20 September 2012
EMA/797671/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VIREAD

International non-proprietary name: TENOFOVIR DISOPROXIL FUMARATE

Procedure No. EMEA/H/C/000419/X/0105/G

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Product information

Name of the medicinal product:	Viread
Applicant:	Gilead Sciences International Ltd. Granta Park, Abington Cambridge CB21 6GT United Kingdom
Active substance:	tenofovir disoproxil (as fumarate)
International Nonproprietary Name/Common Name:	tenofovir disoproxil
Pharmaco-therapeutic group (ATC Code):	Nucleoside and nucleotide reverse transcriptase inhibitors (J05AF07)
Therapeutic indication(s):	Viread is indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infected adults over 18 years of age. The demonstration of benefit of Viread in HIV 1 infection is based on results of one study in treatment naïve patients, including patients with a high viral load (> 100,000 copies/ml) and studies in which Viread was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (< 10,000 copies/ml, with the majority of patients having < 5,000 copies/ml). The choice of Viread to treat antiretroviral experienced patients with HIV 1 infection should be based on individual viral resistance testing and/or treatment history of patients. Hepatitis B infection Viread is indicated for the treatment of chronic hepatitis B (see section 5.1) in adults with: - compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis - decompensated liver disease (see sections 4.4, 4.8 and 5.1).
Pharmaceutical form:	Film-coated tablet and granules
Strengths:	123 mg, 163 mg, 204 mg, 245 mg, 33 mg/g
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	3 x 30 tablets, 30 tablets and 1 x 60 g bottle (granules)

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List of abbreviations

AE	Adverse events
ALT	alanine aminotransferase
ARV	antiretroviral
AUC	Area under the curve
BMD	bone mineral density
CD4	cluster determinant 4
CDC	Centre for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum observed concentration of drug in plasma
d4T	stavudine
DXA	Dual-energy X-ray absorptiometry
EC	European Commission
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
HAART	Highly active antiretroviral therapy
HBV	hepatitis B virus
HIV-1	human immunodeficiency virus type 1
HLA	Human Leukocyte Antigen
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MAH	Marketing Authorisation Holder (
NNRTI	nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
PBT	persistent, bioaccumulative and toxic
PDCO	Paediatric Committee
PI	protease inhibitor
PIP	paediatric investigation plan
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
RMP	risk management plan
RNA	ribonucleic acid
SAG	Scientific advisory group
SmPC	Summary of Product Characteristics
TAM	hymidine analog-associated mutation
TDF	Tenofovir disoproxil fumarate (tenofovir DF, Viread)
US	United States
ZDV	zidovudine

1. Scientific discussion

1.1. Introduction

Problem statement

Tenofovir is a widely used backbone regimen in adult patients due to its virological efficacy and high genetic barrier. Moreover, tenofovir disoproxil fumarate is a once daily regimen, which is of interest especially in children. Given that the current backbone regimens are not only limited but also have limiting factors (hypersensitivity requesting HLA testing, anaemia, lipodystrophy), tenofovir represents an additional therapeutic option in children.

About the product

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 US (26 October 2001), 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 aged 18 years and older.

Viread was subsequently approved for the treatment of chronic hepatitis B in EU (23 April 2008) and US.

Following approval for use in adults, clinical development programs are being undertaken in HIV-1 and HBV infected paediatric subjects. In the EU, a paediatric investigation plan (PIP) for Viread was agreed on 08 February 2010 (EMEA-000533-PIP01-08, Decision Ref. EMA/63121/2010 P/18/2010).

In the United States (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. In Europe, following the major objections raised by the CHMP, mainly driven by the lack of reassurance on the renal and bone toxicity of the drug in this population together with inadequate efficacy demonstration, the MAH has not at that time requested to extend the therapeutic indication to include treatment-experienced adolescents 12 to < 18 years of age and with body weight ≥ 35 kg.

The development programme/Compliance with CHMP Guidance /Scientific Advice

N/A

Type of application and other comments on the submitted dossier

The application relates to a new indication, addition of new strengths and a new pharmaceutical form and consequential changes to the Product Information.

- HIV-1 infection and treatment in paediatric patients

As underlined by the applicant, the pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of ARV therapy 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 (ZDV) and other ARV medications in most perinatally infected children
- Age-specific differences in cluster determinant 4 (CD4) cell counts
- Changes in pharmacokinetic parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance
- Differences in the clinical and virologic manifestations of perinatal HIV infection secondary to the occurrence of primary infection in growing, immunologically immature persons
- Special considerations associated with adherence to ARV treatment for infants, children, and adolescents

Processes involved in growth and development during childhood and adolescence can affect the pharmacokinetics of drugs, and developmental changes associated with aging and growth are often not linear. Recommendations for when to initiate therapy are more aggressive in paediatric patients than in adults because HIV-1 disease progression is more rapid than in adults.

The standard of care for treatment of HIV-1 infection involves the use of a combination of ARV agents, typically a combination of at least 3 drugs, including a non nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) and 2 agents from the nucleoside reverse transcriptase inhibitor (NRTI)/NtRTI class. In recent years, new ARVs have been approved with improved safety profiles and convenient dosing regimens. However, based on results of controlled clinical trials, it is apparent that not all regimens are equivalent in terms of potency or toxicity.

International treatment guidelines list TDF as a preferred NRTI/NtRTI in an ARV regimen for initial therapy in HIV-1 infected adults. Tenofovir DF is listed as a preferred NRTI/NtRTI in an ARV regimen for initial therapy in HIV-1 infected postpubertal or Tanner stage 4 adolescents in the US. However, 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. In Europe, treatment guidelines indicate that TDF 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 TDF can be used as first-line therapy in adolescents (particularly as part of a fixed-dose combination, ie, Truvada or Atripla).

- Content of the submission

Data are provided in this submission to support the use of new formulations of TDF: reduced-strength TDF tablets (150-, 200-, and 250-mg strengths) and a TDF granules formulation. Overall, the 5 formulations/strengths (150-, 200-, 250-, and 300-mg tablets, and the granules) of TDF allow once-daily dosing for patients aged from 2 years and weighing at least 10 kg.

Early clinical studies of TDF in HIV-1 infected paediatric subjects were conducted in the US (GS-01-926, n = 18 and GS-02-983, n = 12) and France (GS-01-927, n = 7). Tenofovir DF formulated as an aqueous suspension was found to be unpalatable in a single-dose study (Study GS-02-983). Tenofovir DF 75-mg strength tablets were used in Studies GS-01-926 and GS-01-927; a dose of four 75-mg strength tablets was shown to be bioequivalent to a single dose of the 300-mg commercial tablet formulation in a clinical study in healthy adults (GS-00-914). The granules formulation has been

developed to allow for dosing flexibility and ease of administration in small children. It can also be used for older subjects who are unable to swallow tablets. Tenofovir DF granules is formulated to be mixed with soft food (ie, food that does not require chewing) and swallowed, because TDF is known to have strong, long-lingering, bitter, and sour aftertastes.

A bioequivalence study between the granules and the commercial tablet formulation in healthy adults (GS-US-104-0312) is provided in the current application.

Pre-study feasibility surveys were used to identify reputable HIV paediatric clinician researchers to conduct Phase 3 studies (GS-US-104-0321 in subjects 12 to < 18 years of age, and Study GS-US-104-0352 in subjects 2 to < 12 years of age). Documentation of experience in conducting HIV paediatric clinical studies and access to qualified facilities for bone assessments (dual-energy x-ray absorptiometry [DEXA] scanners) were required to be considered eligible.

The principal pharmacokinetic, efficacy, and safety data for TDF in HIV-1 infected subjects 2 to < 12 years of age are from an ongoing, long-term, Phase 3 clinical study sponsored by Gilead Sciences. Study GS-US-104-0352 is an open-label, comparator-controlled study in virologically suppressed subjects who were receiving a HAART regimen containing stavudine (d4T) or ZDV at study entry.

Study GS-US-104-0352 had a randomized design to provide a controlled assessment of the efficacy and safety of TDF compared to d4T or ZDV, each given in combination with a background ARV regimen. In the TDF group, TDF granules 8 mg/kg (up to 300 mg/day) was given for those subjects weighing ≤ 37 kg or for those unable to swallow TDF 300-mg tablets, and TDF 300-mg tablets were given for those subjects weighing > 37 kg who were able to swallow the tablets. Following completion of the randomized treatment period, eligible subjects were given the option to participate in 2 consecutive 96-week study extensions (collectively referred to as the extension phase) to receive open-label TDF for a total duration of up to 240 weeks.

Information on paediatric requirements

The paediatric investigation plan (PIP) for Viread was agreed on 08 February 2010 (EMEA-000533-PIP01-08 with PDCO compliance opinion number: EMA/652760/2011). 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.

1.2. Quality aspects

1.2.1. Introduction

This grouped application includes two types of pharmaceutical forms.

The first finished product in this application is presented as granules, an immediate release dosage form containing 4% of drug substance tenofovir disoproxil fumarate (40 mg/g), equivalent to 3.27% tenofovir disoproxil (33 mg/g). It is packaged in 250 ml high density polyethylene bottles.

The second finished product are immediate release tablets containing tenofovir disoproxil fumarate in three dosage strengths of 150 mg / 200 mg / 250 mg, equivalent to 123 mg / 163 mg / 204 mg

tenofovir disoproxil, respectively. The tablets are packed in high density polyethylene bottles with a polypropylene child-resistant cap and silica gel as desiccant.

The composition is described in section 6.1. of the SmPC for each of the dosage forms.

1.2.2. Active Substance

Reference is made to the authorised dosage form, Viread 245 mg film-coated tablets. No new information on the active substance has been submitted with this line extension.

1.2.3. Finished Medicinal Product

GRANULES

The granules are composed of mannitol (filler), hydroxypropyl cellulose (binder), ethylcellulose (microencapsulation agent) and silicon dioxide. (antistatic agent). Purified water, cyclohexane and polyethylene are used as processing aids, not present in the finished product. The excipients comply with compendial requirements. Acceptable in-house specifications are provided for cyclohexane and polyethylene.

Pharmaceutical Development

The aim of the development was to obtain a taste masked oral formulation of tenofovir disoproxil fumarate suitable for paediatric administration that would allow flexibility in dosing to cover a posology of minimum 40 mg – maximum 300 mg of drug substance (as fumarate). The formulation also had to be stable and bioequivalent to the currently marketed Viread tablet.

The chosen formulation are taste masked granules to be sprinkled onto food/drink. The taste masking properties are achieved thanks to using ethylcellulose microencapsulation obtained by coacervation. The suitability of the excipients selected for a paediatric formulation has been discussed. The choice for coacervation using cyclohexane and polyethylene as processing aids has been well justified. The taste masking can be considered as adequately demonstrated even when the finished product is mixed with soft food. The development of the dissolution method has been provided. Dissolution profiles of representative batches have been provided. The proposed measuring device (a dosing scoop) is adequate for intended use.

The formulation used during phase 3 clinical studies is the same that the one used for marketing.

Adventitious agents

None of the excipients used in the manufacture of the finished product are of human or animal origin.

Manufacture of the product

The manufacturing process was sufficiently described. It consists of wet granulation of the drug substance, sizing of the granules, microencapsulation of the granules via coacervation, addition of external phase and packaging. All critical steps are sufficiently controlled by adequate in-process tests.

The process is considered to be a non-standard manufacturing process.

Holding times of 6 months are proposed and justified for bulk in-process materials (bulk granules and bulk final blend). The materials are stored in a temperature controlled facility, in defined containers. To confirm the granted holding times, one batch of Viread granules, prepared from intermediates/bulk stored 6 months each, will be placed on stability and followed until the end of shelf-life (reference is made to chapter 2.2.6 of this report, Recommendations).

Full validation data from three consecutive validation batches have been provided and include validation of re-blending and primary packaging. The data shows that the product can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The drug product specifications cover appropriate parameters for this dosage form. The tests include identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dose units (Ph.Eur.), uniformity of mass of delivered doses from multidose containers (Ph.Eur.), minimum fill, dissolution and microbiological purity (Ph.Eur.).

Description and validation of the analytical methods have been adequately presented.

Batch analysis has been performed on seven batches. The batch analysis results show that the finished product meets the specifications proposed and confirm consistency and uniformity of manufacture.

Stability of the product

Thirty-six months of data on three primary stability batches are available at the long-term (25°C/60% RH) and intermediate (30°C/65% RH) storage conditions and six months of data at the accelerated storage conditions (40°C/75% RH). Photostability of the granules has been assessed as per ICH guideline on photostability testing of new drug substances and products. Additional forced degradation studies in acidic, basic and oxidative conditions will be performed; these studies are not considered critical with respect to product stability behaviour and known degradation patterns of the active substance (reference is made to chapter 2.2.6 of this report, Recommendations).

An in-use shelf-life of 30 days has been established, based on results of an in-use stability study. Stability studies conducted on the drug product comply with the recommendations of the CHMP/ICH guidelines.

The parameters of the product batches are identical to the batches proposed for marketing; in addition, the batches were packed in the primary packaging proposed for marketing.

Appearance, assay, degradation product content, dissolution, and water content were determined at each scheduled time point. The finished product remained within the specification in all cases. The analytical procedures used were stability indicating.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable, with the special condition of "Do not store above 25°C".

LOW STRENGTH TABLETS FOR PAEDIATRIC USE

The lower strength Viread tablets are composed of lactose monohydrate and microcrystalline cellulose, pregelatinised starch (binder), croscarmellose sodium (disintegrant), magnesium stearate (lubricant) and a commercially available white film-coating mixture. All excipients, including components of the coating mixture, are compendial.

Pharmaceutical development

The lower strength immediate release Viread tablets were developed for paediatric use, to be used by children aged from 6 to 12 years. The tablets are white, with shape and debossing depending on the tablet strength. Tablet size acceptability by the target paediatric population will be assessed in an ongoing clinical study. The tablets are packed in high density polyethylene bottle with a polypropylene child-resistant cap and silica gel as a desiccant.

No specific development has been done for the Viread 123 mg / 163 mg / 204 mg tablets as the proposed tablets have the same qualitative and quantitative composition as the authorised Viread 245 mg tablet strength and are dose/weight proportional. Optimisation was performed, to adapt the manufacturing process of the 245 mg tablet to the other dosage strengths. Similarity of the dissolution profiles of Viread 123 mg / 163 mg / 204 mg / 245 mg tablet strengths is considered demonstrated at different pH and supports the biowaiver.

The formulation used during phase III clinical studies is the same that the used for marketing. Bioequivalence study was performed showing bioequivalence between the early clinical formulation and the proposed commercial formulation.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Magnesium stearate is of vegetable origin.

Manufacture of the product

The manufacturing process consists of wet granulation of the drug substance with excipients, drying and calibration of the granules, addition of external phase, compression (tableting), film coating and packaging. All critical steps are sufficiently controlled by adequate in-process tests.

Holding times of 6 months are proposed and justified for bulk in-process materials (final blend, uncoated tablets and coated tablets). The materials are stored in a temperature controlled facility, in defined containers. To confirm the granted holding times post approval, one batch of the 123 mg Viread tablet, prepared from intermediates/bulk stored 6 months each, will be placed on stability and followed until the end of shelf-life (reference is made to chapter 2.2.6 of this report, Recommendations).

The process is considered to be a standard manufacturing process.

The blend manufacturing is considered validated as this blend is identical to the already marketed tablet strength of 245 mg. The compression step and coating step will be validated prior to commercialisation.

Product specification

The finished product release specifications include appropriate tests for this dosage form. The parameters tested are appearance, identification (HPLC, UV), water content (Ph.Eur.), assay (HPLC),

impurities and degradation products (HPLC), uniformity of dosage units (Ph.Eur., weight variation), dissolution, titanium dioxide identification (if tested, Ph.Eur.) and microbiological purity (Ph.Eur.).

The analytical methods are sufficiently described and properly validated.

Batch analysis data are presented for three batches of each strength of Viread tablets, 123 mg, 163 mg and 204 mg. The batch analysis results show that the finished product meets the specifications proposed and confirm consistency and uniformity of manufacture.

Stability of the product

Twelve months of data on three primary stability batches of each tablet strength are available at the long-term (25°C/60% RH) and intermediate (30 °C/75% RH) storage conditions and six months of data at the accelerated storage conditions (40 °C/75% RH). Samples stored at 25 °C/60% RH are not scheduled to be tested unless the drug product exceeds or is likely to exceed the specification acceptance limits at 30 °C/75% RH. The long-term stability studies are conducted according to matrixing design, which is acceptable.

The parameters of the product batches are identical to the batches proposed for marketing; in addition, the batches were packed in the primary packaging proposed for marketing.

No changes in physicochemical properties have been observed in Viread tablets, 123 mg, 163 mg and 204 mg, following 12 months of storage at 30 °C/75% RH and 6 months at 40 °C/75% RH. The finished product remained within the specification acceptance limits for appearance, assay, degradation product content, dissolution, and water content. The analytical procedures used were stability indicating.

Comparative stability data for the authorised strength (245 mg) show similar stability behaviour among the four tablet strengths and support the assigned shelf-life.

An in-use shelf-life of 30 days has been established, based on results of an in-use stability study. Stability studies conducted on the drug product comply with the recommendations of the CHMP/ICH guidelines.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

1.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

1.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

1.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1) One batch of the Viread granules drug product, prepared from intermediate/bulk stored 6 months each, should be placed on stability and followed until end of shelf-life.

2) One batch of the 123 mg Viread tablet, prepared from intermediates/bulk stored 6 months each, should be placed on stability and followed until end of shelf-life.

3) Perform additional forced-degradation studies of Viread 33 mg/g granules in acidic, basic, and oxidative conditions using HPLC method TM-112. The study results should be provided by 31 January 2013.

1.3. Non-clinical aspects

A nonclinical overview summarizing the key available data with a view to the proposed indication in the paediatric patients aged 2-12 years was submitted.

As already mentioned in the currently approved SmPC, bone effects (decreased BMD) were reported in adult humans. In children, cases of hypophosphatemia, decreased BMD and osteomalacia were reported. In addition, data on long-term effects on bone and growth and on the reversibility of these effects is currently insufficient, notably in the paediatric population.

Bone was identified as a target organ in repeat-dose toxicity studies performed in rats, dogs and monkeys with decreased serum phosphate concentrations. Bone toxicity was diagnosed as osteomalacia in monkeys, and reduced bone mineral density (BMD) in rats and dogs. The safety margins for bone effects determined in rats and dogs were weak. As explicitly mentioned in the "guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications" (EMEA/CHMP/SWP/169215/2005), the skeletal system develops up to adulthood. The applicant mentions that rats were 6 weeks and dogs 5-7 months at study initiation; however, this does not represent the whole paediatric population for which the extension of indication is sought, particularly the youngest patients. Additionally, there are some issues regarding the relevance of the studies published by Van Rompay et al (2004, 2008) for risk assessment of tenofovir in these patients. Indeed, they were not designed as toxicity studies, and there were confounding factors which could have attenuated/ masked bone toxicity (e.g. phosphate supplementation). Therefore, the Applicant was requested to re-discuss these juvenile monkey studies based on the most clinically relevant individual data in terms of treatment protocol and examinations (please identify animals according to their identification number) to conclude on the long-term bone toxicity of Viread and its consequences on growth, and on the reversibility of these findings with a discussion on the potential role of phosphate supplementation. The applicant provided a detailed review of the most relevant data, showing induction of bone lesions in some monkeys treated chronically at high dose levels of tenofovir. These lesions improved notably upon dose reduction. On the basis of these data and considering that the issue of reversibility will be addressed in the Risk Management Plan (see discussion in the clinical part), it was considered that there is no need for an additional juvenile toxicity study.

No other non clinical information was submitted and this is acceptable by the CHMP.

1.3.1. Ecotoxicity/environmental risk assessment

An ERA has been submitted in accordance with Article 8(3) of Directive 2001/83 requirements.

Table 1. Summary of main study results

Substance (INN/Invented Name): tenofovir disoproxil fumarate				
CAS-number (if available):				
PBT screening		**Result**		**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.992 at pH 4 1.18 at pH 7 could not be determined at pH 10 due to the instability of TDF in the buffer phase		Potential PBT: no
Phase I				
Calculation	**Value**	**Unit**		**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	1.5	µg/L		> 0.01 threshold
Phase II Physical-chemical properties and fate				
Study type	**Test protocol**	**Results**		
Adsorption-Desorption	OECD 121	K_{oc} = 18 L/kg		
Ready Biodegradability Test	OECD 301	Not readily biodegradable		
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	TDF rapidly underwent primary degradation converting to several degradation products		
Phase IIa Effect studies				
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**
Algae, Growth Inhibition *Pseudokirchneriella subcapitata*	OECD 201	NOEC EC_{50}	14 47	mg/L mg/L
Daphnia, acute immobilisation test / Daphna magnia	OECD 202	NOEC EC_{50}	98 ≥ 98	mg/L mg/L
Fish Acute Toxicity Test Rainbow trout, *Oncorhynchus mykiss*	OECD 203	NOEC LC_{50}	92 >92	mg/L mg/L
Daphnia sp. Reproduction Test *Water fleas*	OECD 211	NOEC EC_{50}	13 21	mg/L mg/L
Fish, Early Life Stage Toxicity Test/ Fathead Minnow, *Pimephales promelas*	OECD 210	NOEC LOEC	1.9 >1.9	mg/L mg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC EC_{50}	600 940	mg/L* mg/L*
Phase IIb Studies				
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	100	mg/kg

* active ingredient

It is considered that Viread is unlikely to represent a risk to the aquatic environment, to micro-organisms, or to sediment dwelling organisms.

1.4. Clinical aspects

1.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2. Overview of Gilead-Sponsored Studies in this Submission

Study (Module 5 Reference)	Design	Geographic Location	Study Population	Treatment	Subjects Treated	Duration (Status)
GS-US-104-0352 (m5.3.5.1)	Randomized, open-label, parallel-group, multicenter, Phase 3 study in HIV-1 infected pediatric subjects	6 sites in the US, 1 site in Panama, and 2 sites in the UK; 4 sites in the US and the 1 site in Panama remain active during the extension phase	HIV-1 infected subjects (2 to < 12 years old) with plasma HIV-1 ribonucleic acid (RNA) < 400 copies/mL; or subjects from GS-US-162-0111 (2 to < 16 years old), naive to TDF, on stable ARV regimen including d4T or ZDV	Switch to TDF or continue d4T or ZDV regimen (randomized phase); after Week 48, all subjects were administered TDF (extension phase). Tenofovir DF 8 mg/kg oral powder (to max 300 mg for subjects ≤ 37 kg or unable to swallow tablet) or 300-mg tablet (subjects > 37 kg)	Week 48: 97 (TDF 48, d4T or ZDV 49; All TDF 89) Weeks 96 and 144: 89 (TDF 48, d4T or ZDV/TDF 41; All TDF 89)	240 weeks (ongoing); 48-week randomized period completed; subjects have completed at least 144 weeks of study drug treatment.
GS-US-104-0312 (m5.3.1.2)	Open label, two way crossover, randomized pharmacokinetic study in healthy adult volunteers	1 site in the US	Healthy male and nonpregnant, nonlactating, female subjects aged 18 to 45 years, inclusive	Single doses of TDF 300-mg tablet and 300-mg oral powder	32	2-way crossover study (completed)

A total of 4 new formulations, 1 granules formulation and 3 reduced-strength tablets (150, 200 and 250mg) are proposed to allow once-daily dosing of paediatric patients. The CHMP considered that an oral solution would have been more suitable formulation than granules based on experience with other drugs in the field. However, it is acknowledged that the bitter taste of the drug substance has been a particular challenge in this development.

The granules formulation is proposed for patients aged from 2 years and weighing at least 10kg. The granules formulation will also permit daily dose adjustment in patients with renal impairment. To mask the bitter taste of TDF, the granules is formulated to be mixed with soft food (eg: applesauce, yoghourt).

Reduced-strength tablets (150-, 200-, and 250-mg strengths) are proposed for paediatric patients 6 to < 12 years of age who weigh 17 to < 35 kg. Of note, contrarily to the granules that was investigated in the phase III pivotal study GS-US-104-0352, the to-be-marketed additional strengths (150-, 200-, and 250-mg) tablets have not been tested in children (children dosed with tablet in the pivotal 352 study were taken the 300 mg adult tablet). Therefore the acceptability of these new tablets characterized by different sizes cannot be appreciated at this stage. However, Study GS-US-104-0352 has been amended (in January 2012) in order subjects whose weight increases to ≥ 17 kg and who are able to swallow tablets may be switched from the granules to the appropriate strength of tenofovir DF tablet. Evaluation of acceptability will be made within 4 to 6 weeks after the switch and data will be presented in Viread RMP. Moreover, given that the applicant is requested to further substantiate the dose in paediatric patients, reassurance on the acceptability will have to be derived as well from this requested study.

1.4.2. Pharmacokinetics

In support of the granules, the MAH has submitted a bioequivalence study (study GS-US-104-0312) between the granules formulation and the commercial 300mg-strengh tablet in adult healthy volunteers. As a limitation of the study design, the study was conducted in *fasted* state while TDF (at least in EU) is to be given with food.

The results are the following:

Table 3. GS-US-104-0312: Statistical Comparisons of Tenofovir Pharmacokinetic Parameters for Test versus Reference Treatments (Pharmacokinetic Analysis Set)

Tenofovir Pharmacokinetic Parameter	Geometric Least-Squares Means[a]		Geometric Least Squares Mean Ratio (%), (90% CI)
	Tenofovir DF Oral Powder 300 mg (N = 30)	Tenofovir DF Tablet 300 mg (N = 30)	
C_{max} (ng/mL)	258.27	353.39	73.08 (66.04, 80.88)
AUC_{last} (h•ng/mL)	2106.22	2262.15	93.11 (83.39, 103.96)
AUC_{inf} (h•ng/mL)	2486.18	2706.66	91.85 (83.37, 101.21)

a Geometric least-squares means were obtained by the back-transformation of least-squares means of the parameters from an analysis of variance using a mixed model based on the natural logarithmic scale.

The bioequivalence criteria were met for the AUC of this intracellularly metabolised drug, but were not met for the Cmax (appr 30% lower). Moreover, the food effect on the granules has not been studied. The applicant is will perform a dedicated study (additional pharmacovigilance activity) – details are included in the RMP.

No PK data have been collected using the reduced-strengths tablets. The proposed new strengths (150, 200 and 250mg) are immediate release tablets and have a proportionally similar quantitative composition to the approved 300mg strength tablet. TDF is characterised by a linear pharmacokinetics within the range 75 to 600 mg. In accordance with the guideline on Investigation of Bioequivalence, the Applicant requested a waiver for in vivo bioequivalence studies (cf. quality assessment).

Finally, it is important to underline that the granules was developed not only for paediatric use but also for better adjustment in case of renal impairment. Indeed, in adult patients with renal impairment spacing the dose was recommended even though not considered optimal as compared to reducing the dose but was the only feasible option with the only available 300mg tablet. The availability of the granules will make possible a daily dose adjustment in renal impairment.

As described in the table below, simulations were performed to derive daily dosing recommendation for patients with moderate and severe renal impairment or patients on hemodialysis.

Table 4. Simulated Tenofovir Steady-state Pharmacokinetics in Renally Impaired Non-HIV-1 Infected Adult Patients

Parameter	Normal to Mild Renal Impairment (CL_{cr} ≥ 50 mL/min) Tenofovir DF 300 mg Once Daily	Moderate Renal Impairment (CL_{cr} 30 to 49 mL/min) Tenofovir DF 160 mg Once Daily	Severe Renal Impairment (CL_{cr} < 10 to 29 mL/min) Tenofovir DF 60 mg Once Daily
AUC_{tau} (ng•h/mL)			
Median	2670	2810	3460
Min–Max	1620 – 4900	1440 – 5400	1060 – 6100
C_{max} (ng/mL)			
Median	331	276	210
Min–Max	252 – 489	103 – 417	90.9 – 350
C_{trough} (ng/mL)			
Median	55.7	65.5	96.0
Min–Max	31.9 – 137	35.9 – 137	21.4 – 176

Simulations performed using a 2-compartment model with derived rate and volume of distribution constants

Table 5. Tenofovir DF Dose Adjustments for Adult Patients with Renal Impairment

	Creatinine Clearance (mL/min)[a]		
	30 to 49 mL/min	< 10 to 29 mL/min	Hemodialysis Patients[b]
Recommended Dose	160 mg (4 scoops) of oral powder every 24 hours or 1 × 300-mg tablet every 48 hours	60 mg (1.5 scoops) of oral powder every 24 hours or 1 × 300-mg tablet every 72 to 96 hours	20 mg (0.5 scoop) of oral powder administered following completion of each 4-hour hemodialysis session or 1 × 300-mg tablet following completion of every 12 hours of hemodialysis

a Calculated using ideal (lean) body weight

b Recommendation assumes hemodialysis sessions of 4-hours duration

The proposed dosing recommendation in patients with severe renal impairment based on PK simulation led to a significant over-exposure as compared to individuals with normal renal function. Over-exposure of a nephrotoxic drug in such a vulnerable population was considered as a cause for concern. The Applicant did not provide sufficient evidence to support its proposed daily dose adjustment. In particular, the applicant should have predicted exposure with a different dose than 60 mg QD for these sub-strata of patients with severe renal impairment. This issue was raised at D120 assessment and the Applicant was asked to further discuss whether the proposed 60mg/d dose is the most appropriate for the patients with severe renal impairment and to provide a more in depth presentation of the rationale for the choice of the 20mg dose after each 4h hemodyalysis session for haemodialysis patients. The applicant clarified that same data and approach were taken for simulation between the original recommendation of daily dose adjustment and the currently proposed dose interval adjustment. However, the data available are very heterogeneous and could hardly support a 60 mg daily dose for patients in severe renal impairment (cl cr < 30 ml/mn). Therefore, further data are needed to allow the possibility for patients with renal impairment to switch from an interval dose adjustment to a daily dose adjustment. The MAH will perform the above mentioned simulations. Moreover, data in patients

with renal impairment will have to be collected (as detailed in the RMP) to provide reassurance on the adequacy of the dosing recommendations in case of renal impairment.

Conclusions on clinical pharmacology

The MAH has submitted a bioequivalence study (study GS-US-104-0312) between the granules formulation and the commercial 300 mg-strength tablet in adult healthy volunteers. The bioequivalence criteria were met for the AUC. The study was conducted under fasting conditions. Fast conditions are more sensitive to detect formulation differences. In order to substantiate the administration of the granules with food, the applicant will perform a dedicated study to assess the food effect on the granules (additional pharmacovigilance activity) as detailed in the RMP.

Moreover, as regards the use the granule formulation as an alternative to dose-interval adjustment in adults with moderate and severe renal impairment, further data are needed. The applicant withdrew this claim from the application.

1.5. Clinical efficacy

1.5.1. Dose selection

In the pivotal paediatric study GS-US-104-0352, children received TDF at the dose of 8mg/kg (up to a maximum 300mg/day). This dose was chosen based on the results of 3 previous PK studies conducted in children 2-16 years of age. A PK sub-study on 23 children (mean age 6 years, range 2-11 years) who received TDF granules formulation at the dose of 8mg/kg/d (up to a maximum of 300mg/d) was conducted to assess the appropriateness of the selected dose. When comparing the data to exposure reported in adults receiving the 300mg tablet in historical studies -901 and -907, a trend for slightly lower exposure in children receiving the granules formulation is noted, which is even more noticeable for children aged 6-<12 years.

Table 6. GS-US-104-0352: 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-104-0352 8 mg/kg (N = 23)[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)	2586.3 (40.9)	2937	3020	3059 (34.3)	2769 (29.4)	2742 (22.9)	3297 (30.8)
AUC_{last} (ng·h/mL) Mean (%CV)	1704.4 (42.9)	—	—	—	—	—	—
C_{max} (ng/mL) Mean (%CV)	238.7 (53.4)	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)	54.5 (43.4)[c]	—	—	66.0 (46.5)	52.2 (46.9)	51.4 (57.0)	80.5 (51.1)
CL/F (L/h)[b] Mean (%CV)	34.7 (71.4)	—	—	—	—	—	—
T_{max} (h) Median (Q1, Q3)	1.93 (1.08, 2.30)	3.0	2.3	2.3	2.3	1.5	2.5
T_{last} (h) Median (Q1, Q3)	12.00 (12.00, 12.00)	—	—	—	—	—	—
$T_{½}$ (h)[b] Median (Q1, Q3)	13.65 (11.43, 16.00)[d]	13.7	14.4	14.0	14.9	12.4	14.5

a Pharmacokinetic substudy following at least 4 weeks of treatment. Pharmacokinetic 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.

c n=21

d n=22

Table 7.

Study	GS-US-104-0352		
Formulation (Dose)	Oral Powder (8 mg/kg up to 300 mg)		
Age	2 to < 12 years (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)
AUC_{last} (ng•h/mL) Mean (%CV)	1704.4 (42.9)	1780.6 (43.5)	1621.3 (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] Mean (%CV)	54.5 (43.4)[b]	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_{last} (h) Median (Q1, Q3)	12.00 (12.00, 12.00)	12.00 (12.00, 12.05)	12.00 (12.00, 12.00)
$T_{½}$ (h)[a] Median (Q1, Q3)	13.65 (11.43, 16.00)[c]	13.85 (9.96, 16.54)	12.31 (11.43, 15.99)

Of note, similar PK were observed with the tablet formulation in adults and adolescents in study GS-US-104-0321. It is unclear to what extent this trend might be driven by the difference in bioavailability between the tablet and the granules. The lower exposure in children aged 6-<12 years as compared to children aged 2-<6 years is unclear and might to some extent translate differential adherence between age groups.

Overall the population from the study 0352 comprised a vast majority of patients with co-administration with lopinavir/ritonavir. Of the 23 subjects who participated in the PK substudy, 21 received lopinavir/ritonavir with TDF. This information is relevant since the combined use with boosted PIs increases the level of exposure to tenofovir.

In the SmPC, the MAH proposes a dose range of 7.1 to 9.1 to bracket the target dose of 8 mg/kg evaluated in Study GS-US-104-0352.

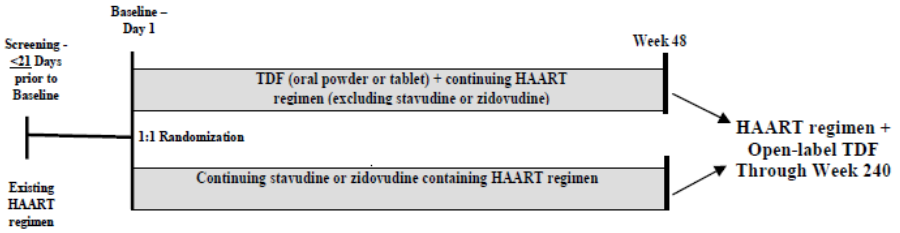
1.5.2. Main study

The main efficacy and safety data in support of the request are from study GS-US-104-0352, a Phase III, 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 HAART. This study compared the ability of TDF versus d4T/ZDV to maintain the virologic suppression. The design of this study is different from the study submitted in adolescents where TDF was added to an optimized background regimen (OBR) vs placebo + OBR to assess the ability of TDF to achieve virologic suppression in patients failing therapy. Therefore, the study design in young children was considered as less discriminating in the aim of deriving reassurance on the dose adequacy.

Design and conduct of clinical studies

The key design aspects for study GS-US-104-0352 are summarized below:

Title of the study	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
Study Centers	9 study centers: 6 in US, 1 in Panama and 2 in UK (**of note, 74% of randomized patients were included in the site in Panama**). Active sites during the second study extension include 3 sites in the US and the 1 site in Panama.
Study Period:	28 December 2006 (first subject screened) 14 March 2008 (last subject randomized) 21 February 2011 (last subject observation for this report)
Objectives	The primary objective of this study was as follows: • To assess the efficacy of switching to TDF compared to continuing stavudine or zidovudine in maintaining virologic suppression (plasma HIV-1 RNA < 400 copies/mL) in HIV-1 infected children at Week 48 The secondary objectives of this study (Weeks 0–48) were as follows: • To evaluate the safety and tolerability of TDF in HIV-1 infected children • To evaluate the effects of switching from stavudine or zidovudine to TDF versus continuing stavudine or zidovudine on bone mineral density (BMD), fasting lipid parameters, and fat distribution • To evaluate the pharmacokinetics of tenofovir in a subset of HIV-1 infected children receiving TDF granules formulation A secondary objective evaluated beyond Week 48 (Weeks 0–240) is as follows: • To evaluate the long-term efficacy, safety, and tolerability of treatment with TDF through **up to 240 weeks** of drug exposure
Population and main inclusion criteria	HIV-1 infected male and female subjects, **2 to < 12 years of age,** with plasma HIV-1 RNA **< 400 copies/mL**. *Subjects enrolled in Study GS-US-162-0111, a Gilead-sponsored study designed to provide continued access to emtricitabine, were eligible for inclusion in this study, since they were receiving stavudine or zidovudine, and were virologically suppressed (HIV-1 RNA < 400 copies/mL), with no significant safety concerns. For these subjects, the age requirement for study entry was 2 to < 16 years of age.* Subjects were naive to TDF, and were **on a stable stavudine- or zidovudine-containing HAART regimen for at least 12 weeks prior to study entry**. Subjects had adequate hematologic, renal, and hepatic functions. Patients with prior history of significant renal or bone disease were excluded.
Number of subjects	Planned: 100 evaluable (50 in each treatment group) **Randomized and treated (RAT): 97** (tenofovir DF: 48, d4Tor ZDV: 49; All TDF: 89 (48 originally randomized in the TDF group + 41 initially randomized to d4T or ZDV who switched to TDF)
Study duration	240 weeks
Criteria for evaluation	Efficacy: The primary efficacy endpoint was the number and percentage of subjects with **HIV-1 RNA < 400 copies/ml at Week 48.** Extension phase efficacy endpoints evaluated beyond Week 48 for the All TDF group were as follows:

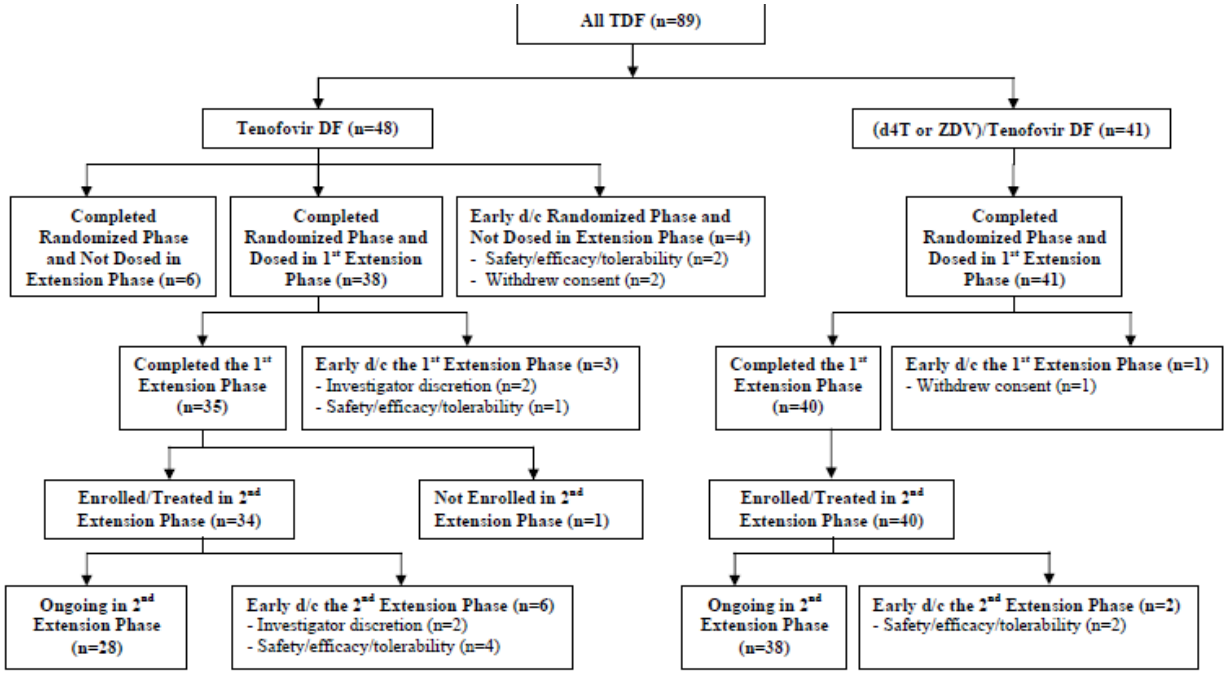
	• The proportion of subjects with HIV-1 RNA < 400 copies/mL • The proportion of subjects with HIV-1 RNA < 50 copies/mL • Change from baseline in CD4 cell count and CD4 percentage Subjects originally randomized to stavudine or zidovudine who switched to tenofovir DF in the extension phase had their baseline reset to their first tenofovir DF dosing date. No treatment comparisons were performed for the All TDF group. Safety: Safety data were collected for the following parameters: adverse events (AEs); clinical laboratory tests; spine and total body **BMD and limb (assessed using DEXA**); bone biochemical markers; height; weight; vital signs; and physical examinations (complete or symptom-directed); and changes from baseline in fasting lipid parameters.
Dosing regimen	•Subjects who weighed ≤ 37 kg or were unable to swallow tenofovir DF tablets received tenofovir DF granules (4% weight/weight tenofovir DF) at a dose of 8 mg/kg (up to 300 mg), once daily, with 2 to 4 ounces of applesauce or an equivalent food (ie, a food that did not require chewing) • Subjects who weighed > 37 kg received a 300-mg tenofovir DF tablet, once daily, **with or without food.** *Rapporteur's comment: Of note, in US tenofovir can be taken with or without food contrarily to the recommendation in EU taking into account the food influence (nevertheless, only 5 children received the tablet).* Subjects whose weight increased to > 37 kg during the extension phase were switched from the granules to the tenofovir DF tablet. No substitution of stavudine, zidovudine, or TDF was allowed during the initial 48 weeks of the study. Changes in the other components of the HAART regimen were permitted only for toxicity management.
Study design	Study GS-US-104-0352 is a Phase 3**, randomized, open-label study** conducted in HIV-1 infected children (2 to < 12 years, and 2 to < 16 years for subjects enrolled in Study GS-US-162-0111 at time of enrollment into GS-US-104-0352), who are virologically suppressed (HIV-1 RNA < 400 copies/mL) on their current stavudine- or zidovudine-containing HAART regimen. 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 stavudine or zidovudine with tenofovir DF (Treatment Group A) or to continue stavudine or zidovudine (Treatment Group B) in their existing HAART regimen for 48 weeks. **Randomization was stratified by whether a subject was currently on stavudine or zidovudine.**  Subjects completing 48 weeks of randomized treatment who continued to be < 18 years of age were given the option to either continue or initiate tenofovir DF in the first of two 96-week study extensions (collectively referred to as the extension phase). Subjects initially randomized to stavudine or zidovudine could only switch to tenofovir DF if the investigator determined that tenofovir DF would be safe and beneficial for the subject. After completing the first 96-week study extension, currently enrolled subjects who were benefiting from tenofovir DF and who continued to be < 18 years old were given the option to continue receiving tenofovir DF for an additional 96 weeks, or until tenofovir DF 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 study extensions was only applicable in those regions where tenofovir DF is commercially available for the treatment of HIV-1 infection in adults.

Study GS-US-104-0352 was initiated in December 2006 and included 97 (48 in the TDF arm and 49 in the d4T/ZDV arm) virologically suppressed children, a large majority being from Panama. The comparison between the continuing regimen or the switch was performed at 48 weeks, then after all patients were to be treated with tenofovir for two periods of extension of 96 weeks each. At this stage of assessment, only the full data for the 1st extension phase of 96 weeks on top of the 48 weeks comparative assessment were available together with some data for the 2nd extension phase of 96 weeks. The study is ongoing with an extension phase through 240 weeks.

As shown in the figure below a total of 89 children of the 97 originally randomized entered the 1st extension phase of the study (38 initially randomized to TDF and 41 who switched from d4T or ZDV to TDF).

Figure 1.



At the time of the 144 weeks analysis, 66 children were still participating in the study.

In study GS-US-104-0352, children ≤ 37 kg received TDF granules (n=40 during the randomized phase) and subjects > 37 kg received the TDF tablet (n=5 + 3 that received both TDF granules and tablets).

The primary endpoint was the percentage of patients with HIV RNA < 400 copies/ml at 48 weeks.

Of note, since patients had undetectable HIV RNA and the goal was to *maintain* the HIV RNA undetectability, 96 weeks time point for the primary analysis would have been more relevant. Nevertheless, to some extent the longer the time for primary analysis the higher the likelihood of the loss of virologic suppression to stavudine or zidovudine for these patients pre-treated by these regimens.

The tested statistical hypothesis was the non inferiority between the switch regimen with TDF and the continuing regimen with d4T/ZDV.

The Applicant did not provide justification for the choice of the wide 15% non-inferiority margin for a switch study in patients already virologically controlled. It was assumed that this choice was rather guided by sample size consideration.

It was nevertheless acknowledged that the clinical efficacy demonstration obtained in adults is generally not to be duplicated for paediatric patients. The purpose of the clinical study was rather to further substantiate the dose that has been selected on the principle that similar PK exposure as in adults would predict similar efficacy/safety.

The critical "a priori" concerns on the use of tenofovir with renal/bone toxicities in this vulnerable population, should have driven better choice for the design of the study by the applicant, i.e. larger sample size and long term comparative data would have been more appropriate to appreciate the safety of the drug in this young population in evolving process of bone modelling.

Study Results

Baseline characteristics of the study population

The targeted patient population is children aged 2 to <12 years. Due to the sharp decrease of vertical transmission in US/EU (less than 1%), the newly infected children fortunately account for a very limited number of HIV infected children in EU/US (and are mainly represented by children from migrant populations). As it might be expected in this age range, the children enrolled mainly came from sites outside US/EU, i.e. in Panama. The extrapolation of the data has not been specifically discussed by the MAH.

51.5% of the population was male, with a mean age of 7 years (range, 2 to 15 years), and most were Mestizo (67.0%) or black (19.6%). The mean value for BMI at screening was 17.08 kg/m2.

79.4% of subjects (77/97) had plasma HIV-1 RNA levels < 50 copies/mL. The mean (SD) baseline CD4 cell count was 1167 (468.6) cells/mm3 and the mean (SD) baseline CD4% was 33.5%.

Table 8.

Baseline Disease Characteristics	TDF[a] (N = 48)	d4T or ZDV[a] (N = 49)	Total[a] (N = 97)	All TDF[a, b] (N = 89)
Plasma HIV-1 RNA				
< 50 copies/mL	36 (75.0%)	41 (83.7%)	77 (79.4%)	70 (78.7%)
50 - < 400 copies/mL	11 (22.9%)	6 (12.2%)	17 (17.5%)	15 (16.9%)
400 - < 1000 copies/mL	1 (2.1%)	1 (2.0%)	2 (2.1%)	3 (3.4%)
>= 1000 copies/mL	0	1 (2.0%)	1 (1.0%)	1 (1.1%)
CD4 Cell Count (/mm^3)				
N	48	49	97	89
Mean (SD)	1190 (541.7)	1144 (388.4)	1167 (468.6)	1179 (464.2)
Median	1061	1149	1095	1095
Q1, Q3	880, 1372	868, 1362	878, 1362	909, 1393
Min, Max	500, 3671	407, 2313	407, 3671	387, 3671

CD4 cell counts and CD4% were similar in the 2 treatment groups in the 2 to < 6 years and 6 to < 12 years age strata. The duration of prior exposure to stavudine or zidovudine was slightly longer in

subjects randomized to the tenofovir DF group than for subjects randomized to continue on their existing regimen. The categorisation by CDC HIV clinical classification was not collected in the study. Finally children having undetectable HIV RNA, it was not possible to appreciate the degree of drug resistance at baseline.

It has to be noted that at baseline a markedly higher proportion in the TDF arm as compared to the d4T/ZDV arm had plasma HIV-1 RNA levels 50 to < 400 copies/mL: 22.9% vs 12.2%, which might to some extent reflect an ongoing process of loss of virologic suppression.

As expected, the vast majority of children was taking lopinavir/ritonavir. When considering that lopinavir/ritonavir is shown to increase TDF exposure, this to some extent adds to the consideration that TDF was put under optimal condition (virologically suppressed patients and combination with drug likely to maximize its activity) for deriving reassurance on the dose adequacy.

Efficacy data

During the randomized 48 weeks phase 47.9% of subjects maintained an adherence rate to tenofovir DF of ≥ 95%. At week 144 data cut off this figure was 57.3%

It has to be underlined from the protocol deviations that a significant number of deviations was due to incorrect dispensing or dosing. Measures have been put in place by the applicant to minimize the risk for medication errors that are presented in the RMP (including a formative qualitative comprehension and usability study of the (US) patient instructions for use of Viread granules to aid parents or caregivers understanding for use of the tenofovir DF granules).

Finally, seven patients discontinued from the study due to poor adherence to TDF (4 were dosed with the granules and 3 were dosed with the tablet at the time of treatment discontinuation).

When considering the virological results, the pre-defined criteria for non-inferiority at week 48 for the MAH chosen primary ITT Missing=Failure analysis was not met as shown in the table below:

Table 9. GS-US-104-0352: Number and Percentage 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[b]	Difference (95% CI)[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%)

a Data collected after first dose of open-label TDF or last dose + 2 days (if terminated) excluded.
b p-values displayed to test for between group differences (randomized phase) are from a Fisher's exact test.
c The 95% CI on the difference in percentages between randomized treatment groups is based on normal approximation.
d Denominator (for %) is the number of ITT Subjects (subjects with missing HIV-1 RNA data counted as failures).
e Denominator (for %) is the number of ITT Subjects with nonmissing HIV-RNA data at the visit.

This was neither met for Per protocol (Missing= Failure) analysis: 83% (39/47) in the TDF arm versus 91.5% (43/47) in the comparator arm: - 8.5% [-21.9% to 4.9].

Differential loss of virologic suppression was not expected and when scrutinizing the reasons for failure, it appears that the difference between both groups is not driven by virologic potency but rather

by a higher rate of discontinuation in the TDF arm (withdrew consent and poor adherence) which is nevertheless of concern in a pragmatic approach. Moreover, it appears that patients who were found to have HIV RNA >400 copies/ml at week 48 rather experienced blip than true virologic failure. Finally, more patients in the TDF arm had at baseline their HIV RNA between 50 -400 c/ml; therefore potentially more prone to loose the virologic suppression.

The results from a post-hoc (FDA-requested) snapshot analysis described below show that TDF met the non-inferiority using this analysis.

Table 10.

Virologic Response at Week 48 (n, %)[a]	TDF (N = 48)	d4T or ZDV (N = 49)	Difference (95% CI)[b]
Virologic Success	42 (87.5%)	43 (87.8%)	–0.3% (–13.4% to 12.9%)
Virologic Failure[c]	5 (10.4%)	5 (10.2%)	
No Virologic Data at Week 48 Window	1 (2.1%)	1 (2.0%)	
Discontinued Study Due to AE or Death[d]	0	0	
Discontinued Study for Other Reason[e]	1 (2.1%)	1 (2.0%)	
Missing Data during Window but on Study	0	0	

a Data collected up to the last randomized phase dose + 2 days were included.

b The 95% CI on the difference in percentages between randomized treatment groups is based on normal approximation.

c Virologic failure includes subjects with HIV-1 ≥ 400 copies/mL in the Week 48 window; subjects who discontinued for lack of efficacy and with no HIV-1 RNA data in the Week 48 window; subjects who changed ARVs for reasons not permitted in the protocol; and subjects who discontinued for reasons other than AEs, death, and lack of efficacy and the last available HIV-1 RNA value before the start of the Week 48 window is ≥ 400 copies/mL.

d Category includes subjects who discontinued due to AE or death if this resulted in no virologic data on treatment during the Week 48 window.

e Category includes 1 subject from each treatment group who withdrew consent.

Clarifications were requested as regards the difference between the two analyses that were provided by the Applicant in the MAH's response to the D120 LoQ:

Using the missing = failure method, 8 subjects in the tenofovir DF group and 4 subjects in the stavudine or zidovudine group were classed as failures at Week 48. Using the snapshot method, 5 subjects in each group were classed as failures and 1 subject in each group had no virologic data in the Week 48 visit window (discontinued due to withdrawal of consent).

Subjects with different outcomes as assessed by missing = failure or snapshot methods for HIV-1 RNA < 400 copies/mL at Week 48 in Study GS-US-104-0352 are presented in the table below:

Table 11. GS-US-104-0352: Subjects with Different Failure/Success Outcomes as Assessed by Missing = Failure or Snapshot Methods for HIV-1 RNA < 400 copies/mL at Week 48

Subject No.	HIV-1 RNA Values in the Week 48 Visit Window[a]	Outcome, Missing = Failure	Outcome, Snapshot
Tenofovir DF			
1578-9019	25,800 copies/mL (Day 338) < 400 copies/mL (Day 365)	Failure	Success

1578-9033	4170 copies/mL (Day 337) < 400 copies/mL (day 367)	Failure	Success
Stavudine or Zidovudine			
1578-9017	< 400 copies/mL (Day 338) 18,300 copies/mL (Day 365)	Success	Failure
1800-9062	< 400 copies/mL (Day 337)	Success	Failure (lopinavir/ritonavir added to regimen on Day 111)

a GS-US-104-0352 Week 48 CSR, Appendix 14, Listing 10.1

Long term Efficacy results

After the 48 weeks comparative period, the study was no longer comparative all patients were receiving TDF.

Table 12. GS-US-104-0352: Proportion of Subjects with Plasma HIV-1 RNA < 400 copies/mL at Weeks 48, 96, and 144 (ITT Analysis Set)

Subjects with Plasma HIV-1 RNA < 400 copies/mL (n, %)	TDF (N = 48)	(d4T or ZDV)/TDF (N = 41)	All TDF (N = 89)
Missing = Failure[a]			
At Week 48	40/48 (83.3%)	36/41 (87.8%)	76/89 (85.4%)
95% CI[b]	69.8% to 92.5%	73.8% to 95.9%	76.3% to 92.0%
At Week 96	31/38 (81.6%)	35/40 (87.5%)	66/78 (84.6%)
95% CI[b]	65.7% to 92.3%	73.2% to 95.8%	74.7% to 91.8%
At Week 144	28/38 (73.7%)	26/29 (89.7%)	54/67 (80.6%)
95% CI[b]	56.9% to 86.6%	72.6% to 97.8%	69.1% to 89.2%
Missing = Excluded[c]			
At Week 48	40/44 (90.9%)	36/40 (90.0%)	76/84 (90.5%)
95% CI[b]	78.3% to 97.5%	76.3% to 97.2%	82.1% to 95.8%
At Week 96	31/36 (86.1%)	35/39 (89.7%)	66/75 (88.0%)
95% CI[b]	70.5% to 95.3%	75.8% to 97.1%	78.4% to 94.4%
At Week 144	28/34 (82.4%)	26/27 (96.3%)	54/61 (88.5%)
95% CI[b]	65.5% to 93.2%	81.0% to 99.9%	77.8% to 95.3%

Note: Roche PCR Ultrasensitive assay. Data collected after the last dose of TDF + 2 days were excluded from analysis.

a Denominator (for %) is the number of ITT subjects (subjects with missing HIV-1 RNA data counted as failures), excluding ongoing subjects who have missing HIV-1 RNA at a visit and have not reached the upper limit of the analysis window for the corresponding visit.

b The 95% confidence interval (CI) for the proportion estimate for a subject group is based on the exact method.

c Denominator (for %) is the number of ITT subjects (subjects with missing HIV-1 RNA data excluded).

Resistance data

A virology genotyping substudy was conducted on HIV-1 from all subjects who discontinued the study due to virologic failure, or who had HIV-1 RNA ≥ 400 copies/mL at Week 48, Week 96, Week 144,

Week 192, Week 240 or upon early discontinuation prior to the data cut-off dates for the Week 96 and Week 144 data analyses. Baseline genotyping was not conducted due to the low HIV-1 viral load at study entry.

K65R was detected in 1 patient; the early detection of the mutation in this patient (week 4) might indicate that mutation was pre-existing at study baseline. M184V and thymidine analog-associated mutations (TAMs) were also detected. However, distinction between pre-existing and emerging mutations could not have been made.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of Efficacy for trial GS-US-104-0352

<table>
<tr><td colspan="3"><u>Title:</u> 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</td></tr>
<tr><td>Study identifier</td><td colspan="2">Gilead protocol number: GS-US-104-0352
EudraCT number: 2007-003418-32</td></tr>
<tr><td>Design</td><td colspan="2">Study GS-US-104-0352 is a Phase 3, randomized, open-label study conducted in HIV-1 infected children (2 to < 12 years, and 2 to < 16 years for subjects enrolled in Study GS-US-162-0111 at time of enrollment into GS-US-104-0352), who are virologically suppressed (HIV-1 RNA < 400 copies/mL) on their current stavudine- or zidovudine-containing HAART regimen.

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 stavudine or zidovudine with tenofovir DF (Treatment Group A) or to continue stavudine or zidovudine (Treatment Group B) in their existing HAART regimen for 48 weeks. Randomization was stratified by whether a subject was currently on stavudine or zidovudine.

Subjects completing 48 weeks of randomized treatment who continued to be < 18 years old were given the option to either continue or initiate tenofovir DF in the first of three 96-week study extensions (collectively referred to as the extension phase). Subjects initially randomized to stavudine or zidovudine could only switch to tenofovir DF if the investigator determined that tenofovir DF would be safe and beneficial for the subject. After completing the first (or second) 96-week study extension, currently enrolled subjects who were benefiting from tenofovir DF and who continued to be < 18 years old were given the option to continue receiving tenofovir DF for an additional 96 weeks, or until tenofovir DF becomes commercially available in the country where the subjects are enrolled, whichever occurs first.</td></tr>
<tr><td></td><td>Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>48 weeks
Not applicable
Up to 288 weeks
(total duration up to 336 weeks including main phase of 48 weeks)</td></tr>
</table>

Hypothesis	Non-inferiority		
Treatments groups	TDF		Tenofovir DF (granules or tablet) + continuing HAART regimen (excluding stavudine or zidovudine) (Weeks 0–48) (n=48). Subjects who weighed > 37 kg and were able to swallow tablets were given one 300-mg tenofovir DF tablet per day. Subjects who weighed ≤ 37 kg or were unable to swallow the tenofovir DF tablet were given tenofovir DF granules (4% weight/weight tenofovir DF) at a dose of 8 mg/kg, once daily, up to a maximum dose of 300 mg.
	d4T or ZDV		Continue prescribed stavudine- or zidovudine-containing HAART regimen (Weeks 0–48) (n=49).
Endpoints and definitions	Primary endpoint	HIV-1 RNA < 400 copies/mL (M=F)	Proportion of subjects with HIV-1 RNA concentrations < 400 copies/mL at Week 48 (Missing = Failure analysis)
	Secondary endpoints (main ones)	HIV-1 RNA < 400 copies/mL (Snapshot)	Proportion of subjects with HIV-1 RNA concentrations < 400 copies/mL at Week 48 (Snapshot analysis)
		HIV-1 RNA < 50 copies/mL (M=F)	Proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 (Missing = Failure analysis)
		Change from baseline CD4%	Change from baseline in CD4 percentage (%) at Week 48
		Change from baseline CD4Count	Change from baseline in CD4 cell count (cells/mm^3) at Week 48
Database lock	21 April 2009 for the primary efficacy analysis		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat – 48 weeks.		
Descriptive statistics and estimate variability	Treatment group	TDF	d4T or ZDV
	Number of subject	48	49
	HIV-1 RNA < 400 copies/mL (M=F) n (%)	40/48 (83.3%)	45/49 (91.8%)
	HIV-1 RNA < 400 copies/mL (Snapshot) n (%)	42/48 (87.5%)	43/49 (87.8%)
	HIV-1 RNA < 50 copies/mL (M=F) n (%)	34/48 (70.8%)	42/49 (85.7%)

	Change from baseline CD4% Mean (standard deviation)	0.3 (4.49)	1.1 (4.73)
	Change from baseline CD4Count Mean (standard deviation)	-97 (416.4)	-11 (280.2)
Effect estimate per comparison	Primary endpoint: HIV-1 RNA < 400 copies/mL (M=F)	Comparison groups	TDF versus d4T or ZDV
		Difference between groups	–8.5%
		95% Confidence Interval	–21.5% to 4.5%
		P-value (Fisher's Exact test)	0.23
	HIV-1 RNA < 400 copies/mL (Snapshot)	Comparison groups	TDF versus d4T or ZDV
		Difference between groups	-0.3%
		95% Confidence Interval	–13.4% to 12.9%
		P-value	Not calculated
	HIV-1 RNA < 50 copies/mL (M=F)	Comparison groups	TDF versus d4T or ZDV
		Difference between groups	–14.9%
		95% Confidence Interval	–31.0% to 1.3%
		P-value (Fisher's Exact test)	0.089
	Change from baseline CD4%	Comparison groups	TDF versus d4T or ZDV
		Difference between groups	–0.8
		95% Confidence Interval	–2.7 , 1.1
		P-value (Wilcoxon Rank Sum Test)	0.45
	Change from baseline CD4Count	Comparison groups	TDF versus d4T or ZDV
		Difference between groups	-86
		95% Confidence Interval	-231, 59
		P-value (Wilcoxon Rank Sum Test)	0.46

1.5.3. Conclusions on clinical efficacy

The clinical study GS-US-104-0352 compared the ability of TDF (switch arm) versus d4T/ZDV (continuing arm) to maintain the virologic suppression in patients already virologically suppressed *(*with HIV RNA levels <400 copies/ml) under treatment with d4T/ZDV. The design of this study was different from the study in adolescents where TDF was added to an optimized background regimen (OBR) vs placebo + OBR to assess the ability of TDF *to achieve* virologic suppression in patients failing therapy. Therefore, the study design in young children was considered as less discriminating in the aim of deriving reassurance on the dose adequacy, but well acceptable. Results show that the vast majority of patients had sustained virological suppression at the 8 mg/kg dose in study 352. At week 48, 83% of patients in the tenofovir disoproxil fumarate treatment group and 92% of patients in the stavudine or zidovudine treatment group had HIV 1 RNA concentrations < 400 copies/ml. The difference in the proportion of patients who maintained < 400 copies/ml at week 48 was mainly influenced by the higher number of discontinuations in the tenofovir disoproxil fumarate treatment group. When missing

data were excluded, 91% of patients in the tenofovir disoproxil fumarate treatment group and 94% of patients in the stavudine or zidovudine treatment group had HIV 1 RNA concentrations < 400 copies/ml at week 48.

Beyond the clinical demonstration is the level of PK data to substantiate the comparable PK exposure between children and adults to predict similar efficacy and safety, as it is a general rule for the clinical development in paediatric patients. To this purpose, the applicant has performed several analyses to achieve a better picture of the PK in children. It remains that determining an optimal dose in children is always a difficult exercise when having to conciliate limited sample size and several sources of variability. In this situation, not only age and weight accounts for as a source of variability but also the treatment with combined agents (boosted PI vs no boosted PI) as well as the food effect (the lack of a dedicated study to assess the food effect on the granules cannot allow to exclude a potential differential food effect between the oral tablet and granules). This overall translates that the dose has to be further substantiated mainly for the granules formulation (in children from 2 to <6 years old) even though it is acknowledged that the vast majority of patients had sustained virological suppression in this study.

Therefore, considering the medical need for additional backbone in paediatric patients as well as the virological data available, the CHMP considered approvable Viread in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected paediatric patients, with NRTI resistance or toxicities precluding the use of first line agents.

However, to further substantiate the above, the applicant needs to perform the following studies:

- a PK bioavailability study to compare the tenofovir disoproxil fumarate (TDF) granules and the 300-mg tablet in the fed state to further substantiate the conclusion that a similar dose can be given regardless of the formulation. Results expected by 31 August 2013.
- collect PK data in Study GS-US-174-0144 (HBV infected subjects 2 to < 12 years of age) to further substantiate the adequacy of the dose in HIV-infected children from 2 years of age through. Results expected by 30 June 2014.

The SmPC of the granules formulation was updated to reflect the conclusions from the data submitted as part of this application and to promote monitoring "Limited clinical data are available at the 6.5 mg/kg dose of the granules. Therefore, close monitoring of efficacy and safety is needed".

1.6. Clinical safety

Similarly to adults or adolescents, the salient aspect of the drug pertains to its bone and renal toxicity. Those are viewed as particularly critical for the most vulnerable population of growing children.

Patient exposure

The median duration of exposure to tenofovir DF through the week 144 data cutoff was 151.9 weeks for the All TDF group with 178.6 weeks for the tenofovir DF subgroup and 151.1 weeks for the (d4T or ZDV)/TDF subgroup.

Adverse events

During the randomized period, a similar proportion of patients in the TDF and d4T or ZDV groups reported at least 1 AE (adverse events) (85.4% [41 subjects] and 83.7% [41 subjects]). More patients

randomized in the TDF group exhibit vomiting (12.5%, 6 subjects versus zero subjects) and musculoskeletal and connective tissue disorders (10.2%, 5 subjects versus zero subjects) than subjects who continue on their d4T/ZDV regimen.

Unfortunately for the appreciation of the long-term safety of the drug, data were no longer comparative after Week 48.

At the Week 144 data cut-off, 83 subjects (93.3%) in the All TDF group reported at least 1 AE. Adverse events considered related to study drug were reported for 23 subjects. Grade 2, 3, or 4 AEs were considered related to study drug for 11 subjects. Grade 3 or 4 AEs were considered related to study drug for 3 subjects.

Table 14. GS-US-104-0352: Overall Summary of Adverse Events Through the Week 144 Data Cutoff (RAT Analysis Set)

Adverse Event Category, n (%)[a,b]	TDF (N = 48)	(d4T or ZDV)/TDF (N=41)	All TDF (N=89)
Any AE	45 (93.8%)	38 (92.7%)	83 (93.3%)
Study Drug-Related AE	14 (29.2%)	9 (22.0%)	23 (25.8%)
Grade 3 or 4 AE	5 (10.4%)	5 (12.2%)	10 (11.2%)
Grade 3 or 4 Study Drug-Related AE	2 (4.2%)	1 (2.4%)	3 (3.4%)
Grade 2, 3, or 4 AE	37 (77.1%)	33 (80.5%)	70 (78.7%)
Grade 2, 3, or 4 Study Drug-Related AE	7 (14.6%)	4 (9.8%)	11 (12.4%)
AE That Caused Permanent Discontinuation From Study Drug	3 (6.3%)	2 (4.9%)	5 (5.6%)
Any SAE	4 (8.3%)	4 (9.8%)	8 (9.0%)
Study Drug-Related SAE	0	0	0

a Denominator (for %) is the number of randomized and treated subjects within the subject group.

b Adverse events with onset after the last tenofovir DF dose date (if terminated) + 30 days were excluded from analysis.

Of note, the incidence of study drug-related arthralgia increased from 2 subjects (2.2%) in the Week 96 analysis to 11 subjects (12.4%) in the Week 144 analysis. Four cases of arthralgia were still ongoing (including 1 grade 3 arthalgia). The MAH was requested to discuss the potential relationship of arthralgia with bone safety concern and to specify the evolution of BMD score as well as creatinine clearance during the study for those patients. No apparent association between artharalgia and BMD Z-score can be found on the basis of the limited data available from this study.

A high percentage of gastrointestinal disorders (25%) including vomiting, nausea and diarrhoea in the all TDF group raised concern on the adherence of the granules (bitter taste, challenging to be masked). Reassurance on the acceptability are expected to be derived from the planned study GS-US-174-0144 (enrolling soon) in HBV infected subjects 2 to < 12 years of age and from the requested drug utilization study (see further).

Serious adverse events and deaths

No subjects died during this study.

Serious adverse events were reported for 8 subjects in the All TDF group; no SAEs were considered related to study drug by the investigator.

Discontinuation due to AES

Five subjects in the All TDF group discontinued study drug due to an AE:

- 2 for hypophasphatemia on day 596 and 1072
- 1 for hypophasphatemia and arthralgia on day 1026
- 1 for glycosuria on day 700
- 1 for brain neoplasm on day 735

Each of the AEs, except for the brain neoplasm, was considered related to study drug by investigators.

Laboratory findings

The majority of subjects in the study had at least 1 treatment-emergent laboratory abnormality reported. The majority of the abnormalities reported were Grade 1 or Grade 2 in severity. Grade 3 or 4 abnormalities were reported for 14 subjects in the All TDF group, including 11 subjects in the tenofovir DF subgroup and 3 subjects in the (d4T or ZDV)/TDF subgroup. Grade 3 or 4 abnormalities were most frequently reported for ALT (6 subjects), amylase (5 subjects), and hypophosphatemia (3 subjects).

Table 15. GS-US-104-0352: Grade 3 or 4 Treatment-Emergent Laboratory Abnormalities Through the Week 144 Data Cutoff (RAT Analysis Set)

Laboratory Assessment with a Treatment-Emergent Grade 3 or 4 Abnormality [a,b,c]	TDF (N = 48)	(d4T or ZDV)/TDF (N = 41)	All TDF (N = 89)
Maximum Post-Baseline Toxicity Grade	48	41	89
Grade 3	8 (16.7%)	2 (4.9%)	10 (11.2%)
Grade 4	3 (6.3%)	1 (2.4%)	4 (4.5%)
ALT	48	41	89
Grade 3	4 (8.3%)	1 (2.4%)	5 (5.6%)
Grade 4	1 (2.1%)	0	1 (1.1%)
Amylase	48	41	89
Grade 3	4 (8.3%)	1 (2.4%)	5 (5.6%)
AST	48	41	89
Grade 3	1 (2.1%)	0	1 (1.1%)
Calcium Corrected for Albumin (Hypocalcemia)	48	41	89
Grade 4	1 (2.1%)	0	1 (1.1%)
Lipase[d]	15	7	22
Grade 4	1 (6.7%)	0	1 (4.5%)
Magnesium (Hypomagnesemia)	48	41	89
Grade 3	1 (2.1%)	0	1 (1.1%)
Phosphate (Hypophosphatemia)	48	41	89
Grade 3	3 (6.3%)	0	3 (3.4%)
Serum Glucose (Hyperglycemia)	48	41	89
Grade 3	1 (2.1%)	0	1 (1.1%)
Urine Glucose (Glycosuria)	47	41	88
Grade 4	0	1 (2.4%)	1 (1.1%)

a A "treatment-emergent abnormality" is at least a 1-grade increase from baseline (missing at baseline = Grade 0) at a postbaseline measurement.

b Data collected after the last tenofovir DF dose date (if terminated) + 30 days were excluded from analysis.

c Denominator (for %) is the number of subjects with any postbaseline result (using data inclusion/exclusion rules stated above).

d Lipase is a reflex test that is performed only when amylase is >=1.5 × upper limit of normal range (ULN).

Laboratory findings of interest (i.e. renal and bone parameters):

Renal Laboratory Parameters

Serum Creatinine

Median serum creatinine concentrations were low at baseline (baseline median 0.40 mg/dL). There were small increases from baseline in serum creatinine in the All TDF group (median change from baseline at Week 144 was 0.10 mg/dL).

No graded serum creatinine abnormalities were reported.

Serum Phosphate

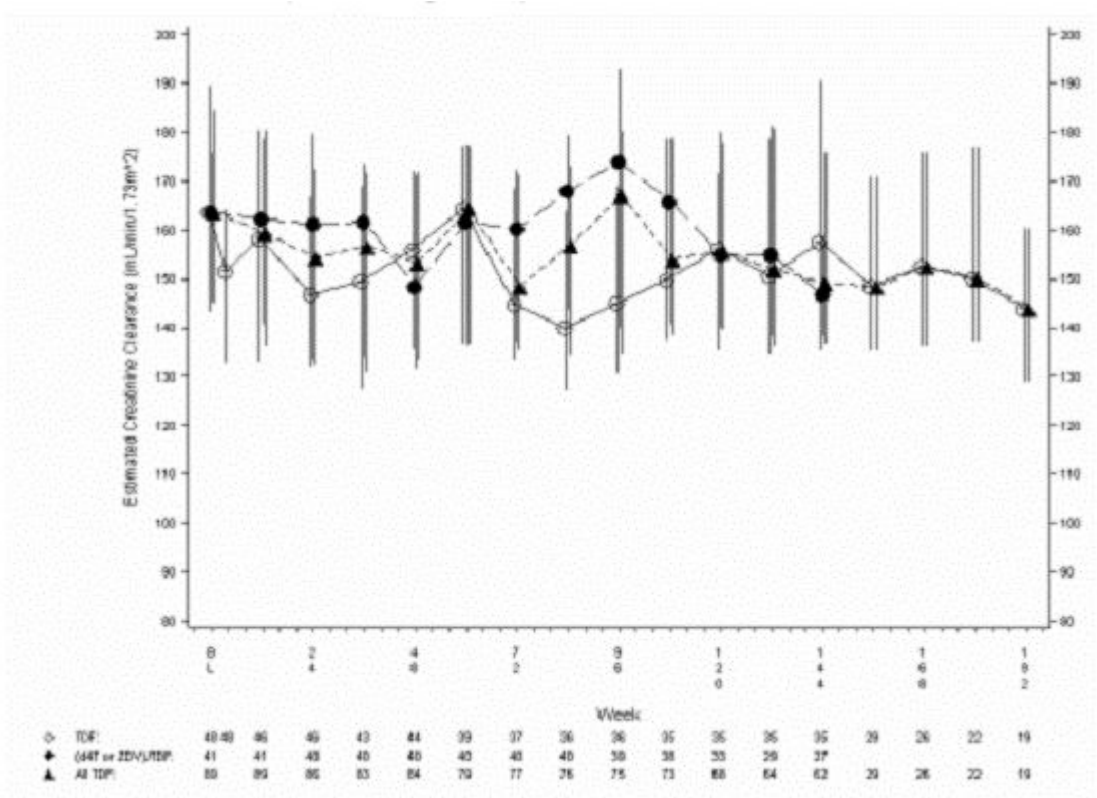
In the All TDF group, treatment-emergent graded hypophosphatemia was reported for 9 subjects (Grade 1 for 5 subjects, Grade 2 for 1 subject, and Grade 3 for 3 subjects [study drug discontinued for these last three subjects]).

Estimated Creatinine Clearance

There were modest decreases from baseline in estimated creatinine clearance in the All TDF group (median values were 163.63 mL/min/1.73 m² at baseline and 149.12 mL/min/1.73 m² at Week 144). At Week 144, the median change from baseline was −11.83 mL/min/1.73 m^2 in the All TDF group (n = 62, p = 0.003). Decrease was more pronounced in children 2 to <6 years of age (-17.5; n=18) as compared to children 6 to <12 years of age (-9.9; n=40).

For the sake of comparison, in the adolescent study GS-US-104-0321 (Week 144 report submitted in fulfilment of Paediatric article 46), the median change from baseline was -38.5 mL/min/1.73 m^2 at Week 144 (median values were 167.6 mL/min/1.73 m^2 at baseline [n = 81] and 135.8 mL/min/1.73 m^2 at Week 144 [n = 16]).

GS-US-104-0352: Median and IQR of Estimated Creatinine Clearance by Visit Through the Week 144 Data Cutoff (RAT Analysis Set)



In this study, patients had normal renal function at baseline. Ten patients (11.2%) had confirmed decrease from baseline ≥ 35%. No subjects had estimated creatinine clearance values < 70 mL/min/1.73 m² during the study. However, 5 subjects had creatinine clearance values between 70 and 90 mL/min/1.73 (including 3 of the patients who discontinued from the study due to proximal renal tubulopathy and 2 who continue on study drug).

Proteinuria

In the All TDF group, treatment-emergent Grade 1 proteinuria was reported for 12 subjects. Grade 2 proteinuria was reported for 10 subjects. No Grade 3 or 4 proteinuria was reported.

Glycosuria

In the All TDF group, treatment-emergent Grade 1 glycosuria was reported for 3 subjects and Grade 4 glycosuria was reported for 1 subject (the latter was reported as an AE and led to study drug

discontinuation).

Proximal Renal Tubulopathy Using a Case Definition

The renal safety data for the 4 subjects who discontinued tenofovir DF due to renal AEs in the extension phase of this study were clinically consistent with proximal renal tubulopathy, a renal disorder identified in postmarketing surveillance of tenofovir DF in adults. Subsequently, renal safety data were systematically reviewed using a case definition to assess whether there were any other subjects who had data consistent with proximal renal tubulopathy. *While there is no standard definition for proximal renal tubulopathy, the following criteria were used to define cases of proximal renal tubulopathy in paediatric patients (modified from the definition being used in a study in adults, GS-US-104-0353): at least 2 of 5 graded laboratory abnormalities consistent with proximal renal tubulopathy (at least Grade 1 proteinuria, glycosuria, hypokalemia, hypocarbia, or hypophosphatemia on at least 2 occasions) and a > 35% reduction from baseline in creatinine clearance*.

A total of 5 subjects (5.6%) met the case definition of proximal renal tubulopathy, which led to permanent discontinuation in 4 cases. The remaining subject developed a > 35% reduction from baseline in creatinine clearance along with grade 1 proteinuria and glycosuria.

Outcome was unclear since a follow-up of only 30 days after drug discontinuation was planned per protocol. Of note, the cases were reported in children aged 9 to 15 years (all were receiving concomitant lopinavir/ritonavir).

This finding was considered of particular concern for the children population when considering that no case of proximal renal tubulopathy was reported in the adolescent study GS-US-352-0321 through week 144 or in longer-term studies in adults.

Table 16. GS-US-104-0352: Proximal Renal Tubulopathy Cases Through the Week 144 Data Cutoff (RAT Analysis Set)

Subject ID	BL CL_{cr} (mL/min/ 1.73 m^2)	Min CL_{cr} (mL/min/ 1.73 m^2)	Maximum Graded Renal Laboratory Abnormalities[a] (± 12 weeks of minimum CL_{cr})				
			Hypophosphatemia	Hypokalemia	Hypocarbia	Proteinuria	Glycosuria
1578-9030	147	79	Grade 3	Grade 1	Grade 2	Grade 2	Grade 1
2767-9071a	185	70	Grade 3	Grade 1	Grade 1	Grade 1	Grade 1
1578-9046	142	84	Grade 1	None	Grade 1	Grade 2	Grade 4
1578-9004	180	118b	Grade 3	Grade 1	None	Grade 1	None
1578-9045	181	88	None	None	None	Grade 1	Grade 1

BL = baseline; CL_{cr} = creatinine clearance; min = minimum

a Subject 2767-9071 had Grade 1 hypocarbia at baseline; no other cases had graded renal laboratory abnormalities at baseline.

b For Subject 1578-9004, graded laboratory abnormalities occurred within ± 12 weeks of the subject's maximum serum creatinine value (0.8 mg/dL; CL_{cr} was 118 mL/min/1.73 m^2 at the same visit). The subject had no graded renal laboratory abnormalities within ± 12 weeks of the minimum CL_{cr} value (103 mL/min/1.73 m^2).

It should be outlined that 3 patients who discontinued study drug due to a renal AE also had worsened clinical status for spine BMD and/or total body BMD Z-scores.

There was no mandatory off-treatment follow-up period beyond the end-of-study visit that was to occur within 30 days of discontinuation of study drug. Therefore, subjects who discontinued TDF due to renal AEs (hypophosphatemia for 3 subjects; glycosuria for 1 subject) were not subsequently followed

to confirm resolution of laboratory abnormalities. The updated RMP will cover specific actions to ascertain the reversibility of TDF renal toxicity.

Bone Parameters

Spine Bone Mineral Density

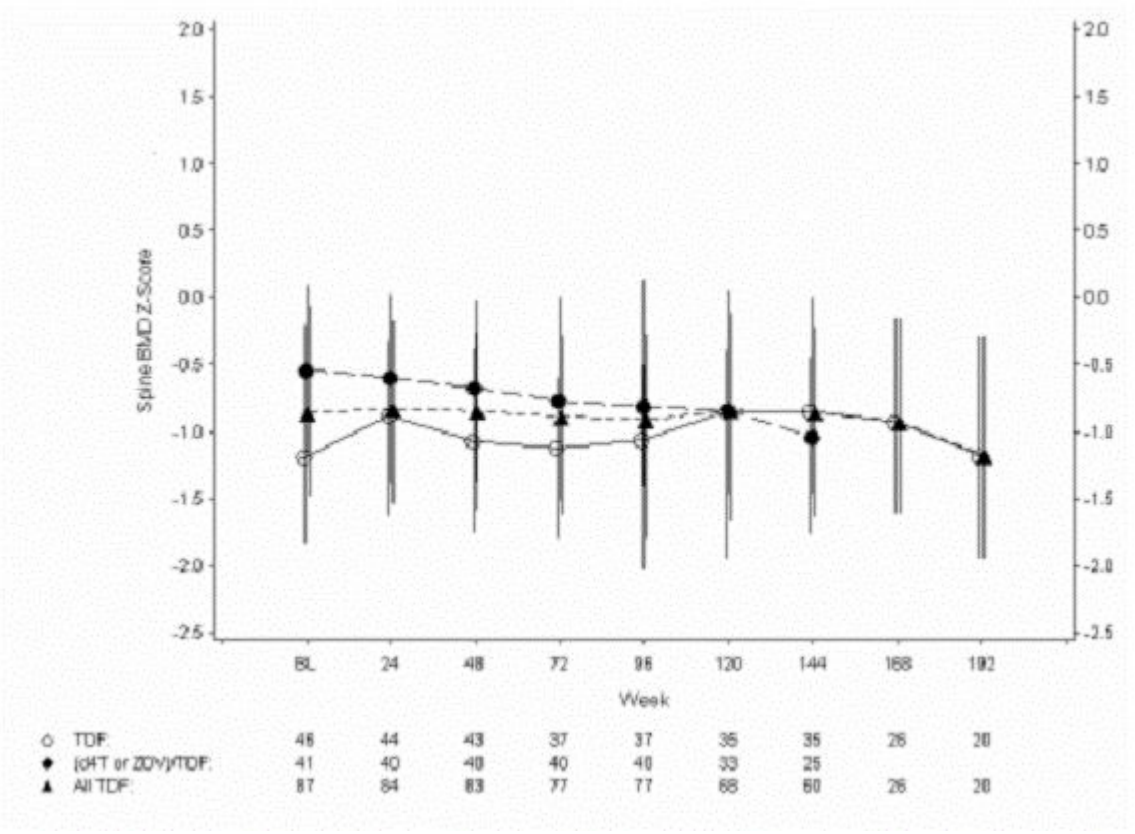
In the randomized treatment period, there were no statistically significant differences between groups in the percentage change from baseline in spine BMD. However, 1 subject randomized to the TDF group and no subjects randomized to the d4T or ZDV group had a > 4% decrease in spine BMD at Week 48.

Spine BMD Z-Score

Baseline spine BMD Z-scores were lower in the TDF group (median −1.042) than in the d4T or ZDV group (median −0.595), and more subjects in the TDF group had abnormal spine BMD at baseline than in the d4T or ZDV group (Z-scores were ≤ −1 for 50% of subjects [23/46] in the TDF group and 30% of subjects [14/46] in the d4T or ZDV group).

At the time of the Week 48 data cutoff, there were no marked changes in median spine BMD Z-scores in either group at week 48.

Figure 2. GS-US-104-0352: Median and IQR of Spine BMD Z-Score by Visit Through the Week 144 Data Cutoff (RAT Analysis Set)



In the All TDF group at baseline, median spine BMD Z-score was **−**0.862, and 44% of subjects (38/87) had abnormal spine BMD (Z-scores **≤ −**1). No statistically significant change in spine BMD Z-score was seen in the All TDF group; the median change from baseline to Week 144 was 0.085 (n = 60, p = 0.61).

Of note, whereas no marked change in spine BMD Z-score were apparent through week 144, data available for the patients who reached 192 weeks tend to indicate a decrease in spine BMD Z-score after week 144. This observation may result from the lower numbers of subjects with available data at later timepoints.

Moreover, from baseline to Week 144, the clinical status category for spine BMD Z-score improved for 10 subjects and worsened for 10 subjects. Details on patients who had worsened BMD Z-score and/or abnormal Z score (Z-score ≤ −1) at week 144 have been provided in the Applicant's response to the D120 list of questions. However, no conclusion can be drawn from these data, especially since there is no well established correlation between BMD decrease and clinical bone events.

Spine BMD Z-Score by Age Subgroup

In the All TDF group, analyses of spine BMD Z-scores by age group showed no marked change from baseline in median values in the 2 to < 6 years group, and modest decreases from baseline in median values in the 6 to < 12 years group. The median changes from baseline at Week 144 were 0.308 (n = 18) and −0.140 (n = 38), respectively.

Total Body Bone Mineral Density

In the randomized treatment period in Study GS-US-104-0352, there was a statistically significant difference in the percentage change from baseline in total body BMD. Median percentage changes were smaller in the TDF group than in the d4T or ZDV group (median changes at Week 48: 1.220% versus 2.679%, p = 0.043). One subject randomized to TDF and 1 subject randomized to d4T or ZDV had a > 4% decrease in total body BMD at or before Week 48.

Total Body BMD Z-Score

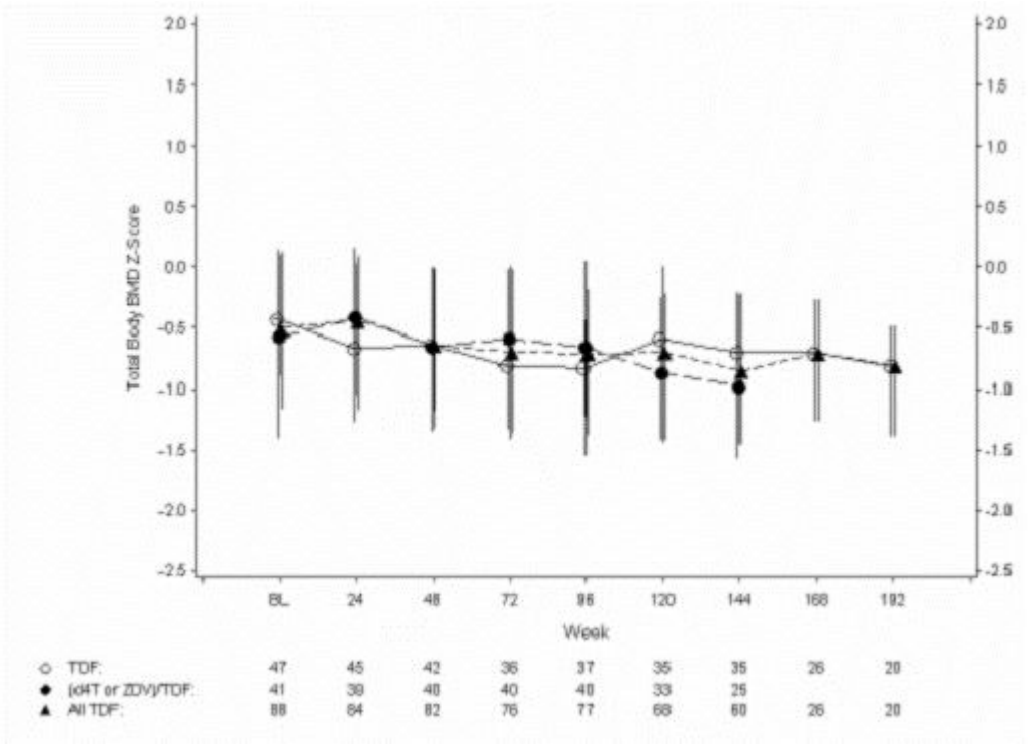
At baseline, total body BMD Z-scores were negative in both groups (median −0.375 in the TDF group and −0.394 in the d4T or ZDV group). Total body BMD was abnormal at baseline (Z-scores ≤ −1) for 34% of subjects (16/47) in the TDF group and 21% of subjects (10/48) in the d4T or ZDV group.

At the time of the Week 48 analysis, there was a modest reduction in total body BMD Z-score in the TDF group (median change at Week 48: −0.215) compared to no change in the d4T or ZDV group.

Moreover, it appears that reductions in median values for total body BMD Z-score progress over time in the All TDF group. At the time of the Week 144 data cutoff, the median change from baseline to Week 48, Week 96, and Week 144 in the All TDF group were as follows (Wilcoxon signed rank test): −0.135 (n = 82, p < 0.001), −0.237 (n = 77, p < 0.001), and −0.299 (n = 60, p = 0.002), respectively.

Analyses of total body BMD Z-scores in the 20 subjects in the tenofovir DF subgroup with Week 192 BMD data showed a modest decrease from baseline in median values. The median change from baseline at Week 192 was −0.318 (p = 0.070, Wilcoxon signed rank test).

Table 17. GS-US-104-0352: Median and IQR of Total Body BMD Z-Score by Visit Through the Week 144 Data Cutoff (RAT Analysis Set)



These findings differ from those seen in adults (Study GS-99-903), in which the majority of the reduction in spine and hip BMD occurred in the first 24 to 48 weeks, with little or no progression in loss of BMD for the remainders of the study.

Moreover, there was some evidence for worsening in the clinical status of total body BMD Z-scores in the All TDF group. From baseline to Week 144, the clinical status category for total body BMD Z- score improved for 3 subjects and worsened for 12 subjects.

Total Body BMD Z-Score by Age Subgroup

In the All TDF group, analyses of total body BMD Z-scores by age group showed decreases from baseline in median values for both the 2 to < 6 years and 6 to < 12 years groups. Decreases in total body BMD Z-score were more marked in the younger age group. The median changes from baseline at Week 144 were −0.776 (n = 18) and −0.120 (n = 38), respectively. This result is worrying, even though, clinical consequences of this demineralization are difficult to evaluate.

Analyses of spine BMD Z-score and total body BMD Z-score by age showed opposite results. According to the MAH, these data suggest bone mineralisation change in trabecular bone among subjects aged 6-12 years, whereas subjects aged 2-6 years are more likely to experienced change in cortical bone

An analysis of the clinical consequences of bone findings in the paediatric population, including potential differences according to age groups has been provided by the Applicant in the response to the D120 list of questions. Moreover, a SAG meeting was held the 3 May 2012 to help the CHMP adequately weight the burden of the safety profile of the TDF in paediatric patients. Both highlight the lack of correlation between DXA measurements and bone events.

Other parameters:

Calcium

Treatment-emergent Grade 1 hypercalcemia was reported for 30 subjects (33%) in the All TDF group in the Week 144 analysis. The MAH should discuss the high frequency of hypercalcemia and the potential relationship with renal toxicity.

Serum Bone Biochemical Markers

Increase in markers of bone turnover (markers of bone formation: bone-Specific Alkaline Phosphatase and markers of bone resorption: N- and C-Telopeptide) were observed at week 48. Increase in the TDF group were greater and statistically significant compared to the d4T/ZDV group. There were no marked change from baseline to Week 144 for those markers. However, modest reductions from baseline (baseline median 27.2 ng/mL) in serum osteocalcin (marker of bone formation) were seen in the All TDF group (median change at Week 144 of −6.3 ng/mL, n = 62, p < 0.001, Wilcoxon signed rank test).

Those data reflect increase in bone remodeling in children 2 to <12 years of age receiving TDF. The Applicant considers there is no evidence of imbalance between bone formation and bone resorption. However, analyses of serum bone biochemical markers were very descriptive and there is no validated standard for the general population to allow for comparison.

Conclusions on clinical safety

Due to its safety profile characterized by renal and bone toxicity, tenofovir was not regarded as an "a priori" optimal candidate for use in paediatric patients in evolving process of bone remodelling. The particular findings of BMD alteration observed in the pivotal GS-US-104-0352 could not allow dispelling these concerns.

In terms of safety, the clinical data derived from the pivotal GS-US-104-0352 study did not give reassurance on the "a priori" concerns on the use of TDF, characterised with renal and bone toxicities, in children in bone modelling evolving process.

- 5 children (5.6%) experienced renal adverse event clinically consistent with proximal renal tubulopathy, while renal tubulopathy was not reported in adult and adolescents clinical studies.
- There was reduction in total Body BMD Z-score in the TDF group (median change from baseline at Week 48: −0.215 compared to no change in the d4T or ZDV group) and this reduction was progressively decreasing over time based on 144 week data. The effect was more marked in children aged 2 to <6 years as compared to children aged 6 to <12 years (median change from baseline at Week 48: -0.776 versus -0.120).

Moreover, since this study is no longer comparative after 48 weeks it does not allow to substantiate the long term impact on bone remodelling in children.

The CHMP requested a SAG (Scientific Advisory Group) meeting to adequately address the bone and renal safety of tenofovir in the paediatric population with medical need. Due to other on going procedures the CHMP endorsed the extension of the SAG scope. The SAG members were invited to give their position on the risk of bone and renal toxicity of Viread in the context of its use in both HIV and HBV infected paediatric and adult patients. PDCO members as experts provided input to the scientific discussion at the SAG.

The SAG meeting was held the 3 May 2012. The discussion focused on the safety burden of tenofovir in the paediatric population and gave important information on the safety monitoring of the use of tenofovir in paediatric patients. Overall, SAG members highlighted the lack of correlation between DXA measurements and bone events and the difficulties to provide specific recommendation as regards supplementation.

As regards renal toxicity in paediatric patients: the SAG members did not foresee any specific reason for the renal toxicity in adults being different in children and adolescents. Only the phosphate loss resulting from tubulopathy could be of differential impact given that paediatric patients are in active process of bone modelling. The current recommendation of renal toxicity monitoring in adults are judged conservative enough and could overall be aligned for paediatric patients, especially having in mind that this paediatric population is expected to be closely managed in clinical practice. As regards the need for treatment interruption in paediatric patients, it was considered that instead of stating a specific threshold for withdrawal, as in adults, it would be more appropriate to give a general message that significant laboratory abnormality suggestive of renal toxicity during treatment should trigger specialised consultation.

As regards bone toxicity, the SAG members have considered that it is currently questioned whether the observed toxicity of the drug could be of any long term consequence. Therefore the discussion on the benefit/risk could be balancing theoretical risks versus established benefit (virological suppression). When considering the need for specific monitoring, the SAG members refute the value of any BMD monitoring given the lack of established correlation with clinical events. Furthermore it represents a burden for paediatric patients and raises practical and technical issues. As regards the need for phosphate and Vit D supplementation, the SAG members have considered that there was no apparent reason to deviate from the general attitude which prevails in clinical practice for a population in active modelling process (i.e. supplementation is considered in case of significant depletion).

The CHMP has agreed with the SAG views. The SmPC was revised to reflect the uncertainties associated with the long term effects of bone and renal toxicity. Since, the reversibility of renal toxicity cannot be fully ascertained a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment and to decide on the appropriate monitoring during treatment (including decision for treatment withdrawal) and to consider the need for supplementation.

To address bone safety concerns the applicant proposed a BMD monitoring at baseline and during therapy in at risk patients. The CHMP did not agree to impose a BMD given the lack of established correlation with clinical event and given the burden it represents for paediatric patients as well acknowledging practical and technical issues.

Furthermore the applicant was requested to perform additional studies. A separate post-authorisation study with a representative sample of HIV- and HBV infected children to help establish evidence-based strategies for management of TDF-associated renal and bone toxicity (protocol synopsis to be submitted by 31 December 2012) and a Drug Utilisation Study in HIV-1 and HBV-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures (draft synopsis to be submitted by 25 October 2012).

In addition, the CHMP considered that the applicant should submit the following safety data: a cumulative review of renal tubulopathy reports in HIV-1 and HBV infected adult patients by 31 December 2012.

Details of these studies are detailed in the RMP.

1.7. Pharmacovigilance system

Risk management plan

The applicant submitted a risk management plan, which included a risk minimisation. The RMP addressed the safety concerns identified with tenofovir.

Risk minimisation plan

The applicant proposed a HIV paediatric educational brochure for children and adolescents aged 2 to <18 years to address renal and bone toxicity and to include dosing recommendations on this population, in addition to the educational brochure for adults. The CHMP recognises the need of this educational material and formalised the ongoing activities in Annex II. The key messages are reflected in annex II of the product information. The CHMP requested the review of the HIV educational brochure for children and adolescents aged 2 to <18 years.

Summary of the risk management plan

Safety Concern	**Proposed Pharmacovigilance Activities (routine and additional)**	**Proposed Risk Minimization Activities (routine and additional)**
Important Identified Risks		
Renal Toxicity	Routine pharmacovigilance activities including a renal tubulopathy targeted follow-up questionnaire for postmarketing reports Observational study (GS-US-104-0353) Cumulative review of reversibility of renal tubulopathy in HIV-1 and HBV infected adult patients Monitoring of renal parameters in HIV-1 and HBV infected adult and pediatric subjects in clinical studies who discontinue tenofovir DF due to renal tubulopathy Post-authorization safety study of HIV-1 and HBV infected pediatric	<u>Routine Risk Minimization Activities</u> Current approved Viread SmPC text is as follows: Statements in Section 4.2 of the Viread SmPC: *Tenofovir is eliminated by renal excretion and the exposure to tenofovir increases in patients with renal dysfunction. There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with moderate and severe renal impairment (creatinine clearance < 50 ml/min) and long term safety data has not been evaluated for mild renal impairment (creatinine clearance 50-80 ml/min). Therefore, in patients with renal impairment tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Dose interval adjustments are recommended for patients with creatinine clearance < 50 ml/min.* *Mild renal impairment (creatinine clearance 50–80 ml/min): Limited data from clinical studies support once daily dosing of tenofovir disoproxil fumarate in patients with mild renal impairment.* *Moderate renal impairment (creatinine clearance 30–49 ml/min): Administration of 245 mg tenofovir disoproxil (as fumarate) every 48 hours is recommended based on modeling of single-dose pharmacokinetic data in HIV negative and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring haemodialysis, but has not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.* *Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients: Adequate dose adjustments cannot be applied due to lack of alternative tablet strengths, therefore use in this group of patients is not recommended. If no alternative treatment is available, prolonged dose intervals may be used as follows:* *Severe renal impairment: 245 mg tenofovir disoproxil (as fumarate) may be administered every 72–96 hours (dosing twice a week).* *Haemodialysis patients: 245 mg tenofovir disoproxil (as fumarate) may be administered every 7 days following completion of a haemodialysis*

	patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients	*session*.* *These dose adjustments have not been confirmed in clinical studies. Simulations suggest that the prolonged dose interval is not optimal and could result in increased toxicity and possibly inadequate response. Therefore clinical response to treatment and renal function should be closely monitored.* ** Generally, once weekly dosing assuming three haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis.* *No dosing recommendations can be given for non-haemodialysis patients with creatinine clearance < 10 ml/min.* Warnings in Section 4.4 of the Viread SmPC: *Co-administration of other medicinal products: Viread should not be administered concomitantly with other medicinal products containing tenofovir disoproxil fumarate.* *Renal function: Renal safety with tenofovir has only been studied to a very limited degree in patients with impaired renal function (creatinine clearance < 80 ml/min).* *It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with tenofovir disoproxil fumarate and renal function (creatinine clearance and serum phosphate) is also monitored every four weeks during the first year, and then every three months. In patients at risk for renal impairment, including patients who have previously experienced renal events while receiving adefovir dipivoxil, consideration should be given to more frequent monitoring of renal function.* *Patients with creatinine clearance < 50 ml/min, including haemodialysis patients: There are limited data on the safety and efficacy of tenofovir disoproxil fumarate in patients with impaired renal function. Therefore, tenofovir disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. In patients with severe renal impairment (creatinine clearance < 30 ml/min) and in patients who require haemodialysis use of tenofovir is not recommended. If no alternative treatment is available, the dosing interval must be adjusted and renal function should be closely monitored.* *If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance is decreased to < 50 ml/min in any patient receiving tenofovir disoproxil fumarate, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations. Consideration should also be given to interrupting treatment with tenofovir disoproxil fumarate in patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).* *Use of tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic medicinal product (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2). If concomitant use of tenofovir disoproxil fumarate and nephrotoxic agents is unavoidable, renal function should be monitored weekly.* *Tenofovir disoproxil fumarate has not been clinically evaluated in patients receiving medicinal products which are secreted by the same renal pathway, including the transport proteins human organic anion transporter (hOAT) 1 and 3 or MRP 4 (e.g. cidofovir, a known nephrotoxic medicinal product). These renal transporter proteins may be responsible for tubular secretion and in part, renal elimination of tenofovir and cidofovir. Consequently, the pharmacokinetics of these medicinal products which are secreted by the same renal pathway including transport proteins hOAT 1 and 3 or MRP 4 might be modified if they are co-administered. Unless clearly necessary, concomitant use of these medicinal products which are secreted by the same renal pathway is not recommended, but if such use is unavoidable, renal function should be monitored weekly.*

		Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained. Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Viread (see section 4.4).* *c. Description of selected adverse reactions* *HIV-1 and hepatitis B:* *Renal impairment: As Viread may cause renal damage monitoring of renal function is recommended (see sections 4.4 and 4.8a).* *e. Other special population(s)* *Patients with renal impairment: Since tenofovir disoproxil fumarate can cause renal toxicity, close monitoring of renal function is recommended in any patient with renal impairment treated with Viread (see sections 4.2, 4.4 and 5.2).* Adverse reactions in Section 4.8b of the Viread SmPC: *Renal and urinary disorders:* *Uncommon: increased creatinine* *Rare: acute renal failure, renal failure, acute tubular necrosis, proximal renal tubulopathy (including Fanconi syndrome), nephritis (including acute interstitial nephritis), nephrogenic diabetes insipidus* *Metabolism and nutrition disorders:* *Very common: hypophosphataemia** *Uncommon: hypokalaemia** *Musculoskeletal and connective tissue disorders:* *Uncommon: rhabdomyolysis*, muscular weakness** *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)*, myopathy** ** This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* Update of labeling as appropriate Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows (based on proposed updates to the Viread 245 mg SmPC): Statement in Section 4.2 of the Viread SmPC: *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.4).* Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.* *Renal effects* *Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to <12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).* *Renal monitoring* *Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment and monitored during treatment as in adults (see above).* *Renal management* *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, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil fumarate treatment. *Co-administration and risk of renal toxicity* *The same recommendations apply as in adults (see above).* *Renal impairment* *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil fumarate should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.* Statement in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1* *Of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due to adverse reactions consistent with proximal renal tubulopathy.* Statements in Section 5.1 of the Viread SmPC *Paediatric population:* *HIV-1:* *In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil fumarate discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil fumarate exposure was 104 weeks).* <u>Additional Risk Minimization Activities</u> Educational initiatives ('HIV and the Kidney' educational program, renal educational program for HBV, educational brochures distributed to prescribers). Update of educational program as appropriate Following the approval of the pediatric applications, renal risk minimization activities will be updated to include information on HIV-1 infected children and adolescents and HBV infected adolescents. Educational brochures specific to the use of Viread in these pediatric populations will be distributed to pediatric prescribers.
Bone events due to proximal renal tubulopathy/loss of bone mineral density	Routine pharmacovigilance activities including monitoring and review in PSURs. Clinical studies (GS-99-903, GS-US-236-0103 GS-US-174-0102, GS-US-174-0103, GS-US-174-0115, GS-US-174-0121, GS-US-104-0321, GS-US-104-0352) Retrospective analyses of pediatric BMD Z-scores adjusted by height (GS-US-174-0115, GS-US-104-0321, GS-US-104-0352) Planned clinical	<u>Routine Risk Minimization Activities</u> Current approved Viread SmPC text is as follows: Statements in Section 4.4 of the Viread SmPC: *Bone effects: In HIV infected patients, in a 144-week controlled clinical study that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz in antiretroviral-naïve patients, small decreases in bone mineral density of the hip and spine were observed in both treatment groups. Decreases in bone mineral density of spine and changes in bone biomarkers from baseline were significantly greater in the tenofovir disoproxil fumarate treatment group at 144 weeks. Decreases in bone mineral density of hip were significantly greater in this group until 96 weeks. However, there was no increased risk of fractures or evidence for clinically relevant bone abnormalities over 144 weeks.* *Bone abnormalities (infrequently contributing to fractures) may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.* *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).* Statements in Section 4.8 of the Viread SmPC *a. Summary of the safety profile* *HIV-1 and hepatitis B: In patients receiving tenofovir disoproxil fumarate, rare events of renal impairment, renal failure and proximal*

	study in HBV infected pediatric patients (GS-US-174-0144) Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients Planned cross-sectional study to assess BMD in HIV-1 infected patients of interest who include those over 50 years of age, particularly women, and who have been exposed to tenofovir DF for at least 3 years (GS-US-104-0423).	*renal tubulopathy (including Fanconi syndrome) sometimes leading to bone abnormalities (infrequently contributing to fractures) have been reported. Monitoring of renal function is recommended for patients receiving Viread (see section 4.4).* Adverse reactions in Section 4.8b of the Viread SmPC *Musculoskeletal and connective tissue disorders:* *Rare: osteomalacia (manifested as bone pain and infrequently contributing to fractures)[1,2]* *[1] This adverse reaction may occur as a consequence of proximal renal tubulopathy. It is not considered to be causally associated with tenofovir disoproxil fumarate in the absence of this condition.* *[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomized controlled clinical trials or the tenofovir disoproxil fumarate expanded access program. The frequency category was estimated from a statistical calculation based on the total number of patients exposed to tenofovir disoproxil fumarate in randomized clinical trials and the expanded access program (n = 7,319).* Statements in Section 5.1 of the Viread SmPC *Paediatric population:* *HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks.* *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.* Update of labeling as appropriate Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows: Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.* *Bone effects:* *If bone abnormalities are detected or suspected in paediatric patients, consultation with an endocrinologist and/or nephrologist should be obtained.* Statement in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1* *Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil*

		fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1). *Chronic hepatitis B* *Reductions in BMD have been observed in HBV-infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo (see sections 4.4 and 5.1).* Statements in Section 5.1 of the Viread SmPC *In study GS-US-104-0352, 97 treatment experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks.* *Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.* *Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 10^5 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks.* *No subjects met the primary safety endpoint of a 6% decrease in lumbar spine BMD. In subjects receiving tenofovir disoproxil fumarate or placebo, mean (SD) lumbar spine BMD Z-score was -0.43 (0.764) and -0.28 (0.813), and mean total body BMD Z-score was -0.20 (1.126) and -0.26 (0.878), respectively, at baseline. The mean (SD) change in lumbar spine BMD Z-score from baseline to week 72 in subjects receiving tenofovir disoproxil fumarate was -0.05 (0.310) and 0.07 (0.377) in those receiving placebo. BMD Z-scores were not adjusted for height and weight. The mean change in whole body BMD Z-score in subjects receiving tenofovir disoproxil fumarate was -0.15 (0.379) and 0.06 (0.361) in those receiving placebo. The mean percentage increase in whole body and lumbar spine BMD from baseline to week 72 was 2.84% and 4.95%, respectively, in subjects receiving tenofovir disoproxil fumarate. These mean percentage increases in whole body and lumbar spine BMD were 2.53% and 3.19% less, respectively, when compared to subjects receiving placebo. Three subjects in the tenofovir disoproxil fumarate group and 2 subjects in the placebo group had a decrease of > 4% in spine BMD.*
Post-treatment hepatic flares in HBV monoinfected and HIV/HBV	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Statement in Section 4.2 of the Viread SmPC: *If Viread is discontinued in patients with chronic hepatitis B with or without HIV co-infection, these patients should be closely monitored for evidence of exacerbation of hepatitis (see Section 4.4).* Warning in Section 4.4 of the Viread SmPC:

coinfected patients		*Flares after treatment discontinuation: Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. Hepatic function should be monitored at repeated intervals with both clinical and laboratory follow-up for at least 6 months after discontinuation of hepatitis B therapy. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.* *Liver flares are especially serious, and sometimes fatal in patients with decompensated liver disease.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Acute exacerbation of hepatitis has been reported in patients on treatment as well as in patients who have discontinued hepatitis B therapy (see section 4.4).* *c. Description of selected adverse reactions* *Exacerbations of hepatitis after discontinuation of treatment: In HBV infected patients, clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of HBV therapy (see section 4.4).* Update of labeling as appropriate.
Interaction with didanosine	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Warning in Section 4.4 of the Viread SmPC (interaction also described in Section 4.5): *Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended. Co-administration of tenofovir disoproxil fumarate and didanosine results in a 40–60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions. Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported. Co-administration of tenofovir disoproxil fumarate and didanosine at a dose of 400 mg daily has been associated with a significant decrease in CD4 cell count, possibly due to an intracellular interaction increasing phosphorylated (i.e. active) didanosine. A decreased dosage of 250 mg didanosine co-administered with tenofovir disoproxil fumarate therapy has been associated with reports of high rates of virological failure within several tested combinations for the treatment of HIV-1 infection.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Co- administration of Viread and didanosine is not recommended as this may result in an increased risk of adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported (see section 4.4).* *c. Description of selected adverse reactions* *Interaction with didanosine: Co-administration of tenofovir disoproxil fumarate and didanosine is not recommended as it results in a 40-60% increase in systemic exposure to didanosine that may increase the risk of didanosine-related adverse reactions (see section 4.5). Rarely, pancreatitis and lactic acidosis, sometimes fatal, have been reported.* Update of labeling as appropriate.
Pancreatitis	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Pancreatitis is listed in Section 4.8b of the Viread SmPC: *Gastrointestinal disorders:* *Uncommon: pancreatitis* There are also warning statements in Sections 4.4, 4.5 and 4.8 of the Viread SmPC regarding the risk of pancreatitis associated with the interaction with didanosine (see above). Update of labeling as appropriate.
Lactic acidosis	Routine	<u>Routine Risk Minimization Activities</u> Warning in Section 4.4 of the Viread SmPC:

and severe hepatomegaly with steatosis	pharmacovigilance activities	*Lactic acidosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. The preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues, is low for tenofovir disoproxil fumarate. However, as tenofovir is structurally related to nucleoside analogues, this risk cannot be excluded. Early symptoms (symptomatic hyperlactataemia) include benign digestive symptoms (nausea, vomiting and abdominal pain), non specific malaise, loss of appetite, weight loss, respiratory symptoms (rapid and/or deep breathing) or neurological symptoms (including motor weakness). Lactic acidosis has a high mortality and may be associated with pancreatitis, liver failure or renal failure. Lactic acidosis generally occurred after a few or several months of treatment.* *Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels.* *Caution should be exercised when administering nucleoside analogues to any patient (particularly obese women) with hepatomegaly, hepatitis or other known risk factors for liver disease and hepatic steatosis (including certain medicinal products and alcohol). Patients co-infected with hepatitis C and treated with alpha interferon and ribavirin may constitute a special risk.* *Patients at increased risk should be followed closely.* Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate (see sections 4.4 and 4.8c).* *c. Description of selected adverse reactions* *Lactic acidosis and severe hepatomegaly with steatosis: Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues. Treatment with nucleoside analogues should be discontinued in the setting of symptomatic hyperlactataemia and metabolic/lactic acidosis, progressive hepatomegaly, or rapidly elevating aminotransferase levels (see section 4.4).* Lactic acidosis is listed in Section 4.8b of the Viread SmPC: *Metabolism and nutrition disorders:* *Rare: lactic acidosis* There are also warning statements in Section 4.4, 4.5 and 4.8 of the Viread SmPC regarding the risk of lactic acidosis associated with the interaction with didanosine (see above). Update of labeling as appropriate.
Lipodystrophy	Routine pharmacovigilance activities	<u>Routine Risk Minimization Activities</u> Precautionary statements in Section 4.4 of the Viread SmPC: *Lipodystrophy: Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors and lipoatrophy and nucleoside reverse transcriptase inhibitors has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.* *Tenofovir is structurally related to nucleoside analogues hence the risk of lipodystrophy cannot be excluded. However, 144-week clinical data from antiretroviral-naïve HIV infected patients indicate that the risk of lipodystrophy was lower with tenofovir disoproxil fumarate than with stavudine when administered with lamivudine and efavirenz.*

		Statements in Section 4.8 of the Viread SmPC: *a. Summary of the safety profile* *Lactic acidosis, severe hepatomegaly with steatosis and lipodystrophy are associated with tenofovir disoproxil fumarate (see sections 4.4 and 4.8c).* *c. Description of selected adverse reactions* *Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).* *In a 144-week controlled clinical study in antiretroviral-naïve patients that compared tenofovir disoproxil fumarate with stavudine in combination with lamivudine and efavirenz, patients who received tenofovir disoproxil had a significantly lower incidence of lipodystrophy compared with patients who received stavudine. The tenofovir disoproxil fumarate arm also had significantly smaller mean increases in fasting triglycerides and total cholesterol than the comparator arm.* Update of labeling as appropriate.
Important Potential Risks		
Development of resistance during long-term exposure in HBV infected patients	Routine pharmacovigilance activities Clinical studies (GS-US-174-0102, GS-US-174-0103, GS-US-174-0121)	<u>Routine Risk Minimization Activities</u> Section 5.1 of the Viread SmPC states the following: *Resistance: No HBV mutations associated with tenofovir disoproxil fumarate resistance have been identified. In cell based assays, HBV strains expressing the rtV173L, rtL180M, and rtM204I/V mutations associated with resistance to lamivudine and telbivudine showed a susceptibility to tenofovir ranging from 0.7- to 3.4-fold that of wild-type virus. HBV strains expressing the rtL180M, rtT184G, rtS202G/I, rtM204V and rtM250V mutations associated with resistance to entecavir showed a susceptibility to tenofovir ranging from 0.6- to 6.9-fold that of wild-type virus. HBV strains expressing the adefovir-associated resistance mutations rtA181V and rtN236T showed a susceptibility to tenofovir ranging from 2.9- to 10-fold that of wild-type virus. Viruses containing the rtA181T mutation remained susceptible to tenofovir with EC_{50} values 1.5-fold that of wild-type virus.* *Clinical resistance: Four hundred and twenty-six HBeAg negative (GS-US-174-0102, n = 250) and HBeAg positive (GS-US-174-0103, n = 176) patients were evaluated for genotypic changes in HBV polymerase from baseline. Genotypic evaluations performed on all patients initially randomised to the tenofovir disoproxil fumarate arm (i.e excluding patients who received double-blind adefovir dipivoxil and then switched to open-label tenofovir disoproxil fumarate) with HBV DNA > 400 copies/ml at week 48 (n = 39), week 96 (n = 24) and week 144 (n = 6) and week 192 (n = 5) on tenofovir disoproxil fumarate monotherapy, showed that no mutations associated with tenofovir disoproxil fumarate resistance have developed.* *In study GS-US-174-0108, 45 patients (including 9 patients with lamivudine and/or adefovir dipivoxil resistance mutations at baseline) received tenofovir disoproxil fumarate for up to 48 weeks. Genotypic data from paired baseline and on treatment HBV isolates were available for 6/8 patients with HBV DNA > 400 copies/ml. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.* Update of labeling as appropriate.
Important Missing Information		
Safety in children (including long-term safety)	Routine pharmacovigilance activities Clinical studies in HIV-1 infected children (GS-US-104-0321,	<u>Routine Risk Minimization Activities</u> Current approved Viread SmPC text is as follows: Statement in Section 4.2 of the Viread SmPC: *Paediatric population: Viread is not recommended for use in children The clinical data available in HIV-1 infected adolescents are inadequate to support the use of tenofovir disoproxil fumarate in this population and no data are currently available in younger children.* *No data are currently available in paediatric patients infected with*

	GS-US-104-0352) Clinical study in HBV infected adolescents (GS-US-174-0115) Planned clinical study, including a PK substudy, in HBV infected children aged 2 to < 12 years (GS-US-174-0144) Planned PK bioavailability study of TDF granules in the fed state Post-authorization safety study of HIV-1 and HBV infected pediatric patients Drug Utilization Study in HIV-1 and HBV infected pediatric patients	*chronic hepatitis B.* Statement in Section 4.4 of the Viread SmPC: *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.* Statement in Section 4.8 of the Viread SmPC: *d. Paediatric population* *Assessment of adverse reactions is based on one randomised trial (study GS-US-104-0321) in 87 HIV-1 infected adolescent patients (aged 12 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with other antiretroviral agents for 48 weeks.* Statements in Section 5.1 of the Viread SmPC: *Paediatric population:* *HIV-1: In study GS-US-104-0321, 87 HIV-1 infected treatment-experienced patients 12 to < 18 years of age were treated with tenofovir disoproxil fumarate (n = 45) or placebo (n = 42) in combination with an optimised background regimen (OBR) for 48 weeks.* *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.* Proposed additional Viread SmPC text specific to the treatment of pediatric patients is as follows (based on proposed updates to the Viread 245 mg SmPC): Statements in Section 4.2 of the Viread SmPC: *Paediatric population* *HIV-1: The safety and efficacy of tenofovir disoproxil fumarate in HIV-1 infected children under 2 years of age have not been established. No data are available.* *Chronic hepatitis B: The safety and efficacy of tenofovir disoproxil fumarate in children with chronic hepatitis B aged 2 to < 12 years or weighing < 35 kg have not been established. No data are available.* *Special populations* *Renal impairment: The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.4).* Statements in Section 4.4 of the Viread SmPC: *Renal and bone effects in paediatric population* *There are uncertainties associated with the long term effects of bone and renal toxicity. Moreover, the reversibility of renal toxicity cannot be fully ascertained. Therefore, a multidisciplinary approach is recommended to adequately weigh on a case by case basis the benefit/risk balance of treatment, decide the appropriate monitoring during treatment (including decision for treatment withdrawal) and consider the need for supplementation.* *Renal effects* *Renal adverse reactions consistent with proximal renal tubulopathy have been reported in HIV-1 infected paediatric patients aged 2 to <12 years in clinical study GS-US-104-0352 (see sections 4.8 and 5.1).*

		Renal monitoring *Renal function (creatinine clearance and serum phosphate) should be evaluated prior to treatment and monitored during treatment as in adults (see above).* *Renal management* *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, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). If renal abnormalities are suspected or detected then consultation with a nephrologist should be obtained to consider interruption of tenofovir disoproxil fumarate treatment.* *Co-administration and risk of renal toxicity* *The same recommendations apply as in adults (see above).* *Renal impairment* *The use of tenofovir disoproxil fumarate is not recommended in paediatric patients with renal impairment (see section 4.2). Tenofovir disoproxil fumarate should not be initiated in paediatric patients with renal impairment and should be discontinued in paediatric patients who develop renal impairment during tenofovir disoproxil fumarate therapy.* *Bone effects:* *If bone abnormalities are detected or suspected in paediatric patients,, consultation with an endocrinologist and/or nephrologist should be obtained.* Statements in Section 4.8 of the Viread SmPC: *Paediatric population* *HIV-1:* *Assessment of adverse reactions is based on two randomised trials (studies GS-US-104-0321 and GS-US-104-0352) in 184 HIV-1 infected paediatric patients (aged 2 to < 18 years) who received treatment with tenofovir disoproxil fumarate (n = 93) or placebo/active comparator (n = 91) in combination with other antiretroviral agents for 48 weeks (see section 5.1). The adverse reactions observed in paediatric patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).* *Reductions in BMD have been reported in paediatric patients. In HIV-1 infected adolescents, the BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who received placebo. In HIV-1 infected children, the BMD Z-scores observed in subjects who switched to tenofovir disoproxil fumarate were lower than those observed in subjects who remained on their stavudine- or zidovudine-containing regimen (see sections 4.4 and 5.1).* *Of 89 patients (2 to < 12 years) who received tenofovir disoproxil fumarate in study GS-US-104-0352 (median exposure 104 weeks), 4 patients discontinued from the study due to adverse reactions consistent with proximal renal tubulopathy.* *Chronic hepatitis B:* *Assessment of adverse reactions is based on one randomised study (study GS-US-174-0115) in 106 adolescent patients (12 to < 18 years of age) with chronic hepatitis B receiving treatment with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks. The adverse reactions observed in adolescent patients who received treatment with tenofovir disoproxil fumarate were consistent with those observed in clinical studies of tenofovir disoproxil fumarate in adults (see section 4.8 Tabulated summary of adverse reactions and 5.1).* *Reductions in BMD have been observed in HBV-infected adolescents. The BMD Z-scores observed in subjects who received tenofovir disoproxil fumarate were lower than those observed in subjects who*

		received placebo (see sections 4.4 and 5.1). Statements in Section 5.1 of the Viread SmPC *In study GS-US-104-0352, 97 treatment experienced patients 2 to < 12 years of age with stable, virologic suppression on stavudine- or zidovudine-containing regimens were randomised to either replace stavudine or zidovudine with tenofovir disoproxil fumarate (n = 48) or continue on their original regimen (n = 49) for 48 weeks.* *Reductions in BMD have been reported in paediatric patients. In patients who received treatment with tenofovir disoproxil fumarate, or stavudine or zidovudine, mean lumbar spine BMD Z-score was -1.034 and -0.498, and mean total body BMD Z-score was -0.471 and -0.386, respectively, at baseline. Mean changes at week 48 (end of randomised phase) were 0.032 and 0.087 in lumbar spine BMD Z-score, and -0.184 and -0.027 in total body BMD Z-score for the tenofovir disoproxil fumarate and stavudine or zidovudine groups, respectively. The mean rate of lumbar spine bone gain at week 48 was similar between the tenofovir disoproxil fumarate treatment group and the stavudine or zidovudine treatment group. Total body bone gain was less in the tenofovir disoproxil fumarate treatment group compared to the stavudine or zidovudine treatment group. One tenofovir disoproxil fumarate treated subject and no stavudine or zidovudine treated subjects experienced significant (> 4%) lumbar spine BMD loss at week 48. BMD Z-scores declined by -0.012 for lumbar spine and by -0.338 for total body in the 64 subjects who were treated with tenofovir disoproxil fumarate for 96 weeks. BMD Z-scores were not adjusted for height and weight.* *In study GS-US-104-0352, 4 out of 89 paediatric patients exposed to tenofovir disoproxil fumarate discontinued due to adverse reactions consistent with proximal renal tubulopathy (median tenofovir disoproxil fumarate exposure was 104 weeks).* *Chronic hepatitis B: In study GS-US-174-0115, 106 HBeAg negative and HBeAg positive patients aged 12 to < 18 years with chronic HBV infection [HBV DNA ≥ 10^5 copies/ml, elevated serum ALT (≥ 2 x ULN) or a history of elevated serum ALT levels in the past 24 months] were treated with tenofovir disoproxil 245 mg (as fumarate) (n = 52) or placebo (n = 54) for 72 weeks.* *No subjects met the primary safety endpoint of a 6% decrease in lumbar spine BMD. In subjects receiving tenofovir disoproxil fumarate or placebo, mean (SD) lumbar spine BMD Z-score was -0.43 (0.764) and -0.28 (0.813), and mean total body BMD Z-score was -0.20 (1.126) and -0.26 (0.878), respectively, at baseline. The mean (SD) change in lumbar spine BMD Z-score from baseline to week 72 in subjects receiving tenofovir disoproxil fumarate was -0.05 (0.310) and 0.07 (0.377) in those receiving placebo. The mean change in whole body BMD Z-score in subjects receiving tenofovir disoproxil fumarate was -0.15 (0.379) and 0.06 (0.361) in those receiving placebo. BMD Z-scores were not adjusted for height and weight. The mean percentage increase in whole body and lumbar spine BMD from baseline to week 72 was 2.84% and 4.95%, respectively, in subjects receiving tenofovir disoproxil fumarate. These mean percentage increases in whole body and lumbar spine BMD were 2.53% and 3.19% less, respectively, when compared to subjects receiving placebo. Three subjects in the tenofovir disoproxil fumarate group and 2 subjects in the placebo group had a decrease of > 4% in spine BMD.* The proposed Viread oral granules SmPC also contains statements indicating that limited clinical data are available at the 6.5 mg/kg dose of the oral granules and therefore close monitoring of efficacy and safety is needed, and that investigations are planned to further substantiate the dose in children from 2 years of age. Following the approval of the pediatric applications, renal risk minimization activities will be updated to include information on HIV-1 infected children and adolescents and HBV infected adolescents. Educational brochures specific to the use of Viread in these pediatric

		populations will be distributed to pediatric prescribers (see Renal Safety Concern).
Safety in pregnancy	Routine pharmacovigilance activities Epidemiological studies (Antiretroviral Pregnancy Registry; Cross-sectional study to assess the risk of mitochondrial disease in children exposed to NRTIs in utero [MITOC group])	Routine Risk Minimization Activities Statements in Section 4.6 of the Viread SmPC: *Pregnancy* *A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil fumarate. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of tenofovir disoproxil fumarate may be considered during pregnancy, if necessary.* Update of labeling as appropriate.
Safety in patients with renal impairment	Routine pharmacovigilance activities Clinical study in HBV infected patients including patients with mild to moderate renal impairment (GS-US-174-0121) Planned clinical study in HBV infected patients with moderate to severe renal impairment (GS-US-174-0127)	Routine Risk Minimization Activities See Renal Safety Concern. A Type II variation application for tenofovir DF 40 mg/g granules is planned to be submitted by Q4 2012 to enable adjustment of daily dose as well as dose interval of tenofovir DF in HIV-1 infected and HBV infected adult patients with moderate or severe renal impairment.
Safety in elderly patients	Routine pharmaco vigilance activities	Routine Risk Minimization Activities Warning in Section 4.4 of the Viread SmPC (also in section 4.8e): *Elderly; Tenofovir disoproxil fumarate has not been studied in patients over the age of 65. Elderly patients are more likely to have decreased renal function; therefore caution should be exercised when treating elderly patients with tenofovir disoproxil fumarate.* Update of labeling as appropriate.
Safety in lactation	Routine pharmaco vigilance activities	Routine Risk Minimization Activities Statements in Section 4.6 of the Viread SmPC: *Breast-feeding* *Tenofovir has been shown to be excreted in human milk. There is insufficient information on the effects of tenofovir in newborns/infants. Therefore Viread should not be used during breast-feeding.* *As a general rule, it is recommended that HIV and HBV infected women do not breast-feed their infants in order to avoid transmission of HIV and HBV to the infant.* Update of labeling as appropriate.
Safety in black HBV infected patients	Routine pharmaco vigilance activities	Routine Risk Minimization Activities Update of labeling as appropriate.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity(ies) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
A PK bioavailability study to compare granules and oral tablet at fed state (with both a light and high fat meal) to further substantiate the conclusion that a similar dose can be given regardless of the formulation in this setting.	31 August 2013
Collection of PK data in study GS-US-174-0144 (HBV infected subjects 2 to < 12 years of age) to further substantiate the adequacy of the selected dose.	30 June 2014
Conduct a separate post-authorisation safety study with a representative sample of HIV- and HBV infected children to help establish evidence-based strategies for management of TDF-associated renal and bone toxicity.	Submit the protocol synopsis by 31 December 2012. Interim study results: 31 December 2014 Final study results: 31 December 2016
To conduct a Drug Utilisation Study in HIV-1 and HBV-infected paediatric patients to follow-up the effectiveness of the risk minimisation measures.	Submit draft synopsis by 25 October 2012 Feasibility assessment alongside a full draft protocol expected: by 28 February 2013. Interim study results: 31 December 2014 Final study results: 31 December 2017

In addition, to further evaluate the safety profile of the product, the CHMP requested the MAH to submit a cumulative review of renal tubulopathy reports in HIV-1 and HBV infected adult patients by 31 December 2012. (LEG)

The CHMP, having considered the data submitted, was of the opinion that the below additional risk minimisation activities are required for the management of the safety profile of the product:

Physician educational pack containing the Summary of Product Characteristics and an appropriate educational brochure, as detailed below:

- HIV renal educational brochure, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure

2. Benefit-risk balance

Benefits

Beneficial effects

Given that the current backbone regimens are not only limited but also have limiting factors (hypersensitivity requesting HLA testing, anaemia, lipodystrophy), tenofovir represents an additional therapeutic option in children. Tenofovir is a widely used backbone regimen in adult patients due to its virological efficacy and high genetic barrier. Moreover, TDF is a once daily regimen, which is of interest especially in children.

Extrapolation from the adult experience together with comparative PK data support the extension of indication in children.

Uncertainty in the knowledge about the beneficial effects

Clinical demonstration in children is not aimed at duplicating the level of demonstration already derived from adults but rather at obtaining reassurance on the adequacy of the dose selected on the principle that similar PK exposure as in adults would predict similar efficacy in children.

Determining an optimal dose in children is always a difficult exercise when having to conciliate limited sample size and several sources of variability. Even though the vast majority of children in this study had sustained adequate suppression at the 8mg/kg dose, further data is expected to give further reassurance on the dose.

Furthermore the applicant is performing a comparability of the PK bioavailability between the granules and the oral tablet at fed state to provide further reassurance on the use under fed conditions.

Risks

Unfavourable effects

The renal and bone toxicity are a source of particular concern for the long-term use of TDF. This is true both for adults and for paediatric patients especially considering that they are in evolving modelling process.

Uncertainty in the knowledge about the unfavourable effects

The long-term effect of TDF on bone mineral acquisition during childhood and the potential reversibility of bone toxicity cannot be determined from the non clinical and clinical data available. However, it is acknowledged that given the lack of correlation between BMD and clinical events, it remains theoretical risk.

Moreover, the reversibility of the renal toxicity cannot be fully ascertained. The CHMP requested a cumulative review of renal tubulopathy reports in HIV-1 and HBV infected adult patients to be submitted by 31 December 2012.

Given the uncertainties related to the use of tenofovir in a population of active modelling process, the CHMP supports the use of tenofovir in the restricted population of treatment NRTI resistance or toxicity problems precluding the use of other first line agent's population from 2 years of age.

Moreover, warnings were added to the SmPC to alert physicians on the uncertainties on the long term effect of bone and renal toxicity and the fact that reversibility of renal toxicity cannot be fully ascertained. A statement was introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation. Promoting multidisciplinary approach appears pragmatic based on the SAG input that management is to be tailored to the child and mostly refer to good clinical practice in paediatric. Furthermore a separate post-authorisation study with a representative sample of HIV- and HBV infected children will help to establish evidence-based strategies for management of TDF-associated renal and bone toxicity.

Discussion on the benefit-risk assessment

Overall, further to the SAG input, the CHMP considers that Viread can be approved for the use in children from 2 years of age provided the indication is targeted to patients with NRTI resistance or toxicity problems precluding the use of first line agents.

Overall, the CHMP consider that given the lack of correlation between BMD decrease and clinical event, long term effect of bone and renal toxicity remains theoretical whereas there are established benefits in a population of paediatric patients in need of treatment. However, there are uncertainties that per se mandate special consideration on the use of tenofovir in a population of active modelling process. Therefore the CHMP could support the use of tenofovir in the restricted population of paediatric patients with NRTI resistance or toxicity problems precluding the use of first line agents from 2 years of age.

The SmPC was revised to include warnings to alert physicians on the uncertainties on the long term effect of bone and renal toxicity and the fact that reversibility of renal toxicity cannot be fully ascertained. A statement was introduced to promote a multidisciplinary management of paediatric patients to adequately weigh the need for treatment, to adequately settle the monitoring and to foresee the need for supplementation. Promoting multidisciplinary approach appears pragmatic based on the SAG input that management is to be tailored to the child and mostly refer to good clinical practice in paediatric.

Further studies are included in the RMP that will help to further understand the safety in this population.

Additionally, the CHMP agreed with the type IB variation for Viread 245 mg tablets to update the SmPC to make reference to the availability of the granules formulation.

3. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Viread in the treatment of paediatric patients with NRTI resistance or toxicity problems precluding the use of first line agents from 2 years of age, that the risk-benefit balance of this new pharmaceutical form and strengths and that the reference to the

availability of the granule formulation is favourable and therefore recommends the authorisation of this grouped application subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow a yearly cycle until otherwise agreed by the CHMP.

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

The Marketing Authorisation Holder (MAH) shall ensure that all physicians who are expected to prescribe/use Viread in adults and/or paediatric patients 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, including the creatinine clearance slide ruler
- HBV renal educational brochure, including the creatinine clearance slide ruler
- HIV paediatric educational brochure
- HBV paediatric educational brochure
-

The HIV and HBV renal educational brochures should contain the following key messages:

- That there is an increased risk of renal disease in HIV and HBV infected patients associated with tenofovir disoproxil fumarate-containing products such as Viread
- That Viread should only be used in patients with impaired renal function if the potential benefits of treatment are considered to outweigh the potential risks

- The importance of dose interval adjustment of Viread in adult patients with creatinine clearance of 30-49 ml/min
- That Viread is not recommended for patients with severe renal impairment (creatinine clearance < 30 ml/min). If no alternative treatment is available, prolonged dose intervals may be used.
- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread 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 Viread therapy
- The importance of regular monitoring of renal function during Viread therapy
- Recommended schedule for monitoring renal function considering the presence or absence of additional risk factors for renal impairment
- That if serum phosphate is < 1.5 mg/dl or creatinine clearance decreases during therapy to < 50 ml/min then renal function should be re-evaluated within one week. If creatinine clearance is confirmed as < 50 ml/min or serum phosphate decreases to < 1.0 mg/dl then consideration should be given to interrupting Viread therapy.
- Instructions on the use of the creatinine clearance slide ruler

The HIV and HBV paediatric 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 and HBV infected patients associated with tenofovir disoproxil fumarate-containing products such as Viread
- That Viread is not recommended for use in paediatric patients with renal impairment
- That use of Viread should be avoided with concomitant or recent use of nephrotoxic medicinal products. If Viread 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 Viread therapy
- The importance of regular monitoring of renal function during Viread 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 Viread treatment
- That Viread may cause a reduction in BMD and the effects of Viread 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/180/2011 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.