European Medicines Agency

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Product Name: Viread
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ASSESSMENT REPORT
FOR
VIREAD

International non-proprietary name**:**
tenofovir disoproxil fumarate

Procedure No: EMEA/H/C/419/II/75

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Introduction

Tenofovir disoproxil fumarate (tenofovir DF) is the salt of the oral prodrug of tenofovir. Tenofovir, a nucleoside monophosphate (nucleotide) analogue is metabolised to the active metabolite, tenofovir diphosphate, a competitive inhibitor of Human Immunodeficiency Virus type 1 (HIV-1) reverse transcriptase. Tenofovir has an *in vitro* and *in vivo* antiviral activity against retroviruses and hepadnaviruses, including HIV-2 and hepatitis B Virus (HBV).

Viread (tenofovir DF), 245 mg film coated tablets in a once daily regimen is approved in the European Union (EU) for the therapeutic management of HIV-1 infected adult patients since 5 February 2002. Tenofovir DF is also approved in fixed-dose combination products (emtricitabine/tenofovir DF and efavirenz/emtricitabine/tenofovir DF) for the treatment of HIV-1 infected adult patients as part of a combination antiretroviral therapy.

The Marketing Authorisation Holder (MAH) applied for an extension of the therapeutic indication of Viread for the treatment of chronic Hepatitis B adult patients in the present type II variation application.

Hepatitis B infection represents a major global health problem with nearly 350 million people being infected. In Europe the carrier rate varies from around 0.5% in the northern regions to 1-8% in the Mediterranean and Eastern regions. The goal of therapy in chronic hepatitis B infected adult patients is to prevent progression to cirrhosis and /or hepatocellular carcinoma and the current treatment strategy is the achievement of a profound and durable suppression of HBV DNA. Current inter-/national guidelines recommend treatment in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B with moderate/severe hepatitis on biopsy, serum HBV DNA ($>10^5$ copies/ml and $>10^4$ copies/ml, respectively) and elevated ALT (alanine aminotransferase) levels.

Currently available treatment options include in addition to interferon the following anti-virals:

- Lamivudine: rapid development of resistance if used as monotherapy (about 2/3 after 4 years);
- Adefovir dipivoxil: estimated cumulative resistance at 5 year about 25%;
- Entecavir: reduced activity in case of lamivudine resistance;
- Telbivudine: selects for mutants cross-resistant to lamivudine/entecavir. Sparse long-term data available;

There is a medical need for new therapeutic options for naïve patients as well as for patients with resistant HBV with improved efficacy and safety profiles, with durable response and with low potential for developing viral resistance.

Non-clinical aspects

Comprehensive non-clinical study programmes have been performed and reviewed at the time of the Marketing Authorisation Applications (MAA) of tenofovir DF, or fixed combination products with tenofovir DF, for the treatment of HIV infection. A summary of non-clinical pharmacokinetics and toxicology with the key findings was submitted together with new non-clinical pharmacology data in relation to the applied therapeutic indication.

Pharmacology

Mechanism of action

Tenofovir disoproxil fumarate is converted to tenofovir by serum esterases. Intracellularly, tenofovir is phosphorylated into its active metabolite, tenofovir diphosphate. Tenofovir diphosphate was reported in human hepatic cells, and in primary human hepatocytes with a half life of 95 hours. Tenofovir diphosphate inhibited recombinant HBV polymerase with a kinetic inhibition constant (K_i) of 0.18 μmol/l. Inhibition of viral polymerases occurs by direct binding competition with the natural deoxyribonucleotide substrate (deoxyadenosine triphosphate - dATP) and, after incorporation into DNA, by DNA chain termination.

In vitro anti-HBV activity

The *in vitro* antiviral activity of tenofovir against an HBV laboratory strain, assessed in the HepG2 2.2.15 cell line, was characterised by EC_{50} values in the range of 0.14 to 1.5 μmol/l, with CC_{50} (50% cytotoxicity concentration) values > 100 μmol/l. Tenofovir inhibited various wild-type HBV clinical isolates (genotypes A, C, D) with a comparable activity with values ranging from 0.3 to 0.7 μmol/l.

In vitro resistance

No HBV polymerase mutations associated with resistance to tenofovir DF have been currently identified.

An HBV rtA194T mutation, developed in the background of the rtL180M+rtM204V lamivudine associated combined mutation, was reported in two patients receiving antiretroviral treatments including tenofovir DF and lamivudine. Studies showed that rtA194T mutation alone has no significant effect on tenofovir DF susceptibility (1.5-fold increase in tenofovir EC_{50}). The rtA194T mutation in combination with the rtL180M+rtM204V mutations led to a 2.4-fold increase in tenofovir EC_{50} which is not significantly different from the 2.1-fold increase observed with rtL180M+rtM204V mutations alone.

Clinical studies have shown that tenofovir DF inhibited lamivudine-resistant HBV suggesting that a 2- to 3- fold change in *in vitro* susceptibility to tenofovir is not clinically relevant.

Tenofovir DF demonstrated similar activity against all four major patterns of lamivudine resistance mutations identified in patients who failed lamivudine therapy.

Table 1. *In vitro* antiviral activities against lamivudine resistant hepatitis B virus

HBV mutant	**Tenofovir**	**Lamivudine**
Wild type	EC50 (μM) 0.77	EC50 (μM) 0.06
rtL180M + rtM204V	0.8 fold change	>700 fold change
rtV173L + rtL180M + rtM204V	1.8 fold change	>1000 fold change
rtM204I	2.1 fold change	>1000 fold change
rtL180M + rtM204I	0.7 fold change	>1000 fold change

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 DF ranging from 0.7 to 3.4-fold that of wild type virus.

HBV strains expressing rtA181V and rtN236T mutations associated with resistance to adefovir dipivoxil showed a 2.9- to 4.5-fold reduced sensitivity to tenofovir DF *in vitro*. The effects of other adefovir resistance associated mutations or combinations of mutations, rtA181T, rtA181V/rtN236T and rtA181T/rtN236T resulted in a reduction in susceptibility to tenofovir of 1.5-, 10- and 3.0-fold each, respectively. The clinical significance of these *in vitro* results is currently unknown.

Table 2. *In vitro* antiviral activities against adefovir resistant hepatitis B virus

HBV mutant	**Tenofovir**	**Adefovir**
Wild type	EC50 (μM) 0.92±0.23	EC50 (μM) 1.17±0.43
N236T	4.0	7.0
A181V	3.2	4.3
A181V+N236T	10	18
A181T+N236T	3.0	5.2
A181T	1.5	1.2

The mutations conferring resistance to entecavir have been identified as changes at rtI169T, rtT184G, rtS202I/G and rtM250V in combination with the pre-existing lamivudine resistance mutations. *In vitro* phenotypic analysis showed that the tested entecavir resistance mutations resulted in increased EC_{50} values for tenofovir DF ranging from 0.6- to 6.9-fold.

Table 3. *In vitro* antiviral activities against entecavir resistant hepatitis B virus

HBV mutant	Tenofovir	Entecavir
Wild type	1	1
L180M+M204V	2.3	70
L180M+T184G+S202I+M204V	6.9	366.7
V173L+L180M+M204V	1.5	7.0
I169T+V173L+L180M+M204V	0.6	63.3
I169T+V173L+L180M+M204V+M250V	0.6	1333
M250V	1.6	7.0
Wild-type a)	1	1
L180M+S202G+M204V a)	2	210
L180M+V173V/L+A181G/A+S202G+M204V a)	1	770

Laboratory isolates. a) Clinical isolates

In vitro activity of tenofovir is similar to that of adefovir. Combinations of tenofovir DF with lamivudine, telbivudine, entecavir, adefovir and emtricitabine resulted in additive to slightly synergistic anti-HBV activity. Tenofovir DF has shown activity against lamivudine, telbivudine and entecavir resistant HBV and appears to retain activity against some adefovir resistant HBV strains. Mutations in the HBV polymerase associated with resistance to tenofovir DF are currently unknown.

In vivo efficacy in animal models

An *in vivo* study in HBV infected woodchucks showed that tenofovir DF administered orally at 15 mg/kg for 48 weeks produced a mean serum viral load reduction of 2.9 $\log_{10}$ copies/ml and combination with lamivudine or emtricitabine resulted in a reduction of 5.8 and 6.1 $\log_{10}$ copies/ml, respectively. There was no evidence of toxicity in woodchucks treated with tenofovir DF, either alone or in combination. There were 11 deaths during the study. Post mortem findings in 7 cases included hepatocellular carcinoma. Group sizes were small to allow a definitive conclusion.

Pharmacokinetics

The absorption, distribution, metabolism and excretion of tenofovir/tenofovir DF were evaluated in a variety of animal models in pharmacokinetic and toxicokinetic studies at the time of the MAA of tenofovir DF, or fixed combination products with tenofovir DF. In addition, the *in vitro* interaction profile was characterised with human cytochrome 450 (CYP) isoforms and renal transporters.

Upon hydrolysis, the prodrug forms two molecules of formaldehyde for each molecule of the active compound. Formaldehyde exposure was estimated to be 0.5 mg/kg/day for a 70 kg person. The potential effects of formaldehyde were discussed in a comprehensive summary of long term oral studies in rats. Based on a no-observed-effect level (NOEL) of 30 mg/kg/day for gastro-intestinal toxicity in the chronic rat study, a 6-fold safety margin relative to formaldehyde exposure in humans following a 300-mg/day dose of tenofovir DF could be determined. Mouse and rat carcinogenicity studies previously performed, concluded that there were no significant concerns, regarding the carcinogenic potential of tenofovir DF in patients.

Little or no inhibition of CYP P450 isozymes was observed in human hepatic microsomes. The protein binding of tenofovir DF was low. Tenofovir was excreted unchanged in the urine of all animal species tested, and renal excretion was identified as the primary route of elimination. Results of *in vitro* studies indicate that active renal tubular secretion of tenofovir DF in humans is mediated by the uptake of tenofovir from the plasma into proximal tubule cells by the influx transporters hOAT1 and hOAT3 (human organic anion transporters 1 and 3) and its efflux from proximal cells into the urine by the MRP4 (multidrug resistant protein 4). The active transporters involved in the luminal transport and the possibility of polymorphism in these were further discussed has predictor factors of renal toxicity. The currently available information is limited and not consensual to allow a conclusion.

Toxicology

High doses of tenofovir DF have been coupled to nephrotoxicity resulting in acute renal failure. No effect dose levels were identified in monkey and dogs. Clinical data on long-term use of tenofovir DF

in HIV-1 infected patients suggests no causal association between tenofovir DF therapy and renal events. However, postmarketing safety data indicates that tenofovir DF may, in rare circumstances, cause renal adverse reactions, including renal failure, Fanconi syndrome, and other proximal tubulopathies.
The potential for renal toxicity of tenofovir DF is well known and has been documented clinically. Management of the risk of renal toxicity is recommended in the product information.

In rat and monkey, tenofovir DF was shown to decrease serum phosphate levels. Clinical data (studies GS-98-902 and GS-99-907) showed that the incidence of hypophosphatemia in the tenofovir DF group was slightly higher than in the placebo group following 24 weeks of treatment (13% *vs* 8% of patients). The rate of occurrence of hypophosphatemia does not appear to increase over time.

In non-clinical studies, the bone was a target organ (osteomalacia or reduction in bone mineral density). Currently, there is no evidence from clinical studies that dosing with tenofovir DF is associated with an increased risk of fractures. Long-term clinical data demonstrated a minimal risk of bone toxicity. Osteomalacia, occurring as a result of tenofovir DF associated proximal tubulopathy, was identified as a rare adverse reaction during postmarketing surveillance.

No marked hepatotoxicity of tenofovir DF was reported in non-clinical studies. Tenofovir is not metabolised, does not interact significantly with P450 enzymes, and is not excreted to any significant extent by the liver. Results from a pharmacokinetic study in patients with hepatic impairment demonstrated that tenofovir DF 300 mg once daily may be administered without regard to hepatic function.

Ecotoxicity/environmental risk assessment
An ecotoxicology/environmental risk assessment (ERA) according to the currently applicable guidelines was submitted. In Phase I a worst-case PEC (predicted environmental concentration) in surface water of 3.0 µg/l was calculated. This was higher than the action limit of 0.01 µg/l and a Phase II environmental fate and effects analysis was performed.

The phase II analysis did not indicate any environmental concerns with the use of tenofovir DF. The final report of study AD-104-2007 (*Tenofovir Disoproxil Fumarate – Aerobic and Anaerobic Transformation in Aquatic Sediment Systems Following OECD Guideline 308*) for which interim results were available will be provided as a post-approval follow-up measure.

Clinical aspects

The main clinical data to support this application included efficacy and safety information of tenofovir DF 300 mg once daily in patients with chronic HBV from two identical randomised, 48 week double-blind, controlled phase III studies evaluating tenofovir DF *vs* adefovir dipivoxil:

- in HBeAg negative patients: Study GS-US-174-102;
- in HBeAg positive patients: Study GS-US-174-103;

Supportive data included interim data from two phase II, randomised, double-blind studies:

- blinded efficacy and safety data from GS-US-174-106 exploring tenofovir DF *vs* emtricitabine/tenofovir DF fixed dose combination in patients currently receiving adefovir dipivoxil with persistent viral replication;
- blinded safety data from study GS-US-174-108, which compares tenofovir DF, emtricitabine/tenofovir DF, and entecavir in the treatment of chronic hepatitis B in subjects with decompensated liver disease.

In addition, data from study GS-00-484 (ACTG 5127), a randomised, double-blind, study comparing tenofovir DF with adefovir dipivoxil in patients co-infected with HIV-1 and chronic hepatitis B with prior lamivudine experience and data from a pharmacokinetic study (GS-US-174-105) evaluating the potential interactions between the combination of emtricitabine/tenofovir DF and tacrolimus in healthy volunteers were also provided.

Clinical pharmacology

Pharmacokinetics

The results of pharmacokinetic studies of tenofovir DF, including studies in HIV-1 infected subjects, special populations, and drug interaction studies, have been previously submitted and are reflected in the product information for Viread.

One new clinical pharmacology study (GS-US-174-105) was submitted. This is an interaction study, evaluating potential pharmacokinetic interaction between tacrolimus and the fixed-dose combination of emtricitabine and tenofovir DF.

Target population

No pharmacokinetics studies have been performed with tenofovir DF in patients with hepatitis B virus infection. Due to the renal excretion of tenofovir and to the low degree of protein binding no pharmacokinetic differences are expected as compared to healthy subjects.

Special populations

Renal impairment

The pharmacokinetic profile of tenofovir DF in non−HIV-1 and non-HBV infected subjects with either normal renal function or varying degrees of renal impairment, including end-stage renal disease (ESRD) requiring hemodialysis, is mainly based on study GS-01-919 results. The current dosing recommendation (interval adjustment) in HIV-1 infected patients with various degrees of renal impairment is based on limited data and at the time considered not an optimal option. However, as no other alternative dosage formulation was available and due to the identified medical need it was agreed not to absolute contraindicate the use of tenofovir DF in severe renal impairment HIV infected patients.

The main clinical studies submitted in support of tenofovir DF in HBV infected patients, excluded patients with creatinine clearance <70 ml/min. This again raised concerns regarding the appropriateness of the current dose recommendation in subjects with moderate and severe renal impairment in cases where treatment benefit outweighs the risk in this new patient population.

The MAH presented simulated tenofovir steady-state pharmacokinetic parameters following dose-interval adjustment for subjects with varying degrees of renal impairment from study GS-01-919 (Table 4), based on which estimations for each 24 hours over the week were done in subjects with severe renal impairment (Table 5).

Table 4. Simulated tenofovir steady-state following dose-interval adjustment for subjects with varying degrees of renal impairment (study GS-01-919)

Tenofovir PK Parameters a	**Renal Function (Creatinine Clearance)**			
	≥ 50 ml/min	**30 to 49 ml/min**	**10 to 29 ml/min b**	
	Tenofovir DF 300 mg Every 24 Hours	**Tenofovir DF 300 mg Every 48 Hours**	**Tenofovir DF 300 mg Every 72 Hours**	**Tenofovir DF 300 mg Every 96 Hours**
Average Daily AUC (ng•hr/ml)				
Median	2670	2635	5368	4591
Min–Max	1620–4900	1355–5050	1735–9514	1343–8075
Cmax (ng/ml)				
Median	325	412	565	595
Min-Max	252–484	154–619	341–970	349–1020
Ctau (ng/ml)				
Median	55.7	36.4	67.6	35.4
Min–Max	31.9–137	20.4–93.3	6.13–157	1.75–125

a Median (minimum, maximum) simulated values from the two-compartment model.

b Represents alternating twice weekly Q 96 followed by Q 72 dosing and recalculated from simulated steady-state tenofovir concentration-time data presented in the GS-01-919 Clinical Study Report.

Table 5 Simulated tenofovir steady-state exposure for every 24 hours over the week for subjects with severe renal impairment (study GS-01-919)

Tenofovir PK Parameters a	Renal Function						
	Creatinine Clearance: 10 to 29 ml/mina						
	1st Tenofovir DF 300 mg Dose of the Week (96-Hour Dosing Interval)				2nd Tenofovir DF 300 mg Dose of the Week (72-Hour Dosing Interval)		
Time Interval (hr)	0–24	24–48	48–72	72–96	96–120	120–144	144–168
Average Daily AUC (ng•hr/ml)							
Median	9963	4659	2448	1233	9427	4378	2300
Min–Max	3917–17273	1070–8660	301–4788	85–3510	3855–16317	1053–8191	296–4429

a Represents alternating twice weekly Q 96 followed by Q 72 dosing and recalculated from simulated steady-state tenofovir concentration-time data presented in the GS-01-919 Clinical Study Report.

Even considering that the estimated *in vitro* hepatocellular half-life is 95 hours, the consequences of having Cmin values ranging from 1.75 to 157 (Table 4) in the severe renal impairment group and with a dosing interval of 72-96 hours cannot be clearly determined.

The exposure for each 24 hours for subjects with severe renal impairment illustrates variability in addition to difference in renal function. The exposure is very high during the days of dosing (3-6 times higher than subjects with creatinine clearance >50 ml/min but with a wide range at later hours). The CHMP agrees that the current dosing is not optimal. However, it is acknowledge that due to circumstances of medical need, in which tenofovir DF could be the only option even in the setting of moderate or severe renal compromise with end-stage liver disease, lamivudine-resistant virus or persistent viral replication on adefovir dipivoxil treatment, the CHMP agrees that tenofovir DF should not be absolute contraindicated in severe renal impairment patients. Rather a strong warning stressing that tenofovir DF should only be used in patients with chronic HB and moderate/severe renal impairment, if the potential benefits of treatment outweigh the potential risks, was included in the SPC. Consequently the wording on dosing regimens was amended.

The MAH committed to generate additional data in subjects with moderate and severe renal impairment and chronic HBV infection, including safety data and steady-state pharmacokinetics. A comprehensive plan of action will be submitted within 3 months of approval for the hepatitis B indication. A new study in HBV patients with decompensated liver disease with baseline creatinine clearance between 20 and 60 ml/min will be submitted, and data will be collected from 2 ongoing studies (study GS-203-107 in stable subjects who have undergone orthotopic liver transplantation with calculated clearance ≥ 40 ml/min and study GS-174-108 in subjects with decompensated liver disease with calculated creatinine clearance ≥ 50 ml/min).
In addition to the above plans pertaining to moderate/severe renal impairment, there will be a 250-patient, multicenter, randomised study including participants with mild renal impairment (creatinine clearance ≥ 50 ml/min) and lamivudine-resistant HBV.

Furthermore, the MAH has undertaken the post-approval commitment to provide the CHMP with the status of the development of an alternative dosage formulation.

Hepatic impairment
The pharmacokinetics of tenofovir after a 300 mg dose of tenofovir DF were studied in non HIV-1 infected patients with varying degrees of hepatic impairment according to the Child-Pugh-Turcotte (CPT) classification (Study GS-01-931 A/B). Tenofovir pharmacokinetics were not substantially altered as compared with unimpaired patients. No dose adjustment is required in patients with hepatic impairment.

Gender
An Ad hoc analysis of study GS-US-174-102 comparing tenofovir DF pharmacokinetic parameters in female and male subjects with chronic HB showed no major difference in plasma pharmacokinetics. However, based on the average profiles it seems as the plasma concentration time profile differs i.e. females have higher Cmax (65%) and slightly higher AUCtau (22%). From the findings in the HIV

programme it is agreed that in general tenofovir plasma exposure are similar between females and males.

Elderly
Pharmacokinetics has not been studied in the elderly population (subjects>65). Considering that this population is more likely to have a decreased renal function, caution should be exercised when treating elderly with tenofovir DF.

Interactions
Study GS-US-174-105, an open-label, randomised, three-way crossover study evaluated the effect of coadministration of tacrolimus on the steady-state pharmacokinetics of emtricitabine/tenofovir DF fixed dose combination in 31 healthy volunteers (18-45 years of age). The pharmacokinetics of tacrolimus was not altered upon coadministration with emtricitabine/tenofovir DF.
The geometric mean Cmax for tenofovir was the only pharmacokinetic parameter with the 90% confidence intervals (CI) upper bound above the predefined limit of 125%. The 13% increase in Cmax of tenofovir in the presence of tacrolimus, is unlikely to be of clinical relevance.

The possibility that tacrolimus inhibits any of the transport proteins involved in active secretion of tenofovir, potentially increasing the risk for renal toxicity was further discussed, as well as other possible inhibitors of transport proteins (e.g cyclosporine) expected to interact with the luminal efflux transport. Based on the currently available data, no renal drug interactions caused by inhibition of these transport proteins have been identified.

All clinically relevant pharmacokinetic interactions between tenofovir DF and other antiretroviral drugs tested are reflected in the interaction section of the SPC. Furthermore, it has been shown that the co-administration of atazanavir/ritonavir or lopinavir/ritonavir with tenofovir DF increased tenofovir exposure. A precautionary statement was included in the SPC to inform prescribers that, in case of co-administration, the higher tenofovir concentrations could potentiate tenofovir associated adverse events, including renal disorders. *In vitro* studies suggested that the mechanism is mediated through inhibition of intestinal p-glycoprotein (p-gp) by these protease inhibitors.

Based on raw data no interactions have been currently observed between entecavir and tenofovir DF. This information is reflected in the interactions table of the product information.
No relevant pharmacokinetic interactions have been identified when a single-dose of adefovir dipivoxil was co-administered with tenofovir DF in healthy volunteers. However, given their common renal toxicity, their co-administration is not recommended. A warning statement was therefore included in the SPC and referred in the interactions table.

Clinical efficacy

Dose-response studies
No dose-activity studies were conducted in patients with chronic HB. The K_i of tenofovir against HBV polymerase (0.18 μmol/l) was similar to the K_i against HIV-1 reverse transcriptase (0.02-1.6 μmol/l). Similar concentration produced 50% inhibition of viral replication (EC_{50}) *in vitro* (HBV EC_{50} = 0.14–2.5 μmol/l, HIV EC_{50} = 0.5–2.2 μmol/l). Since 300 mg of tenofovir DF has been established as the optimal dose for HIV-1, it is also considered to be optimal for HBV.

However, given the potency of the drug, it cannot be excluded that a lower dose could have allowed to obtain an acceptable efficacy level with an improved renal tolerance as compared to that observed in HIV infected patients.

Main Studies
The 48 week results from two pivotal phase III studies (GS-US-174-102 and GS-US-174-103) were submitted. These studies were similar in design, involving 48 weeks of double blind therapy with TDF 300 mg once daily (QD) or adefovir dipivoxil (ADV) 10 mg QD, followed by open-label TDF treatment through week 240 (ongoing). An overview of the main clinical studies is presented in the table below.

	Study-102	Study-103
Design	randomised, double-blind, multicentre, parallel group of TDF vs ADV in HBeAg - subjects	randomised, double-blind, multicentre, parallel group of TDF vs ADV in HBeAg + subjects
Population	Adult subjects with CHB, HBeAg–, nucleoside/nucleotide naïve or experienced (3TC or FTC), baseline HBV DNA $> 10^5$ copies/ml, screening ALT > ULN (upper limit of normal) but ≤ 10 × ULN, Cr CL ≥ 70ml/min Knodell necroinflamation score ≥3 and Knodell fibrosis score< 4	Adult subjects with CHB, HBeAg+, nucleoside/nucleotide naïve, baseline HBV DNA $> 10^6$ copies/ml, screening ALT > 2 × ULN but ≤ 10 × ULN, Cr CL ≥ 70ml/min Knodell necroinflamation score ≥3 and Knodell fibrosis score< 4
Study duration	48 weeks double blinded + extended open label phase 240 weeks (ongoing)	48 weeks double blinded + extended open label phase 240 weeks (ongoing)
Stratification	Prior LAM or FTC exposure, geographic region	ALT (≤ 4ULN or > 4 ULN), geographic region
N randomised	382 randomised (2:1) 250 in the TDF 300 mg group 125 in the ADV group	272 randomised (2:1) 176 in the TDF 300 mg group 90 in the ADV group

The inclusion criterion on renal function was considered too restrictive. Although the criteria for study -103 seemed consistent with the inclusion of the HBeAg+ target population on need for HBV therapy, a necroinflammatory score ≥ 4 (rather than ≥ 3) should have preferably been chosen.

Endpoints

The primary efficacy endpoint for both studies was complete response at week 48 (HBV DNA levels < 400 copies/ml and histologic improvement defined as at least a 2-point reduction in the Knodell necroinflammatory score without worsening in Knodell fibrosis score).

The secondary endpoints included histology, virologic response, biochemical and serology response, and genotypic changes from baseline.

In line with the EU guideline on anti-HBV drugs development the composite primary endpoint should have encompassed the biochemical response. The MAH was therefore requested to present the studies results as recommended in the guideline, i.e. combining virological, histological and biochemical response (see the "efficacy results" below).

Statistical analysis

For both studies, primary efficacy analyses were performed using the randomised-and-treated (RAT) analysis set, which included all patients who were randomised and received at least one dose of study medication, with no data exclusion.

The population for ALT normalisation analyses was all RAT subjects with an ALT value above the ULN at baseline. In study -102 subjects with a normal ALT value at baseline were excluded from these analyses. This population is referred to as the biochemically evaluable RAT analysis set.

For study -103 the population for analyses of HBeAg loss and seroconversion was all RAT subjects with a baseline value of positive for HBeAg status. Subjects with a value of negative at baseline for HBeAg were excluded from all serology related analyses. This population is referred to as the serologically evaluable RAT analysis set.

Efficacy analyses were adjusted for the covariate baseline ALT (≤ 2 × ULN or > 2× ULN for study -102 and ≤ 4 × ULN or > 4 × ULN for study -103) but not for the geographical region nor for prior lamivudine or emtricitabine experience for study -102.

Results

Population

The majority of patients in both studies completed the first year of blinded treatment: 95.6% (239/250) in the TDF group *vs* 92.8% (116/125) in the ADV group in study -102 and 89.8% (158/176) in the TDF group *vs* 93.3% (84/91) in the ADV group in study -103.

In both studies, screening failure accounted for nearly 70% due to failure in meeting the eligibility criteria for ALT levels, HBV DNA levels, or both. The ALT criterion was the main reason for screen failure in both studies, in a higher percentage in HBeAg+ study (30% in study -103 *vs* 17% in study -102). The lower bound for ALT criteria for HBeAg+ patients was consistent with the EU guidelines. These screening failures do not hamper the extrapolation of the data to the target population in clinical practice.

Some demographic and baseline disease characteristics of patients from studies -102 and -103 (RAT population) are displayed in Table 6, below. Seven and 6 patients did not receive study medication in study -102 and -103, respectively.

Table 6 Demographic and baseline disease characteristics

Characteristics	Study 102 (N =375)	Study 103 (N =266)
Age (years)		
Mean (SD)	44 (10.4)	34 (11.6)
Min, Max	18 - 69	18 - 64
Gender		
Male, n (%)	290 (77.3%)	183 (68.8%)
Female, n (%)	85 (22.7%)	83 (31.2%)
Race		
Caucasian, n (%)	242 (64.5%)	138 (51.9%)
Asian, n (%)	93 (24.8%)	96 (36.1%)
Black, n (%)	12 (3.2%)	18 (6.8%)
Pacific Islander, n (%)	9 (2.4%)	7 (2.6%)
Other, n (%)	19 (5.1%)	7 (2.6%)
HIV-1 RNA (log_{10} copies/ml)		
Mean (SD)	6.90 (1.294)	8.72 (1.033)
Min, Max	2.23 – 9.84	4.67 – 10.92
ALT Strata		
ALT≤ 2 ULN	135 (36.0%)	N/A
ALT ≥ 2 ULN	240 (64.0%)	N/A
ALT≤ 4 ULN	N/A	189 (71.1%)
ALT ≥ 4 ULN	N/A	77 (28.9%)
HBV Genotype		
A	42 (11.4%)	59 (22.6%)
B	39 (10.6%)	35 (13.4%)
C	41 (11.1%	69 (26.4%)
D	235 (63.9%)	86 (33.0%)
E	7 (1.9%)	4 (1.5%)
F	1 (0.3%)	8 (3.1%)
G	1 (0.3%)	-
H	2 (0.5%)	-

For both studies, the baseline characteristics were well balanced between the tenofovir and the adefovir treatment groups. The European population was well represented (62.4% in study 102 and 54.9% in study 103). The genotype distribution reflects the ethnicity of the enrolled patients.

Approximately 17% and 16% of patients in study -102 and -103 respectively had prior interferon exposure.

Overall approximately 20% percent of patients in study -102 had cirrhosis at baseline; a similar percentage was seen in study -103, 18%.

Efficacy results

An overview of the efficacy endpoints achieved in both studies is shown in the following table:

Parameter	Study GS-US-174-0102 (HBeAg−)		Study GS-US-174-0103 (HBeAg+)	
	TDF 300 mg (N=250)	ADV 10 mg (N=125)	TDF 300 mg (N=176)	ADV 10 mg (N=90)
Complete Response (%) [a]	70.8*	48.8	66.5*	12.2
Histology				
Histological Response (%)[b]	72.4	68.8	74.4	67.8
HBV DNA (%)				
< 400 copies/mL (69 IU/mL)	93.2*	63.2	76.1*	13.3
< 300 copies/mL (52 IU/mL)	92.0*	59.2	73.9*	12.2
< 169 copies/mL (29 IU/mL) (undetectable)	91.2*	56.0	68.8*	8.9
ALT(%)				
Normalized ALT[c]	76.3	77.1	68.0*	54.4
Serology (%)				
HBeAg Loss/Seroconversion	Not applicable	Not applicable	22.2/20.9	17.5/17.5
HBsAg Loss/ Seroconversion	0/0	0/0	3.2*/1.3	0/0

Study -102

The mean reduction from baseline in plasma HBV DNA at week 48 was significantly greater in the tenofovir DF group (−4.57 log10 copies/ml) than in the adefovir dipivoxil group ((−4.07 log10 copies/ml ($p < 0.001$)). Nearly all subjects treated with tenofovir DF reached the assay LLQ (lower limit of quantification).

Most biochemically evaluable subjects in both groups had normalised ALT at week 16 even though at baseline, normal ALT was uncommon (5.6% in both groups).

At week 48, mean change from baseline in ALT was −95.0 U/l (102.31) in the tenofovir DF group and was −124.4 U/l (137.23) in the adefovir dipivoxil group ($p = 0.040$). Mean (SD) baseline ALT was higher, however, in the adefovir group (163.6 U/l [146.02]) than in the tenofovir group (127.5 U/l [101.21]).

Study -103

A significant higher percentage of patients achieved the primary endpoint in the tenofovir DF group compared to the adefovir dipivoxil group. This superiority of tenofovir was mainly driven by the higher virological response (HBV DNA <400 copies/ml), with a difference estimate between arms of 65.9%.

The mean reduction from baseline in plasma HBV DNA at week 48 was significantly greater in the tenofovir group (−6.17 log10 copies/ml) than in the adefovir group (−3.93 log10 copies/ml) ($p < 0.001$). The observed mean change in the tenofovir DF group was limited by the LLQ (lower limit of quantification) of the assay, since the majority of subjects in that group reached the LLQ. Borderline significant superiority in terms of normalised ALT was also demonstrated.

The proportion of subjects with HBV DNA < 400 copies/ml over time showed that virological response was rapidly achieved in the tenofovir DF group, where more than 50% of patients had HBV DNA < 400 copies/ml after 24 weeks of treatment.

Although few patients achieved HBsAg loss (n= 5), a statistically significant difference in number of patients who achieved HBsAg loss is reported in the tenofovir DF group. Two subjects in the tenofovir

DF treatment group had achieved HBsAg seroconversion (defined as HBsAg loss and positive result for anti-HBs) at week 48.

In line with the virological response, a statistically significant difference was observed in terms of biochemical response in the tenofovir DF group as compared to the ADV group.
However, the high difference in terms of virologic response was not associated with any statistical difference in terms of histological response, with most of the patients having no change in the fibrosis score. The magnitude of the treatment difference in terms of histological response is around 10% of that in terms of virologic response. Nevertheless, the histological response is expected to take more time to develop and 48 weeks might not be sufficient to observe any translation of the virological suppression on the progression of the disease.

The MAH was requested to present combining virological, histological and biochemical results reported with and without adjustment for base stratification variables. An adjusted analysis as regards the protocol defined primary endpoint was also requested. ALT change [from] baseline data using baseline ALT level as covariate was also needed. A secondary analysis using a combined endpoint was performed. Consistent with the protocol-specified, composite, primary endpoint, tenofovir DF was superior to adefovir dipivoxil ($p < 0.001$) for the triple combined endpoint. Results for both studies were similar regardless of whether or not the statistical analyses were adjusted for baseline ALT. However, the CHMP request was only partially addressed. The combined endpoint for HBeAg+ patients (study -103) did not include HBeAg loss. Given that no statistically significant difference between tenofovir DF and ADV was achieved on HBeAg loss, the superiority of tenofovir DF might have been lost on this combined endpoint.
In addition, the CHMP requested an analysis with and without adjustment for base stratification variables which was not provided. ALT change from baseline using baseline ALT level as covariate was not provided for study-103.
Given the reliability of the efficacy demonstration on the HBV DNA driven primary endpoint, the CHMP agreed that the remaining points could be addressed in a post approval follow-up measure.

The viral response data (as plots of viral load over time) reported separately for patients with and without HBeAg seroconversion at week 48, showed that for the subgroup of seroconverters in both tenofovir DF (n = 36) and adefovir dipivoxil (n = 16) groups, mean HBV DNA at the time of seroconversion was 2.51 $\log_{10}$ copies/ml and 3.68 log10 copies/ml, respectively. Twenty-four weeks after seroconversion, the mean change in HBV DNA (log10 copies/ml) was –0.27 and –0.69 for tenofovir DF-treated subjects (n = 19) and adefovir dipivoxil-treated subjects (n = 7), respectively.
Overall, seroconverters had a more pronounced decrease in HBV DNA during the first 24 weeks of treatment, however no major difference in mean change in HBV DNA was observed in tenofovir DF-treated patients with *vs* without seroconversion. The MAH did not provide the evolution of HBV DNA after conversion, precluding further discussion on the durability of seroconversion. This will be address by the MAH as a post-approval follow-up measure.

The per protocol analysis result requested by the CHMP for both studies were consistent with the results from the ITT analysis, providing further confidence in the superiority of TDF over ADV on the primary endpoint and viral suppression in the pivotal studies.

Resistance analysis
Study -102
Genotypic testing was performed in all 50 viremic subjects (13.3% of the total RAT population) as a component of the year 1 resistance surveillance. After 48 weeks of treatment with tenofovir DF, 4/250 (1.6%) subjects had active viral replication (HBV DNA levels > 400 copies/ml) without experiencing viral rebound during the study. Four of 250 (1.6%) subjects had experienced viral rebound. No subject in the tenofovir DF group discontinued after week 24 with active viral replication. No subject in the tenofovir DF group had conserved site change at week 48.
At baseline two individuals in the tenofovir group harboured virus with lamivudine resistance mutations. Both achieved full suppression (<LOQ). At baseline one subject in the adefovir group harboured virus with lamivudine resistance mutations and also achieved full suppression (<LOQ).

No conserved site mutations were detected in association with tenofovir DF therapy for 48 weeks. However, at this stage it cannot be excluded that mutations in polymorphic sites may be associated with reduced sensitivity. It is expected that this issue will be addressed in patients with rebound viral failure in the ongoing resistance follow-up.

Study -103
Genotypic testing was performed in all 106 viremic subjects (39.8% of the total RAT population 13) as a component of the year 1 resistance surveillance. After 48 weeks of treatment with tenofovir DF 24/176 (13.6%) subjects had active viral replication (HBV DNA levels ≥ 400 copies/ml) without experiencing viral rebound during the study. Six of 176 (3.4%) had viral rebound[1], and 1 additional subject discontinued after week 24 with active viral replication (6.1-$\log_{10}$ decrease from baseline in HBV DNA at time of discontinuation). Two subjects in the tenofovir DF group had conserved site changes at week 48 with decreases in HBV DNA levels ranging from 5.3 to 6.6 $\log_{10}$ copies/ml. These conserved-site changes occurred at the following loci: rtS74 and rtH156. The clinical significance of these changes is currently unknown. The fact that certain mutations in polymorphic sites may be associated with reduced sensitivity cannot be excluded.

Overall, 426 HBeAg negative and HBeAg positive subjects were evaluated for genotypic changes in HBV polymerase and no nucleoside-naïve or nucleoside-experienced subject treated with tenofovir DF for 48 weeks developed mutations associated with tenofovir DF resistance.

The activity of tenofovir in case of lamivudine resistance has been documented in *in vitro* studies and in some literature data. Given the limited *in vitro* cross resistance, the MAH will conduct a phase IIIb study in lamivudine-resistant subjects for which the protocol synopsis will be submitted to the CHMP as a post-approval follow-up measure.

Resistance will be monitored quarterly in all patients without viral suppression in the HBV pivotal studies. Quarterly results should be reported yearly with PSURs submission or upon CHMP request.

Results of sub group analyses
Integrated subgroup analyses were performed. For each treatment group the effect of several demographic (age, gender and race) and baseline disease characteristics (HBV DNA, ALT, Knodell necroinflammatory and fibrosis scores, genotype [A–D], prior lamivudine/emtricitabine experience) on complete response and its components (HBV DNA response and histological response) were assessed. Age subgroups were examined within each rather than across each of the two studies due to the known age difference between HBeAg+ and HBeAg– subjects.

The histological results reported in the sub-group of patients having cirrhosis at baseline (81 in the tenofovir group and 42 in adefovir group) were similar to those reported in each treatment group in the whole chronic HBV population. No advantage of tenofovir DF over adefovir dipivoxil was seen in this subgroup of patients.

A marginal influence of baseline HBV DNA level on complete response and the proportion of subjects with HBV DNA < 400 copies/ml at week 48 was observed. This finding was more pronounced within the adefovir dipivoxil-treated subjects, leading to an overall larger difference between treatment groups in favour of tenofovir DF in the subjects with baseline viral load above the median across the two studies.

In both studies, the percentage of tenofovir DF treated subjects achieving complete response (73% and 69%) and HBV DNA below 400 copies/ml (90% and 88%) were similar in treatment-experienced subjects (n = 51) and treatment-naïve subjects (n = 375), respectively.

[1] Rebound define as HBV DNA ≥400 copies/ml after having HBV DNA levels <400 copies/ml and/or 1-log10 increase (confirmed) in HBV DNA above nadir

Analysis of potential predictors of response for the tenofovir DF-treated subjects using the endpoint of HBV DNA < 400 copies/m at week 48 were performed using pooled data from the two pivotal studies. Baseline HBV DNA (≤ 9 $\log_{10}$ copies/ml vs. > 9 $\log_{10}$ copies/ml) ($p < 0.0001$) and baseline body mass index (BMI) (< 30 vs. ≥ 30) ($p = 0.0052$) were the two identified baseline factors significantly associated with virologic response. However, considering the under-exposure of patients with BMI ≥ 30 kg/m2, the MAH will comment on the possibility to recommend a higher dose in patients with BMI ≥ 30 kg/m2. This will be address as a post-approval follow-up measure.

Moreover, results showed response at 24-week as a strong positive predictive value on treatment response at week 48 in both populations. However, given the poor negative predictive value of the 24-week results on treatment response at week 48 in HBeAg positive and negative patients, this cannot be used to support therapeutic decision. The analysis of the predictive value of the 24-week response on treatment-emergent resistance will have to be assessed when long-term data are available. In addition the MAH will assess predictive factors of seroconversion.

Supportive studies

Twenty-four week interim data from a phase II, randomised, double-blind study GS-US-174-106 exploring the efficacy and safety of tenofovir monotherapy *vs* emtricitabine/tenofovir DF fixed-combination in the treatment of HBeAg+ and HBeAg- chronic HB infected patients being treated with adefovir dipivoxil and having persistent viral replication was submitted.

The majority of subjects were male (76%), mean age 39 years and mean baseline HBV DNA 5.97 $\log_{10}$ copies/ml. The primary endpoint was the proportion of patients with plasma HBV DNA levels < 169 copies/ml (LLQ) at week 48. A total of 105 patients were randomised and treated and 60 individuals were evaluated for efficacy at week 24: 46/60 (76.7%) subjects showed HBV DNA <400 copies/ml and 37/60 (61.7%) had plasma HBV DNA level <LLQ (169 copies/ml).

Clinical studies in special populations

A prospective "Adult AIDS Clinical Trials Group" study– ACTG study A5127 – performed in HIV/HBV co-infected patients was provided. This was a randomised, 48 week double-blind, placebo-controlled trial of 10 mg daily of adefovir dipivoxil *vs* 300 mg of tenofovir DF in patients with HBV and HIV co-infection on stable ART, with serum HBV DNA > 100,000 copies/ml, and plasma HIV-1 RNA < 10,000 copies/ml. The study was closed early as interim results showed that the primary non inferiority end point had been achieved without safety issues.

Fifty-two subjects were randomised. At baseline, 73% of subjects had a plasma HIV-1 RNA < 50 copies/ml, 86% were HBeAg+, 94% were lamivudine resistant, median serum ALT was 52 IU/l, and 98% had compensated liver disease. The mean time-weighted average change in serum HBV DNA from baseline to week 48 was -4.44 $\log_{10}$ copies/ml for tenofovir DF and -3.21 $\log_{10}$ copies/ml for adefovir.

No difference in terms of toxicity between the 2 treatment groups was observed. Eleven patients (5 adefovir group and 6 tenofovir DF group) experienced elevations of serum ALT on treatment but none accompanied with signs of hepatic decompensation. Over 48 weeks, treatment with either adefovir or tenofovir DF resulted in clinically important suppression of serum HBV DNA.

Clinical safety

The safety assessment was based on the data from the main pivotal studies (GS-174-102 and GS-174-103). Additional safety data was provided from blinded phase of study GS-US-174-108, comparing tenofovir DF, emtricitabine/tenofovir DF, and entecavir in the treatment of chronic hepatitis B in subjects with decompensated liver disease.

Patient exposure

In the two pivotal studies, a total of 603 subjects (94%, 399/426 in the tenofovir DF group and 95%, 204/215 in the adefovir group) completed 48 weeks of double-blind treatment. The mean duration of exposure was similar between treatment groups (328.9 in the tenofovir DF group and 327.4 in adefovir group). Long-term data (exposure more than one year) for tenofovir DF in the treatment of patients with chronic hepatitis B is currently not available. The 96 week and the final 240 week report for the

two pivotal studies will be provided to substantiate the long term safety of tenofovir in chronic HB patients.

Cumulative worldwide exposure to tenofovir DF (mainly in HIV-1 indication) since 26 October 2001 to 31 May 2007 is estimated to be 1,364,784 patients-years of treatment.

Adverse events (AEs)

The overview of the treatment-emergent adverse events, 48 weeks data is presented below.

	TDF (N=426)	**ADV (N=215)**
Adverse Event	317 (74.4%)	158 (73.5%)
Grade 2, 3 or 4	128 (30.0%)	68 (31.6%)
Grade 3 or 4	37 (8.7%)	17 (7.9%)
Study Drug-Related Adverse Event	96 (22.5%)	39 (18.1%)
Grade 2, 3 or 4	23 (5.4%)	16 (7.4%)
Grade 3 or 4	5 (1.2%)	6 (2.8%)
AE causing permanent discontinuation	5 (1.2%)	3 (1.4%)
Study Drug-Related SAE	7 (1.6%)	5 (2.3%)

Note: Subjects are included only once in each category.

A similar proportion of patients in the tenofovir DF group and in the adefovir group experienced an AE that caused discontinuation of study drug or a change in dose or temporary interruption of study drug.

The most commonly reported possibly or reasonably attributable to study drug adverse events are presented in the below table.

Treatment Related AEs by System Organ Class and Preferred Terma (n, %)b	**TDF (N=426)**	**ADV (N=215)**
Any Study Drug-Related Adverse Event	96 (22.5%)	39 (18.1%)
Gastrointestinal Disorders		
Nausea	23 (5.4%)	2 (0.9%)
Abdominal Distension	7 (1.6%)	2 (0.9%)
Diarrhoea	6 (1.4%)	1 (0.5%)
Vomiting	6 (1.4%)	0
Abdominal Pain Upper	5 (1.2%)	0
Flatulence	5 (1.2%)	0
Constipation	4 (0.9%)	0
Abdominal Discomfort	2 (0.5%)	1 (0.5%)
Abdominal Pain	3 (0.7%)	0
Dyspepsia	2 (0.5%)	0
Nervous System Disorders		
Headache	12 (2.8%)	6 (2.8%)
Dizziness	4 (0.9%)	1 (0.5%)
Lethargy	4 (0.9%)	0
Paraesthesia	2 (0.5%)	2 (0.9%)
General Disorders and Administration Site Conditions		
Fatigue	14 (3.3%)	3 (1.4%)
Asthenia	3 (0.7%)	2 (0.9%)
Investigations		
Alanine Aminotransferase Increased	6 (1.4%)	5 (2.3%)
Blood Creatinine Increased	1 (0.2%)	4 (1.9%)
Blood Creatine Phosphokinase Increased	1 (0.2%)	3 (1.4%)
Aspartate Aminotransferase Increased	2 (0.5%)	1 (0.5%)
Creatinine Renal Clearance Decreased	1 (0.2%)	2 (0.9%)
Lipase Increased	0	2 (0.9%)
Skin and Subcutaneous Tissue Disorders		
Pruritus	4 (0.9%)	2 (0.9%)
Rash	4 (0.9%)	1 (0.5%)
Acne	1 (0.2%)	2 (0.9%)
Metabolism and Nutrition Disorders		

Anorexia	3 (0.7%)	1 (0.5%)
Decreased Appetite	3 (0.7%)	1 (0.5%)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3 (0.7%)	1 (0.5%)
Myalgia	3 (0.7%)	1 (0.5%)
Psychiatric Disorders		
Insomnia	3 (0.7%)	1 (0.5%)
Renal and Urinary Disorders		
Renal Impairment	1 (0.2%)	2 (0.9%)

The more commonly reported adverse events in the tenofovir DF group irrespective of causality were gastro-intestinal disorders. Abdominal pain, diarrhoea and nausea were reported at a higher frequency in tenofovir DF treatment compared to treatment with adefovir. This is in line with the current safety profile of tenofovir DF in HIV-1 infected patients.

The higher frequency of nausea in the overall tenofovir DF group was mainly due to the greater frequency of this adverse event reported in in HBeAg+ patients (13.6% in tenofovir DF group *vs* 1.1% in adefovir group) compared to HBeAg- patients (6.4% in tenofovir DF group *vs* 4.0% in adefovir group). The large difference observed in the reporting of nausea between tenofovir group in each studies is unclear.

Serious adverse events (SAE) and Death

No deaths were reported in the two pivotal studies -102 and -103. However, 3 subjects died during the course of study -108, in subjects with decompensated liver disease. None were considered related to study medication. The data are still blinded for study -108 therefore this will be further discussed when the final report for this study is provided.

Treatment-emergent serious adverse events occurred at similar frequencies in both treatment groups (6.3% tenofovir DF and 6.5% adefovir dipivoxil). The most frequently SAE reported was ALT increased, reported in 9 patients (2.1%) treated with tenofovir DF and in 4 patients (1.9%) treated with adefovir dipivoxil. Increased in ALT in 5 (1.2%) of the 9 patients was considered related to tenofovir DF treatment. Other SAEs reported in more than 1 subject was AST increased in 4 subjects (3 on tenofovir DF and 1 on adefovir dipivoxil) with 1 considered related to tenofovir treatment. Thrombocytopenia, and hepatitis B (ALT flare) were also reported as SAE related to tenofovir treatment (1 subject each).

Hepatocellular carcinoma (HCC) and hepatitis B were reported in three patients on tenofovir DF treatment, compared to none on adefovir. Further information provided is not sufficient to determine the causality to tenofovir DF. HCC will be specifically monitored in future PSURs and in any ongoing or planned clinical studies.

Adverse events of interest

Liver toxicity

- ALT flares

In the pivotal studies, a slight trend towards a higher proportion of on-treatment ALT flares[2] was observed in tenofovir DF treated patients (2.6%, n=11) compared to adefovir-treated (1.9%, n=4).

Most of ALT flares occurred in patients with HBeAg+ chronic hepatitis B (8/11 tenofovir DF-treated and 3/4 adefovir –treated). Among the 8 in the tenofovir DF group, 5 had a seroconversion to anti-HBe at week 24 or 36. Among the 3 in the adefovir group, 1 seroconverted to anti-HBe at week 8. The majority of ALT flares occurred in patients with baseline ALT > 2N or with baseline HBV DNA > 7.88 $\log_{10}$ copies/ml. No patients with ALT flares had signs of hepatic decompensation.

[2] Defined by: elevation of ALT > 2 × baseline and > 10 × ULN with or without associated symptoms or, abnormal laboratory parameters suggestive of worsening hepatic function (abnormal bilirubin ≥ 2 mg/dl above baseline, abnormal PT ≥ 2 sec above baseline, international normalised ratio (INR) ≥ 0.5 over baseline, abnormal albumin ≥ 1 g/dl decrease from baseline, or elevated serum lactate levels >2 × ULN) along with any ALT elevation (i.e., 1-grade shift or 2 × previous value).

In the tenofovir DF, all except one patient experienced ALT flares during the first two months of study. All patients responded to tenofovir DF treatment and had concomitant decreases in HBV DNA.

Overall, on-treatment ALT flares reported in tenofovir DF-treated patients seemed more likely related to immunologically-mediated inflammatory response associated with viral clearance since all had a reduction from baseline in HBV DNA that coincided with the ALT flare.
A warning on the risk of exacerbations of hepatitis in some patients with serum HBV DNA levels decrease and on the higher occurrence observed in HBeAg+ chronic HB patients was added to the SPC.

Study drug discontinuation with treatment-free follow-up was contraindicated for subjects with bridging fibrosis or cirrhosis due to the potential risk of exacerbation of hepatitis.

As of 25 January 2008, post-treatment exacerbation developed in 3 patients in study -102 and in no patient in study -103**.** Lesser ALT elevations were observed in 3 additional patients (1 from study -102 and 2 from study -103) who had grade 3 ALT levels ≥ 2 months following study drug discontinuation with no other liver function test abnormalities coincident with grade 3 ALT elevation.

Of the 3 subjects with post-treatment exacerbation of hepatitis B, 1 with cirrhosis who discontinued study -102, developed flare with concomitant grade 3 bilirubin (3.7 mg/dl). Commercial anti-HBV treatment (entecavir) was started within 2 days of flare onset with resolution of the exacerbation episode.

Data on post-treatment exacerbation of hepatitis B following discontinuation of tenofovir DF is currently limited due to the small sample size and incomplete (currently ongoing) follow-up. Post-treatment flare is a known consequence of withdrawal of oral nucleoside or nucleotide treatment.
In case of treatment discontinuation, hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months. Warnings on post-treatment hepatic flare are included in the SPC.

A specific section pertaining to all cases of on-treatment and post-treatment ALT flares reported in chronic HB patients should be presented and discussed in each future PSUR for tenofovir DF.

➢ Hepatic events

Hepatitis and increased liver enzymes (most commonly AST, ALT, and gamma-glutamyl transferase) have been identified as potential adverse drug reactions from postmarketing HIV experience.
Fourteen patients (3.3%) treated with tenofovir DF for chronic HBV and 13 subjects (6.0%) treated with adefovir dipivoxil experienced treatment-emergent hepatobiliary disorders by week 48. Only 2 were considered to be related to tenofovir DF and one related to adefovir dipivoxil. All cases of hepatic events will be closely monitored.

Renal toxicity
The number of patients with renal impairment studied in tenofovir DF clinical trials is very low. The clinical studies performed in patients with HBV excluded patients with creatinine clearance <70 ml/min. Therefore, the patient population possibly more prone to experience safety problems (renal and possibly bone) with tenofovir DF, has not been studied.

Renal/urinary adverse events considered treatment-related were seen in 7/426 patients (1.6%) on tenofovir DF and in 7/215 patients (3.3%) on adefovir dipivoxil. Overall the percentage of patients with renal and urinary adverse events was 6.5% tenofovir DF *vs* 5.1% adefovir dipivoxil. Confirmed decreased in serum phosphorus < 2mg/dl was reported in 1.4% of patients on tenofovir DF *vs* none adefovir group. One case of drug-related hypophosphatemia was reported in the tenofovir DF group. No renal event or laboratory abnormality resulted in dose modification, interruption, or discontinuation of treatment.

The MAH provided a summary report regarding renal and bone safety in all patients (HIV and HBV) with renal impairment (creatinine clearance < 80 ml/min), who were long-term exposed to tenofovir in clinical studies by CHMP request.
Data from the pivotal HBV studies showed that none of the 25 tenofovir DF-treated patients with creatinine clearance < 80ml/min at baseline had experienced significant alteration in renal function. Data available from other studies (GS-US-174-106 and GS-US-174-108) are limited and the treatment

remains blinded. Data from HIV development program regarding subjects with mild renal impairment (creatinine clearance > 50ml/min to <80ml/min) from HIV studies is very limited (GS-99-903, GS-US-934 (n=28) and GS-104-235 (n=5)).

From the clinical experience of tenofovir in the treatment of HIV infection, it is clear that the renal safety of tenofovir is compromised in patients with moderate renal dysfunction or with concomitant therapy including medicinal products that (moderately) lower tenofovir clearance. Hence, for the present dosage 300 mg QD, patients with a clearance of ~50-70 ml/min will be studied separately with focus on renal (tubular) as well as bone safety. The MAH will conduct a phase 3b study in lamivudine-resistant patients. This patient population will include patients with mild renal impairment (with a lower threshold for creatinine clearance of 50 ml/min). A protocol synopsis will be provided to the CHMP within 3 months of approval of the indication of hepatitis B.

The renal monitoring should be focused on parameters related to tubular damage (serum phosphorus, urine-albumin, urine-β2 microglobuline) rather than renal function as measured by creatinine clearance. As retrospective dosages of urine-β2-microglobulin and bone-specific ALP from stored samples are not feasible, the MAH will conduct DEXA scans of the spine and hip at regular intervals (every 6 to 12 months) through week72- 240 for patients in studies GS-US-174-102 and -103.

The CHMP agreed not to absolute contraindicate tenofovir DF in severe renal impairment patients. Rather a strong warning stressing that tenofovir DF should only be used in patients with moderate/severe renal impairment if the potential benefits of treatment are considered to outweigh the potential risks was included in the SPC. Consequently the wording on dosing regimens was restricted accordingly.

Bone toxicity

In the pivotal studies in HBV, bone toxicity was monitored by phosphorus levels in serum and by reported fractures. Other serum bone markers were not reported and DEXA scanning was not undertaken. This issue was more intensely studied in the treatment of HIV-infection.

Tenofovir does not appear to be bone toxic *per se*. However, as tenofovir will be given to patients with chronic hepatitis B for long time periods, including women (with higher background incidence of osteoporosis), the renal function of these patients will eventually decrease, as part of aging process and this way increasing the group of patients which might be more prone to tenofovir toxicity.

Renal – and bone – toxicity is better studied in HBV patients than in HIV patients. In the former group tenofovir DF is given as a single agent, and co-morbidities and other complicating factors are likely to be more common in HIV patients. Hence, the MAH will include DEXA scanning as part of the requested safety study in patients with moderate renal dysfunction.

Gastro-intestinal toxicity

The most commonly gastro-intestinal disorders in tenofovir DF-treated patients are nausea and vomiting. A slightly higher incidence of mild nausea (20%) was observed among tenofovir DF-treated subjects compared with control subjects (15%) in a pooled analysis. Similar trend was observed in tenofovir DF clinical program in patients with chronic hepatitis B.

Nausea was more frequent among females treated with tenofovir DF (23.7%) than among females treated with adefovir (7.4%). In males, the incidence of nausea was slightly higher in tenofovir DF but the difference was less pronounced than in female patients.

Overall, female patients on tenofovir DF experienced more gastro-intestinal disorders than female patients on adefovir and with a higher rate compared to male patients. Similar differences are observed for most gastro-intestinal disorders, fatigue and dizziness.

Discontinuation due to AEs

No major difference was observed between both treatment groups. The proportion of patients having discontinued study treatment was similar in tenofovir DF-treated patients and adefovir–treated patients.

Dose modifications and interruptions were also reported in a similar number of patients in each treatment group (0.9% for both adefovir and tenofovir DF). In tenofovir DF group, the reasons for interruption or dose modification included nausea, vomiting and headache in one subject and cervical haemorrhage, head injury and increased creatinine phosphokinase in one subject each.

Special populations
Safety data of tenofovir DF used in HIV/HBV co-infected subjects are available from study ACTG A5127; from small subsets of co-infected subjects who participated in clinical studies in HIV-1 infection (studies GS-99-903, GS-01-934, GS-99-907 and GS-98-902) and from investigators-led studies on HIV/HBV co-infected subjects.
Overall, the safety profile of tenofovir DF in subjects with HIV/HBV co-infection did not seem to differ from that in subjects with HBV mono-infection. However, due to the risk of development of HIV resistance, tenofovir should only be used as part of an appropriate antiretroviral combination regimen in HIV/HBV infected patients.

No data are available for the use of tenofovir DF in patients undergoing liver transplantation. Special attention should be paid to the off label use of TDF in this specific population of patients since they are at higher risk of having underlying renal insufficiency (the authorisation did not include liver transplant patients). Moreover, the potential for an increased risk when tenofovir is combined with other nephrotoxic medicinal products must be taken into account.

Risk management plan

The MAH submitted a revised risk management plan (RMP), which covered the approved indication in HIV-1 infected patients and the applied indication in the treatment of chronic HBV infected patients.

Furthermore the MAH will distribute a Direct Healthcare Professional Communication (DHPC) to all new concerned Health Care professionals [1]

in order to adequately inform them of the risk of renal toxicity associated with tenofovir and the existence of specific recommendations to manage the renal tolerance. A draft DHPC letter will be provided for CHMP agreement on the final wording at the April 2008 plenary meeting.

A summary of the RMP for tenofovir DF highlighting the associated safety concerns is presented below:

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks		
Renal Toxicity		
Appropriate management of patients (including dosing of tenofovir DF in patients with abnormal renal function)	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data	- Statements in section 4.2 and warnings in section 4.4 of the SPC - Educational initiatives; - Communications via published literature and conference presentations. - Planned distribution of a Dear Healthcare Provider Letter (following approval of HBV indication)
Off-label use of tenofovir DF in children aged < 18 years (risk of overdose and associated increased risk of renal toxicity)	Regular analysis of postmarketing safety data Observational study in UK (CHIPS cohort)	- Statement in section 4.2 and in section 4.4 of the SPC.
Concurrent use of Viread/Truvada[1]/Atripla[2] (risk of overdose and associated increased risk of renal toxicity)	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data	- Warning in section 4.4 of the SPC.

[1] Emtricitabine/tenofovir DF
[2] Efavirenz/emtricitabine/tenofovir DF

Events resulting from tenofovir DF renal toxicity: bone (osteomalacia manifested as bone pain and infrequently contributing to fractures), muscle (rhabdomyolysis, muscular weakness, myopathy), or possibly resulting from renal toxicity (e.g. certain cardiac events)	Enhanced follow up of postmarketing adverse event reports; Regular analysis of postmarketing safety data; Clinical studies (long term safety studies – GS-99-903 and GS-01-934, ACTG 5202); Clinical studies in HIV infected children (GS-US-104-0321, GS-US-104-0352); Clinical studies in HBV infected patients (long term safety studies – GS-US-174-0102, GS-US-174-0103, GS-US-174-0121).	- Warning in section 4.4 in the SPC. - Osteomalacia and myopathy listed in section 4.8 of the SPC. - Warning in Viread CCSI (Section 3.9): - Adverse reactions listed in Viread CCSI (Section 7.3). -Type II variation to be filed 2Q08 to update the Viread, Truvada and Atripla SPCs to be in line with the Viread CCSI. - Update of labeling as appropriate. - Update of educational program as appropriate
Reversibility of tenofovir DF renal toxicity (possible long-term damage)	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data GS-US-104-0353	Not applicable
Fatal outcome	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data	Not applicable
Off-label use of tenofovir DF in liver transplant patients	Enhanced follow up of postmarketing adverse event reports Regular analysis of postmarketing safety data GS-US-203-0107	-Statement in section 4.4 of the SPC.
Incidence of, and risk factors for tenofovir DF renal toxicity	Enhanced follow up of postmarketing adverse event reports (to generate hypotheses which can be assessed formally in observational studies) Regular analysis of postmarketing safety data Observational studies (EuroSIDA, Kaiser and NADIS Cohort Studies) GS-US-104-0353	- Statement in section 4.4 of the SPC - Update of labeling as appropriate - Communication of findings concerning renal toxicity through publication in the scientific literature and conferences. - Update of educational program as appropriate
Genetic pre-disposition to tenofovir DF renal toxicity	Pharmacogenomics study (under discussion)	- Update of labeling as appropriate - Communication of findings concerning renal toxicity through publication in the scientific literature and conferences. - Update of educational program as appropriate
Mechanism of tenofovir DF renal toxicity	Nonclinical Studies (Renal Transporters)	- Update of labeling as appropriate - Communication of findings concerning renal toxicity through publication in the scientific literature and conferences. - Update of educational program as appropriate
Important Identified Risks continued		
Post-treatment hepatic flares in HBV monoinfected and HIV/HBV coinfected patients	Regular analysis of postmarketing safety data Clinical studies in HBV infected patients (GS-US-174-0102, GS-US-174-0103, GS-US-174-0106, GS-US-203-0101, GS-US-174-0121)	- Statement in section 4.2 and warning in section 4.4 of the SPC
Interaction with didanosine	Regular analysis of postmarketing safety data	-Warning in section 4.4 and section 4.5 of the SPC.

Important Potential Risks		
Development of resistance in HBV infected patients	Clinical studies in HBV infected patients (GS-US-174-0102, GS-US-174-0103, GS-US-174-0106, GS-US-174-0108, GS-US-203-0101, GS-US-174-0121)	- Update of labeling as appropriate. - Section 5.1 of the SPC.
Tenofovir DF monotherapy in HIV/HBV coinfected patients	Regular analysis of postmarketing safety data	- Statement and warning in section 4.4 the SPC.
Important Missing Information		
Safety in children	Regular analysis of postmarketing safety data Clinical studies in HIV infected children (GS-US-104-0321, GS-US-104-0352) Clinical studies in HBV infected adolescents (GS-US-174-0115) Observational study in UK (CHIPS cohort)	- Statement in section 4.2 and in section 4.4 of the SPC. - Update of labeling as appropriate - Communication of findings concerning renal toxicity through publication in the scientific literature and conferences. - Update of educational program as appropriate
Safety in elderly patients	Regular analysis of postmarketing safety data	- Warning in section 4.4 of the SPC - Update of labeling as appropriate - Communication of findings concerning renal toxicity through publication in the scientific literature and conferences. - Update of educational program as appropriate
Safety in pregnancy and lactation	Regular analysis of postmarketing safety data Epidemiological study (Antiretroviral Pregnancy Registry; Cross sectional study to assess the risk of mitochondrial disease in children exposed to NRTIs *in utero* [MITOC group])	- Statements in section 4.6 of the SPC
Safety of long-term exposure in HBV infected adults	Clinical studies in HBV infected patients (long term safety studies – GS-US-174-0102, GS-US-174-0103, GS-US-174-0106, GS-US-174-0108)	- Update of labeling as appropriate
Safety in renal impairment	Regular analysis of postmarketing safety data Clinical study in HBV infected patients with mild renal impairment (GS-US-174-0121) Planned clinical study in HBV infected patients with decompensated liver disease and creatinine clearance in the range 20 to 60 ml/min	- Appropriate management of patients (including dosing of tenofovir DF in patients with abnormal renal function) regarding warnings in the SPC. - Update of labeling as appropriate - Communication of findings concerning renal toxicity through publication in the scientific literature and conferences. - Update of labeling and educational program as appropriate
Safety in patients with hepatic decompensation and liver transplant recipients	Regular analysis of postmarketing safety data Clinical study GS-US-174-0108 in HBV infected patients with decompensated liver disease Planned clinical study in HBV infected patients with decompensated liver disease and creatinine clearance in the range 20 to 60 ml/min Clinical study GS-US-203-0107 in HBV infected patients post liver transplantation	- Statements and warnings in Section 4.4 of the SPC - Update of labeling as appropriate

In addition to the above identified safety concerns and activities, the MAH will include black patients as important missing information in the next update of the RMP. Comparing HBV-infected patients to HIV-infected patients in clinical studies, there were more Asian (32.3% *vs* 0.7%) and less black (5%

vs 16.4%) in HBV-infected patients treated with tenofovir DF. The information in this population (only 39 HBV-infected black patients treated with tenofovir DF) is therefore limited.

Overall conclusion and Benefit-Risk assessment

The data provided showed superiority of tenofovir DF over adefovir dipivoxil in term of proportion of patients with a complete response (defined as HBV DNA < 400 copies/ml and histological improvement indicated by at least a 2-point in Knodell necroinflammatory score without worsening in Knodell fibrosis score) at week 48 in both populations of Hbe Ag positive and negative patients.

The superiority of tenofovir DF was mainly driven by the virological response. No significant difference was seen in terms of histological and serological responses.

No mutations demonstrated to be associated with viral failure have been detected for tenofovir DF in the submitted studies at week 48. Resistance will be monitored every quarterly and results will be reported yearly.

As for the HIV infected patients the prominent aspects of tenofovir DF safety profile remains. The renal safety that would need particular monitoring is already recommended. A strong warning stressing that tenofovir DF should only be used in patients with chronic HB and moderate/severe renal impairment, if the potential benefits of treatment outweigh the potential risks, was included in the SPC. Additional data in subjects with moderate and severe renal impairment and chronic HBV infection, including safety data and steady-state pharmacokinetics will be provided. In addition, a study including participants with mild renal impairment and lamivudine-resistant HBV will be conducted. A Direct Healthcare Professional Communication (DHPC) will be send to all concerned Health Care professionals in order to adequately inform them of the risk of renal toxicity associated with tenofovir and the existence of specific recommendations to manage the renal toxicity.

Regarding bone toxicity, periodic DEXA scanning will be performed ongoing HBV pivotal trials and in the planned study in lamivudine resistant patients. Warning regarding potential ALT flares, on-treatment and post-treatment exacerbations of hepatitis, are reflected in the product information and will be periodically monitored.

Long term efficacy and safety data will be provided from ongoing and planned studies as committed by the MAH.

In conclusion, the benefit/risk balance for tenofovir DF in the treatment of chronic hepatitis B 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 is positive.

Conclusion

On 19 March 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.