MAH was asked to discuss whether bone safety should be considered as an identified risk and to update pharmacovigilance plan and minimisation activities accordingly.

The MAH acknowledged the inclusion of bone events/loss of bone mineral density (BMD) as an important identified risk to the Viread RMP.

Additional pharmacovigilance actions associated with the risk of bone events/loss of BMD will include ongoing long-term studies in which BMD is being measured by dual-energy x-ray absorptiometry (DEXA) in adult and pediatric subjects for both HIV-1 and hepatitis B virus (HBV) indications. The planned, randomized, controlled clinical study of HBV infected subjects 2 to < 12 years of age (Study GS-US-174-0144) will be used to elucidate the relationship between BMD changes and proximal renal tubulopathy, in order to contribute to the understanding of the mechanism(s) leading to decreases in BMD, and potentially support the development of appropriate management recommendations. *In vitro* non-clinical studies to be conducted to evaluate a potential inhibitory effect of tenofovir DF on absorption of phosphate in the gastrointestinal tract.

The routine risk minimization activities include an additional warning and description of data on BMD in the Viread SmPC, as described below:

Section 4.4 Special Warnings and Precautions for Use

Paediatric population: Viread may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).

Section 5.1 Pharmacodynamic properties

Paediatric population: (…) In patients who received treatment with tenofovir disoproxil fumarate or placebo, mean lumbar spine BMD Z-score was -1.004 and -0.809, and mean total body BMD Z-score was -0.866 and -0.584, respectively, at baseline. Mean changes at week 48 (end of double-blind phase) were -0.215 and -0.165 in lumbar spine BMD Z-score, and -0.254 and -0.179 in total body BMD Z-score for the tenofovir disoproxil fumarate and placebo groups, respectively. The mean rate of BMD gain was less in the tenofovir disoproxil fumarate group compared to the placebo group. At week 48, six adolescents in the tenofovir disoproxil fumarate group and one adolescent in the placebo group had significant lumbar spine BMD loss (defined as > 4% loss). Among 28 patients receiving 96 weeks of treatment with tenofovir disoproxil fumarate, BMD Z-scores declined by -0.341 for lumbar spine and -0.458 for total body.
The efficacy and safety data derived from this study do not support the use of Viread in adolescents.

An ongoing RMP update and evaluation is currently being performed (submission in parallel with the PSUR). Following the assessment of the clinical data submitted during this variation procedure, further updates in the RMP as mentioned above are required regarding bone toxicity risk. These updates on the RMP should be submitted at the time of the next PSUR submission.

2.5. Changes to the product information

Section 4.1 "Therapeutic indication"

This section was not updated. The MAH's initially proposed to extend the approved indication to include treatment experienced adolescents from 12 to < 18 years of age and with body weight ≥ 35 kg. Due to the major objections raised by the CHMP (no statistical difference observed between tenofovir and

placebo treatment and concerns on bone toxicity) the claim of the MAH was not accepted. The MAH not pursued anymore the request to extend the therapeutic indication.

Section 4.2 "Posology and method of administration"

This section was updated to reflect the clinical data available in HIV-1 infected adolescents. These data are inadequate to support the use of tenofovir disoproxil fumarate in this population. A reference was included to sections 4.4 and 5.1.

A further sentence was included to mention that no data are currently available in paediatric patients infected with chronic hepatitis B.

Section 4.4 "Special warnings and precautions for use"

A warning was included concerning bone toxicity. Viread may cause a reduction in BMD. The effects of tenofovir disoproxil fumarate-associated changes in BMD on long-term bone health and future fracture risk are currently unknown (see section 5.1).

Section 4.6 "Pregnancy and lactation"

This section was updated on CHMP request to comply with the latest available QRD templates version 7.3.1 .

Section 4.8 "Undesirable effects"

This section was updated to reflect the study on paediatric population.

Section 5.1 "Pharmacological properties"

This section was updated to reflect the results of study GS-US-104-032. Furthermore, data on the BMD loss observed in this study was included.

This section was further updated to include a sentence concerning the deferral of the obligation to submit the results of studies with tenofovir disoproxil fumarate in one or more subsets of the paediatric population in HIV and chronic hepatitis B.

Section 5.2 "Pharmacokinetic properties"

This section was updated with pharmacokinetic data.

A further statement was included to mention that pharmacokinetic studies have not been performed in children under 12 years or with renal impairment.

5.3 Preclinical safety data

This section was updated with bone toxicity data in young adult rats and dogs and in juvenile infected monkeys.

Annex IIB Conditions of the marketing authorisation

The sentence on pharmacovigilance system was updated according to QRD templates.

The PSUR cycle was corrected to reflect the 6 month PSUR cycle. Following evaluation of PSUR 13 (period covered: 01.04.09 - 31.03.10) the CHMP considered that due to the extension of indication of Viread in HBV patients with decompensated liver disease, the PSUR should follow a 6 month cycle.

3. Benefit risk assessment

To support the extension of the indication for Viread in treatment-experienced adolescents infected with HIV, the MAH submitted the 48 weeks results of an ongoing study, GS-US-104-0321. This study is a Phase 3, double-blind, randomized, placebo-controlled study of the Safety and Efficacy of Tenofovir DF as Part of an Optimized Antiretroviral Regimen in HIV-1 Infected Adolescents. The study initiated in 2006 is characterized by an outdated design and was conducted exclusively in Brazil and Panama. No EU adolescents were included in the pivotal study and few data from EU children are available to support the application. The study population consists of highly treatment experienced adolescents.

The study failed to meet its primary efficacy endpoint. No significant differences were found in virologic response between patients treated with TDF or placebo (+OBR). The 300mg TDF yielded to similar exposure in adolescents as compared to adult patients. The poor efficacy reported in the TDF arm could reflect the pejorative baseline characteristics (in terms of OBR susceptibility and TDF resistance) in adolescent included in the TDF arm. However, concerns remain to judge the benefit of a drug in adolescents on a basis of a "negative" study on virologic endpoints.

As regards the safety, the bone toxicity of this drug makes it "a priori" a non optimal candidate for the paediatric population. The trend for a lower increase of total BMD in the tenofovir group compared to the placebo group as well as the occurrence of osteopenia after a medium term duration raises concerns on bone toxicity. Furthermore, no long term data are available in this population.

Overall, the study submitted raised concerns on the safety and efficacy of Viread in adolescents and cannot be regarded as an adequate basis for the extension of indication of Viread in this target population and the CHMP raised major objections.

Following the major objections raised by the CHMP the MAH has not pursued anymore the request to extend the therapeutic indication to include treatment-experienced adolescents 12 to < 18 years of age and with body weight ≥ 35 kg. The results of this study are reflected in the SmPC as detailed in section 3.5.

4. Recommendation on PIP

PIP partly completed

The CHMP reviewed the available paediatric data of study GS-US-104-0321 in adolescents subject to the agreed Paediatric Investigation Plan and the results of this study are reflected in the SmPC.

5. Conclusion

The MAH has submitted an extension of the therapeutic indication for the treatment of HIV-1 to include treatment-experienced adolescents aged 12 to 18 years old and with body weight ≥ 35 kg.

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II(90)

Due to the major objections raised by the CHMP the MAH has not pursued anymore an extension of indication.

On 17 February 2011 the CHMP considered the variation:

"Update of sections 4.2, 4.4, 4.6, 4.8 5.1, 5.2 and 5.3 based on the 48-week results of a safety and efficacy study GS-US-104-0321 in treatment-experienced adolescents aged 12 to 18 years old. Annex II was updated to reflect the 6 month PSUR cycle and to be in line with QRD templates"

to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Annex II.

Follow-up measures undertaken by the marketing authorisation holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area	**Description**	**Due date**
Clinical	Monitoring of the literature and clinical trials for the occurrence of K65R among patients infected with subtype C HIV-1. Results of monitoring to be summarized in future PSURs for Viread and other tenofovir DF containing products, as appropriate.	PSUR submissions for Viread and other tenofovir DF containing products, as appropriate
Clinical	Treatment interventions (threshold level for initiating supplementation with vitamin D and calcium and dosing recommendation) for patients receiving tenofovir DF. Review of available data and treatment recommendations to be submitted with the next PSUR	With the next Viread PSUR submission: 31 May 2011

6. Glossary

AE - Adverse Event
ANRS - French National Agency for AIDS Research
ART - antiretroviral therapy
ARV - antiretroviral
AUCtau - area under the concentration versus time curve from time zero (predose) over the blood mononuclear cells
BMD - Bone Mineral Density
Cmax - maximum observed concentration of drug in serum, plasma, or peripheral
DEXA - dual energy X-ray absorptiometry
C50 median effective dose
EMA - European Medicines Agency
EU - European Union
GSS - genotypic sensitivity score
HIV-1 - human immunodeficiency virus type 1
ITT - intent-to-treat (population)
LOCF - last observation carried forward
M = E - missing = excluded
MAH - Marketing authorisation holder
NNRTI - nonnucleoside reverse transcriptase inhibitor
NOAEL - no observed adverse effect level
NOEL - no observed effect level
NRTI - nucleoside reverse transcriptase inhibitor
NtRTI - nucleotide reverse transcriptase inhibitor
OBR - optimized background regimen
PK – pharmacokinetic
PR – protease
RT - reverse transcriptase
SmPC - Update of Summary of Product Characteristics
TDF - Tenofovir disoproxil fumarate (tenofovir DF)
US - United States